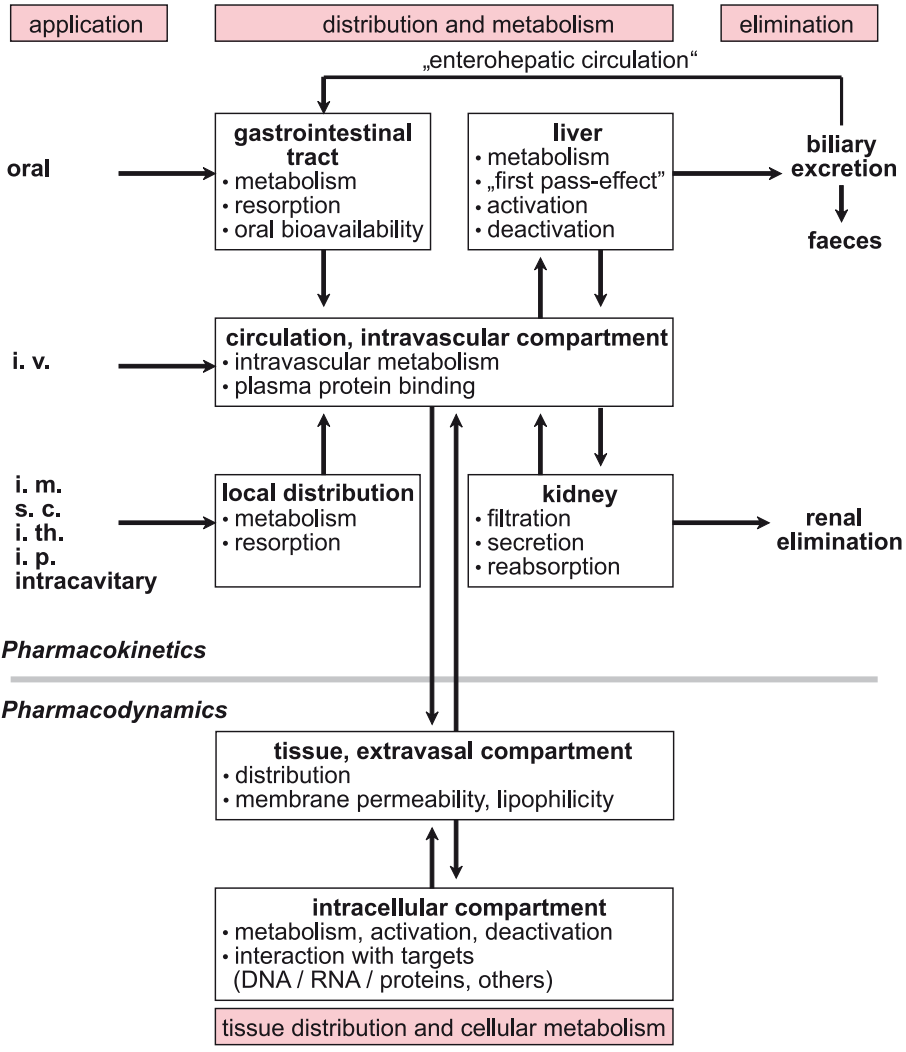
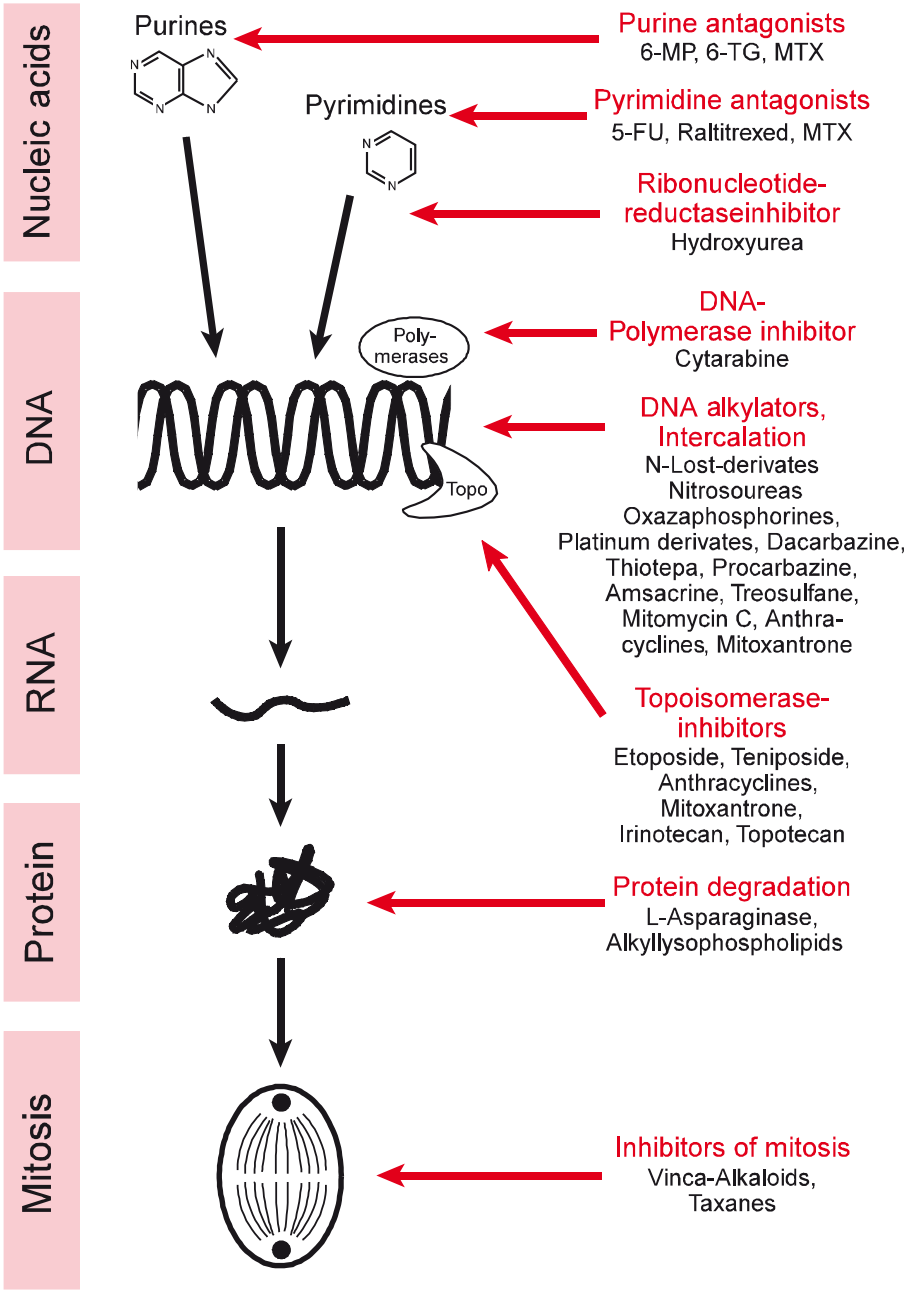
3.1 Basic Principles of Chemotherapy

D.P. Berger, R. Engelhardt, H. Henß

Pharm: **Pharmacokinetics and pharmacodynamics. Fundamental terms and influencing variables in application, distribution, metabolism, and elimination of cytostatic drugs**

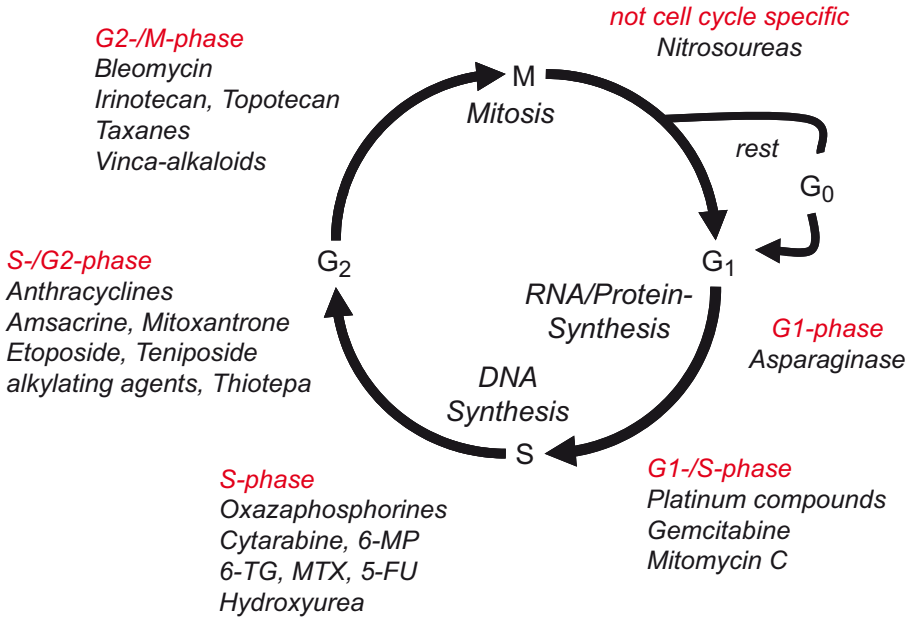


Ma: **Targets of clinically used cytostatic drugs**



Topo topoisomerases, *MP* mercaptopurine, *TG* thioguanine, *MTX* methotrexate, *FU* fluorouracil

Cell cycle and phase specifity of cytostatic drugs



MP mercaptopurine, *TG* thioguanine, *MTX* methotrexate

Mechanisms of Resistance

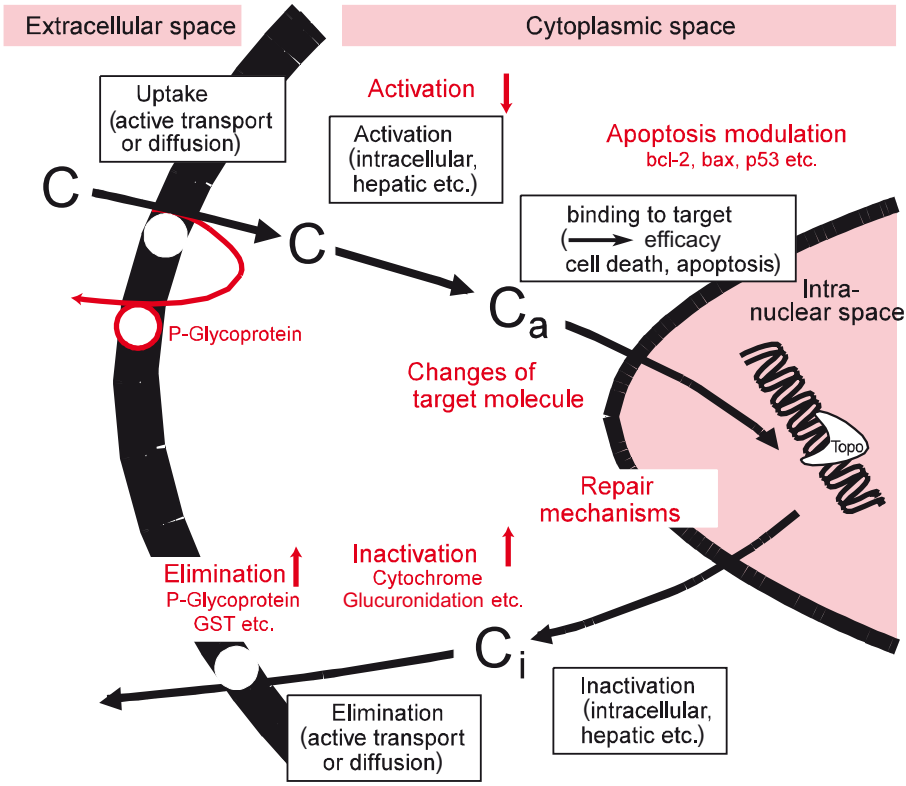
Resistance to cytostatic drugs limits the effect of chemotherapy. Types of resistance:

- Primary resistance ("a priori resistance"): pre-existing resistance against certain compounds
- Secondary resistance: acquired resistance following chemotherapy

Specific Mechanisms of Resistance

- *"Multidrug resistance (MDR)"* via P-glycoprotein (P170, membrane protein, 170 kDa): ATP-dependent transport of naturally occurring toxins out of the cell → inhibition of effect of anthracyclines, vinca alkaloids, taxanes, epipodophyllotoxins. Physiological expression of P170 in gastrointestinal tract, biliary ducts, kidney. Induction of expression in malignant cells by cytostatics.
- *Topoisomerase II resistance* due to changes of the target molecule DNA-topoisomerase II → reduced effect of epipodophyllotoxins and anthracyclines.
- *Antimetabolite resistance:* altered expression of target enzymes (e.g., thymidylate synthase TS, dihydrofolate reductase DHFR) → reduced effect of 5-FU, methotrexate, etc.
- *Glutathione (GSH) and glutathione-S transferase (GST):* reduced glutathione and GST contribute to intracellular detoxification of alkylating agents and platinum compounds → reduced effect caused by increased intracellular GSH levels or increased expression of GST.
- *O^6-Alkyltransferase (AT):* DNA-repairing enzyme, corrects alkylation of O^6 position of guanine induced by nitrosoureas → reduces effect of carmustine, lomustine, nimustine.

Mechanisms of cytoplasmic effect and resistance



C cytostatic, *Ca* active metabolite, *Ci* inactive metabolite, *black* cellular pharmacokinetic effects, *red* resistance mechanisms

Ref:

1. Anderson CM. Drug profiles. In: Perry MC, Anderson CM, Doll DC et al. (eds) Companion Handbook to the Chemotherapy Sourcebook, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, 2004, pp 419–72
2. Chauncey TR. Drug resistance mechanisms in acute leukemia. Curr Opin Oncol 2001;13:21–6
3. Egorin MJ. Overview of recent topics in clinical pharmacology of anticancer agents. Cancer Chemother Pharmacol 1998;42(Suppl):22–30
4. Fischer DS, Knobf MT, Durivage HJ et al. The Cancer Chemotherapy Handbook. Mosby, Philadelphia, 2003, pp 48–241
5. Rowinsky EK. The pursuit of optimal outcomes in cancer therapy in a new age of rationally designed target-based anticancer agents. Drugs 2000;60(Suppl 1):1–14
6. Skeel RT. Antineoplastic drugs and biological response modifiers. Classification, use and toxicity of clinically useful agents. In: Skeel RT (ed) Handbook of Cancer Chemotherapy, 6th edn. Lippincott Williams & Wilkins, Philadelphia, 2003, pp 53–156

Web:

1. http://www.druginfonet.com/ Drug Information, Information on Antineoplastic Agents
2. http://www.meds.com/DChome.html Information on cytostatics
3. http://chemfinder.cambridgesoft.com Chemical Data Base

3.2 Cytostatic Drugs

D.P. Berger, R. Engelhardt, H. Henß

Substance class	Group	Compound	Abbreviation / synonym
Alkylating agents	Nitrogen mustard derivatives	Busulfan	BUS, BU
		Chlorambucil	CBL
		Melphalan	L-PAM, MPL
		Bendamustine	BM
	Nitrosourea derivatives	Nimustine	ACNU
		Carmustine	BCNU
		Lomustine	CCNU
	Oxazaphosphorines	Cyclophosphamide	CY, CTX
		Ifosfamide	IFO
		Trofosfamide	
	Platinum derivatives	Cisplatin	CDDP, DDP
		Carboplatin	CBCDA
		Oxaliplatin	
	Triazine	Altretamine	HMM
	Tetrazines	Dacarbazine	DTIC
		Temozolomide	
	Aziridines	Thiotepa	
	Other	Amsacrine	AMSA, m-AMSA
		Estramustine phosphate	
		Procarbazine	PBZ
		Treosulfan	TREO
Antibiotics	Anthracyclines	Daunorubicin	DNR
		Doxorubicin	Adriamycin, ADR, DXR
		Epirubicin	EPI
		Idarubicin	IDA
	Anthracenediones	Mitoxantrone	MITOX
	Other	Actinomycin D	Dactinomycin, DACT, ActD
		Bleomycin	BLEO
		Mitomycin C	MMC
Antimetabolites	Antifolates	Methotrexate	MTX
		Raltitrexed	
		Pemetrexed	
	Purine antagonists	6-Mercaptopurine	6-MP
		6-Thioguanine	6-TG

[a] RNR ribonucleoside reductase

Substance class	Group	Compound	Abbreviation / synonym
		2'-Deoxycoformycin	Pentostatin, DCF
		Fludarabine phosphate	F-Ara-ATP
		2-Chlorodeoxyadenosine	2-CDA, cladribine
	Pyrimidine antagonists	5-Fluorouracil	5-FU
		Capecitabine	
		Cytosine arabinoside	Cytarabine, AraC
		Difluorodeoxycytidine	Gemcitabine, DFDC
		UFT	Tegafur-uracil
	RNR[a] inhibitors	Hydroxyurea	Hydroxycarbamide, HU
Alkaloids	Podophyllotoxin derivatives	Etoposide	VP-16
		Teniposide	VM26
	Vinca alkaloids	Vinblastine	VBL
		Vincristine	VCR
		Vindesine	VDS
		Vinorelbine	VRLB
	Taxanes	Docetaxel	Taxotere
		Paclitaxel	Taxol
	Camptothecin derivatives	Irinotecan	CPT-11
		Topotecan	
Enzymes		L-asparaginase	ASP
Other	Arsenic derivative	Arsenic trioxide	As_2O_3
	Alkylphosphocholine	Miltefosine	HDPC

[a] RNR ribonucleoside reductase

Web:

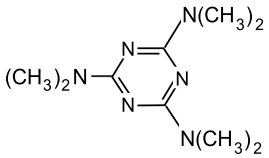
1. http://www.druginfonet.com/ Drug Information Network
2. http://chemfinder.cambridgesoft.com/ Chemfinder Database
3. http://www.meds.com/DChome.html Dose Calculation of Cytostatics

3.2.1 Characteristics of Clinically Used Cytostatic Drugs

H. Henß, J. Scheele, R. Engelhardt, D.P. Berger

Altretamine (Hexamethylmelamine, HMM)

Chem: N,N,N',N',N,N-hexamethyl-1,3,5-triazine-2,4,6-triamine, hexamethylmelamine



MOA: DNA alkylation and intercalation, inhibition of DNA and RNA synthesis

Pkin:
- *Kinetics:* good oral absorption (75–90%), half-life: t½ 4–13 h
- *Metabolism:* extensive first-pass hepatic metabolism to active metabolites, hepatic degradation (cytochrome P450-dependent), renal excretion of demethylated metabolites

Se:
- *Bone marrow:* myelosuppression (20–40%), with neutropenia, thrombocytopenia, anemia
- *Gastrointestinal:* nausea, vomiting, abdominal cramps, diarrhea, loss of appetite
- *Liver:* transaminase elevation (rare), impaired liver function
- *Skin:* alopecia (rare), erythema, pruritus, urticaria, allergic reactions
- *Nervous system:* dose-limiting peripheral and central neurotoxicity with irreversible neuropathies, paresthesia, sensory disturbances, hallucinations, confusion, ataxia, lethargy, somnolence
- *Local toxicity:* damaged capsules extremely irritating to mucous membranes
- *Other:* cystitis (rare), severe hypotension with concurrent administration of altretamine and monoamine oxidase inhibitors

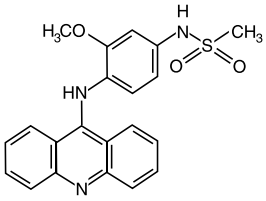
Ci: Impaired liver function

Th: *Approved indications:* ovarian cancer
Other areas of use: lymphomas, solid tumors (endometrial cancer, cervical cancer, small cell lung cancer)

Dosage and Administration
- Oral administration after food, 260–320 mg/m²/day (8–12 mg/kg/day) p.o., in 3–4 daily divided doses, for 14–21 days, repeat every 4–6 weeks; in combination therapy 150–200 mg/m²/day (4 mg/kg/day)
- Dose modification ► Chap. 3.2.4
- ATTN: cimetidine and barbiturates alter effect (t½) due to cytochrome P450 induction or inhibition
- BEFORE TREATMENT: full blood count, liver and renal function tests, neurological evaluation

Amsacrine (AMSA, m-AMSA)

Chem: 4'-(9-Acridinylamino)-3'-methoxymethanesulfonanilide, alkylating agent, topoisomerase II inhibitor



MOA:
- DNA alkylation and intercalation, inhibition of topoisomerase II
- Cell-cycle-specific: S/G2 phases

Pkin:
- *Kinetics:* Half-life: t½ 2 h, prolonged with impaired liver function
- *Elimination:* biliary and renal excretion of unchanged drug and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, especially leukopenia, moderate thrombocytopenia, anemia
- *Cardiovascular:* arrhythmias, heart failure, cardiac arrest (especially in presence of hypokalemia)
- *Gastrointestinal:* nausea, vomiting (30%), mucositis (10%), diarrhea (10%)
- *Liver:* transient elevation of transaminases
- *Skin:* alopecia, jaundice, erythema (rare), urticaria, allergic reactions
- *Nervous system:* rare, peripheral and central neurotoxicity with headache, confusion, seizures
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* orange urine

Ci:
- Hypokalemia, electrolyte disturbances
- Impaired liver and renal function

Th: *Approved indications:* AML

Dosage and Administration
- Standard dose: 75–150 mg/m²/day i.v. on days 1–5, repeat every 1–3 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, urea and electrolytes, liver and renal function tests, cardiac evaluation

Arsenic Trioxide

Chem: Arsenic trioxide, As_2O_3

MOA: Induction of differentiation, apoptosis and DNA fragmentation of PML-RARα-positive cells in acute promyelocytic leukemia, antiangiogenetic effect

Pkin:
- *Kinetics:* intravenous administration, intravascular binding to hemoglobin (96%), half-life: t½ 12 h
- *Metabolism:* hepatic degradation (90%), renal excretion (10%)

Se:
- *Bone marrow:* myelosuppression (15%), with anemia, neutropenia, thrombocytopenia
- *Cardiovascular:* tachycardia (50%), QT prolongation, AV block, ventricular arrhythmia (torsades de pointes)
- *Gastrointestinal:* nausea, vomiting, mucositis, sore throat, diarrhea, abdominal pain (50%), gastrointestinal bleeding (rare), weight loss
- *Liver:* elevated transaminases, impaired liver function, hyperglycemia
- *Kidney:* hypokalemia, hypocalcemia, hypomagnesemia, impaired renal function (rare)
- *Skin:* dermatitis, erythema, urticaria, pruritus, cutaneous bleeding (ecchymosis, petechiae (rare)), epistaxis (25%)
- *Nervous system:* headache (60%), insomnia, anxiety disorders, arthralgia, paresthesias
- *Local toxicity:* phlebitis, local edema, erythema
- *Other:* "differentiation syndrome": fever, leukocytosis, cough, dyspnea, hypoxia, thoracic pain, pleural / pericardial effusions, hypotension, edema. Treatment with corticosteroids (e.g., dexamethasone 10 mg twice a day). Coagulation disorders (rare), DIC (disseminated intravascular coagulation)

Ci:
- Severely impaired liver or renal function
- Electrolyte disturbances, QT prolongation (especially > 500 ms), AV conduction disorders

Th: *Approved indications:* acute promyelocytic leukemia (APL, AML FAB M3) with translocation t(15;17) or PML-RARα expression

Dosage and Administration
- Induction 0.15 mg/kg/day until remission, 8 weeks maximum, then no therapy for 3–6 weeks, consolidation 0.15 mg/kg/day for 4–5 weeks
- BEFORE TREATMENT: full blood count, urea and electrolytes, liver and renal function tests, ECG (exclude QT prolongation)

L-Asparaginase (L-ASP), PEG-Asparaginase (Pegaspargase)

Chem: Enzyme derived from *Escherichia coli* or *Erwinia carotovora*. Covalently linked with polyethylene glycol (PEG) to form PEG-asparaginase

MOA:
- Catalyses hydrolysis of L-asparagine to L-asparaginic acid and ammonia, intravascular depletion of asparagine and inhibition of protein synthesis of malignant lymphatic cells (normal cells are capable of asparagine synthesis by induction of asparagine synthetase)
- Cell-cycle-specific: G1 phase

Pkin:
- *Kinetics:* terminal half-life: t½ 8–30 h (depending on dose and compound), t½ prolonged to 3–6 days with PEG-asparaginase
- *Elimination:* metabolic degradation (proteolysis)

Se:
- *Gastrointestinal:* moderate nausea / vomiting (60%), mucositis, loss of appetite, diarrhea (rare)
- *Liver / pancreas:* impaired liver function, elevated transaminases (50% of patients), hepatitis, pancreatitis, hyperglycemia, impairment of clotting factor synthesis (especially fibrinogen and antithrombin III), thromboembolic events, hemorrhage
- *Kidney:* transient increase of serum creatinine and uric acid, acute renal failure (rare) or severely impaired renal function (rare)
- *Nervous system:* acute: reversible encephalopathy in 25–50% of patients: lethargy, somnolence, confusion; chronic: psychotic organic brain syndrome
- *Other:* dose-limiting allergic reactions: fever, chills, urticaria, skin reactions, bronchospasm, laryngospasm, asthma, anaphylactic shock. Reduced immunogenicity with PEG-asparaginase

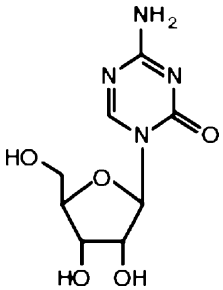
Ci:
- Known intolerance
- Pancreatitis
- Impaired liver function, pre-existing coagulation disorders

Th: *Approved indications:* ALL
Other areas of use: AML, NHL, CML in lymphatic blast crisis, CLL

Dosage and Administration
- L-Asparaginase 5,000–20,000 IU/m²/day i.v. for 10–20 days, i.m. application possible
- PEG-asparaginase: 2,500 IU/m²/day i.v. every 14 days, i.m. application possible
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: coagulation disorders: if fibrinogen < 0.8 g/l or ATIII < 70%, give fresh frozen plasma (FFP) or ATIII. If fibrinogen < 0.5 g/l or Quick's test < 30%, end treatment. Allergic Reactions: close observation of the patient, monitor blood pressure. Allergic reactions must be treated acutely with antihistamines and corticosteroids. Change preparation if necessary (allergic reactions commonly due to bacterial impurities)
- BEFORE TREATMENT: full blood count, liver and renal function tests, blood glucose, clotting studies. Pretherapy intradermal skin test (dose: 2 IU) to exclude possible hypersensitivity is recommended

Azacytidine (5-aza-cytidine)

Chem: 4-Amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one, pyrimidine nucleoside analog



MOA:
- Causes demethylation and hypomethylation of DNA, potentially with functional changes of genes regulating differentiation and proliferation of hematopoietic cells → direct cytotoxicity on abnormal hematopoietic cells in the bone marrow

Pkin:
- *Kinetics:* terminal half-life t½ after subcutaneous administration 2.5–4.2 h
- *Elimination:* hepatic metabolism, renal elimination 85%, fecal excretion < 1%

Se:
- *Bone marrow:* anemia, leucopenia, neutropenia, thrombocytopenia
- *Respiratory:* cough, dyspnea, respiratory tract infections, pharyngitis
- *Cardiovascular:* tachycardia, hypotension, atrial fibrillation (rare), cardiac failure (rare)
- *Gastrointestinal:* nausea / vomiting, diarrhea, constipation, anorexia, abdominal pain
- *Liver / pancreas:* impaired liver function, hepatic coma (rare)
- *Kidney:* serum creatinine ↑, impaired renal function, renal tubular acidosis (rare), hypokalemia
- *Skin:* erythema, rash, injection site reactions, ecchymosis, pruritus
- *Nervous system:* headache, confusion, dizziness, anxiety, depression, lethargy, insomnia, syncope
- *Other:* fever, infections, fatigue, weakness, rigors, arthralgia, myalgia, back pain, edema

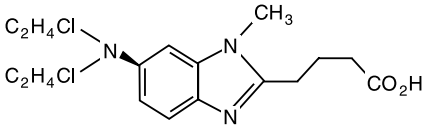
Ci:
- Known intolerance to azacytidine or mannitol
- Severe hepatic impairment, advanced malignant hepatic tumors
- Severe renal impairment

Th: *Approved indications:* MDS
Other areas of use: AML, CML, sickle cell disease, β-thalassemia, malignant mesothelioma

Dosage and Administration
- 75 mg/m²/day s.c. days 1–7 every 4 weeks, or 105 mg/m²/day s.c. days 1–5 every 4 weeks. Intravenous application possible
- ATTN: azacytidine may be embryotoxic, teratogenic, and mutagenic in humans. Appropriate precautions should be taken to avoid pregnancy and fathering. Monitoring of blood counts, liver enzymes, and renal function required
- BEFORE TREATMENT: full blood count, liver and renal function tests, electrolytes

Bendamustine

Chem: Gamma-(1-methyl-5-bis(beta-chloroethyl)aminobenzimidazole-(2)-butyric acid, alkylating agent, nitrogen mustard derivative



MOA: Cross-linking of DNA single and double strands by alkylation, DNA-protein and protein-protein linking

Pkin:
- *Kinetics:* initial half-life: t½ 6–10 min, terminal t½ 28–36 min
- *Metabolism:* hepatic hydrolysis to cytotoxically active β-hydroxy-bendamustine (β-OH-BM), predominantly renal elimination

Se:
- *Bone marrow:* myelosuppression
- *Cardiovascular:* arrhythmias, myocardial infarction (isolated cases)
- *Gastrointestinal:* nausea, vomiting, loss of appetite, constipation, diarrhea
- *Skin:* erythema, skin changes, alopecia, mucous membrane irritation
- *Nervous system:* weakness, fatigue, tiredness, peripheral neuropathy
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis with perivascular administration

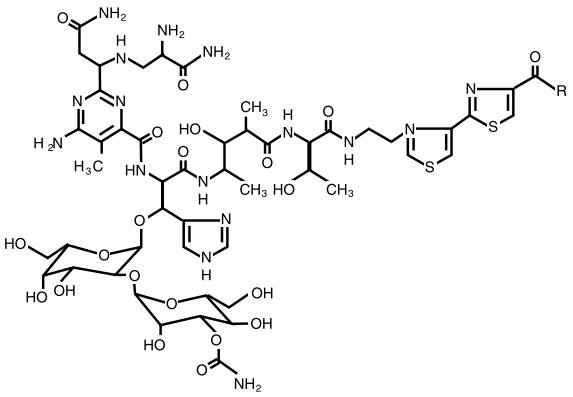
Ci:
- Impaired renal function
- Severely impaired liver function

Th: *Approved indications:* NHL, CLL, plasmacytoma, breast cancer

Dosage and Administration
- Standard dose: 25 mg/m²/day i.v. for 3 weeks or longer
- Dose modification ► Chap. 3.2.4, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests

Bleomycin

Chem: Antibiotic, mix of different bleomycins



MOA:
- DNA strand breaks, inhibition of DNA ligase, DNA intercalation
- Cell-cycle-specific: G2/M phase

Pkin:
- *Kinetics:* initial half-life: t½ 30 min, terminal t½ 2–5 h
- *Metabolism:* cytochrome P450-dependent hepatic activation, intracellular degradation (50%) by aminohydrolase (low levels in lung and skin → organotoxic), renal excretion of unchanged drug (50%) and metabolites

Se:
- *Bone marrow:* mild myelosuppression
- *Pulmonary:* dose-limiting interstitial pneumonitis and pulmonary fibrosis in up to 10% of cases with cough, dyspnea, hypoxia. Cumulative toxicity especially with total doses > 300 mg, increased in patients aged < 15 years and > 65 years
- *Gastrointestinal:* nausea / vomiting, loss of appetite, mucositis, diarrhea
- *Skin:* dose-dependent in 50% of patients: alopecia, erythema, urticaria, exanthema, striae, hyperpigmentation, edema, hyperkeratoses, nail changes, pruritus
- *Local toxicity:* phlebitis, pain at injection site
- *Other:* flu-like symptoms (fever, chills, myalgia). In 1% of patients allergic reactions up to anaphylaxis. Raynaud's syndrome

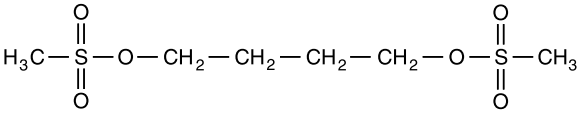
Ci:
- Pre-existing lung disease (especially chronic obstructive pulmonary disease), previous lung radiation, assisted ventilation with increased O_2 concentration
- Severely impaired liver or renal function

Th: *Approved indications:* testicular cancer, Hodgkin's disease, NHL, squamous cell carcinoma (head and neck region, esophagus, penis, cervix, vulva)
Other areas of use: solid tumors, instillation (malignant effusions)

Dosage and Administration
- Standard dose: 15–30 mg absolute, 1–2×/week, administration i.v. / i.a. / s.c. or i.m. possible
- With intracavitary administration (pleural effusion, pericardial effusion, urinary bladder) 30–180 mg absolute
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: not to be given in combination with nephrotoxic or pneumotoxic drugs (busulfan, cyclophosphamide, melphalan, mitomycin)
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), pulmonary function tests. Pretherapy test dose (1–2 mg) to exclude possible hypersensitivity is recommended

Busulfan

Chem: Tetramethylene dimethane sulfonate, bifunctional alkylating agent



MOA:
- DNA and RNA alkylation (N7 position of guanine), DNA strand breaks and cross-linking
- Cell-cycle-specific: S/G2 phase

Pkin:
- *Kinetics:* oral or intravenous administration, terminal half time t½ 2.5 h, entering cerebrospinal fluid
- *Metabolism:* hepatic degradation to inactive metabolites (tetrahydrofuran, methane sulfonic acid), renal excretion of unchanged drug and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, long neutropenic phase (following treatment, nadir between days 11 and 30), thrombocytopenia, anemia
- *Cardiovascular:* hypertension, hypotension, tachycardia, thromboembolic events
- *Pulmonary:* pulmonary fibrosis ("busulfan lung," rare), especially with cumulative dose > 3,000 mg (threshold dose 500 mg). Increased risk with lung radiation and assisted ventilation with increased O_2 concentration
- *Gastrointestinal:* moderate nausea / vomiting, mucositis, loss of appetite
- *Liver:* transient disturbances of liver function, hepatic veno-occlusive disease (VOD) after high-dose therapy
- *Skin:* erythema, hyperpigmentation, alopecia
- *Nervous system:* central nervous system toxicity (rare), with visual disturbances, confusion, seizures, especially with high-dose therapy
- *Other:* infertility, cataracts, gynecomastia (rare), other fibroses (rare): pulmonary, retroperitoneal, endocardial. Hemorrhagic cystitis (rare)

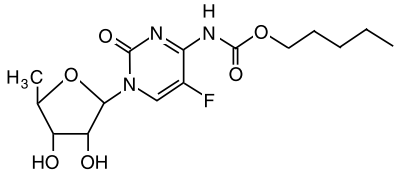
Ci: Pre-existing lung disease (especially chronic obstructive pulmonary disease)

Th: *Approved indications:* CML (palliative), polycythemia vera
Other areas of use: other myeloproliferative diseases, conditioning prior to autologous / allogeneic transplantation in patients with leukemia or lymphoma

Dosage and Administration
- Standard dose: 0.5–8 (–12) mg/day p.o. or 0.05–0.06 mg/kg body weight/day p.o.
- High-dose therapy: 4 mg/kg body weight/day for 4 days (*ATTN:* only in transplant centers)
- Stability ► Chap. 3.2.7
- ATTN: cumulative dose of > 500 mg: increased risk of pulmonary fibrosis
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), pulmonary function tests

Capecitabine

Chem: Pyrimidine analog, antimetabolite



MOA:
- Inhibition of thymidylate synthetase by FdUMP and thymidine synthesis
- Incorporated into RNA, inhibition of RNA synthesis by FUTP
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* half-life: t½ 0.7–1.2 h
- *Metabolism:* oral administration, rapid and complete absorption. Intracellular conversion of the prodrug by hepatic carboxylesterase to 5'-deoxy-5-fluorocytidine (5'DFCR), subsequent intracellular metabolism by thymidine phosphorylase to 5-fluorouracil (5-FU), intracellular activation and phosphorylation (formation of FdUMP, FUTP). Degradation in liver and intestinal mucosa by dihydropyrimidine dehydrogenase (DPD)
- *Excretion:* renal elimination of unchanged drug and metabolites

Se:
- *Bone marrow:* myelosuppression with neutropenia, thrombocytopenia, anemia
- *Cardiovascular:* lower limb edema, cardiac ischemia (rare, may occur with pre-existing coronary heart disease), ECG changes
- *Gastrointestinal:* diarrhea (40%), mild nausea / vomiting (40%), mucositis, abdominal pain, stomatitis, loss of appetite
- *Liver:* elevated transaminases (reversible), hyperbilirubinemia
- *Skin:* hand-foot syndrome (palmar-plantar erythrodysesthesia, 50%), dermatitis (25%), alopecia
- *Nervous system:* headache, paresthesias, dysgeusia, vertigo, insomnia, confusion (rare), ataxia
- *Other:* fatigue, loss of appetite, fever, weakness, lethargy, mucositis, dehydration

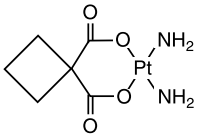
Ci: Known hypersensitivity to fluorouracil (DPD deficiency)

Th: *Approved indications:* colorectal cancer, breast cancer
Other areas of use: head and neck tumors, pancreatic cancer

Dosage and Administration
- Standard dose: 2,000–2,500 mg/m²/day p.o. on days 1–14, every 3 weeks. To be taken with water in 2 daily divided doses, 30 min after food
- Dose modification ► Chap. 3.2.4
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Carboplatin (CBCDA)

Chem: cis-Diamine(1,1-cyclobutanedicarboxylato)platinum (II), platinum derivative



MOA:
- Covalent binding of DNA and protein, DNA intercalation, strand breaks
- Cell-cycle-specific: G1/S phases

Pkin:
- *Kinetics:* enters cerebrospinal fluid, initial half-life t½ 60–90 min, terminal t½ 3–6 h
- *Metabolism:* intracellular formation of reactive platinum complexes, renal excretion of unchanged drug (60%) and metabolites (40%)

Se:
- *Bone marrow:* myelosuppression, especially prolonged thrombocytopenia (dose-limiting), leukopenia and cumulative disturbances of erythropoiesis
- *Gastrointestinal:* nausea / vomiting, loss of appetite, mucositis
- *Liver:* transient elevation of transaminases
- *Kidney:* nephrotoxicity (rare), electrolyte disturbances (Na^+ ↓, K^+ ↓, Mg^{2+} ↓)
- *Skin:* alopecia (rare), erythema, pruritus
- *Nervous system:* peripheral neurotoxicity (rare, mainly in patients > 65 years), hearing disorders (rare) or optic neuritis (rare)
- *Local toxicity:* pain at injection site
- *Other:* infertility, fever, chills, allergic reactions (rare)

Ci:
- Impaired renal function, dehydration
- Pre-existing hearing disorders, acute infections

Th: *Approved indications:* epithelial ovarian cancer, cervical cancer, lung cancer, head and neck tumors
Other areas of use: other solid tumors, refractory leukemia, lymphoma

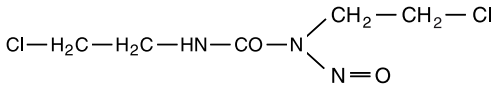
Dosage and Administration
- Standard dose: 300–400 mg/m²/day i.v. on day 1, every 4 weeks
- Pharmacological dose calculation: calculation of total dose in mg according to the target AUC ("area under the curve," area under the concentration-time curve in mg/ml × min) and the renal function (GFR, glomerular filtration rate in ml/min):

$$\text{Dose} = \text{AUC} \times (\text{GFR} + 25)$$

- The target AUC for carboplatin is 5–7 mg/ml/min in monotherapy protocols and 4–6 mg/ml/min in polychemotherapy protocols
- High-dose therapy: 500 mg/m²/day i.v. on days 1–3 (*ATTN:* only in transplant centers)
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: not to be given in combination with nephrotoxic or ototoxic drugs (aminoglycosides, NSAIDs, loop diuretics, etc.). Fluid replacement
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Carmustine (BCNU)

Chem: 1,3-Bis(2-chloroethyl)-1-nitrosourea, bifunctional alkylating agent



MOA:
- DNA and RNA alkylation (O^6 position of guanine), DNA strand breaks, cross-linking
- Cell cycle non-specific (including G0 phase)

Pkin:
- *Kinetics:* lipophilic compound, enters cerebrospinal fluid, initial half-life: t½ 4–7 min, terminal t½ 20–70 min
- *Metabolism:* spontaneous hepatic degradation into inactive metabolites (isocyanate, diazohydroxide), renal excretion of unchanged drug and metabolites

Se:
- *Bone marrow:* prolonged and cumulative myelosuppression (dose-limiting), leukocyte and thrombocyte nadir 3–5 weeks after administration
- *Pulmonary:* with repeated administration, interstitial pneumonitis, pulmonary infiltrates and pulmonary fibrosis (cumulative toxicity)
- *Gastrointestinal:* nausea / vomiting for 8–24 h, mucositis, diarrhea; rarely: esophagitis, ulcers, gastrointestinal bleeding
- *Liver:* transient elevation of transaminases, hepatic veno-occlusive disease (VOD) with high-dose therapy
- *Kidney:* impaired renal function
- *Skin:* alopecia, dermatitis, erythema, hyperpigmentation
- *Nervous system:* peripheral and central neurotoxicity with confusion, psychotic organic brain syndrome, neuroretinitis, optic neuritis, ataxia
- *Local toxicity* (extravasation ► Chap. 9.9): venous irritation, necrosis
- *Other:* infertility

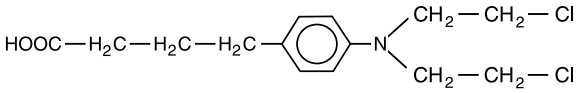
Ci:
- Pre-existing disorders of bone marrow function, acute infections
- Severe liver or renal disorders

Th: *Approved indications:* CNS tumors, cerebral metastases, multiple myeloma, lymphomas, gastrointestinal tumors
Other areas of use: breast cancer, melanoma

Dosage and Administration
- Standard dose: 100 mg/m²/day i.v. with protection from light, on days 1–2, every 6–8 weeks
- High-dose therapy: 300–600 mg/m²/day i.v. on day 1 (*ATTN:* only in transplant centers)
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative, delayed, and prolonged myelotoxicity. Increased risk of pulmonary toxicity with total cumulative dose > 1,000 mg/m². Increased toxicity with concurrent administration of metronidazole, cimetidine, or verapamil.
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), pulmonary function tests

Chlorambucil

Chem: 4-(4-[Bis(2-chloroethyl)amino]phenyl)butanoic acid, alkylating agent



MOA:
- DNA and RNA alkylation, DNA strand breaks, cross-linking
- Cell cycle non-specific (including G0 phase)

Pkin:
- *Kinetics:* oral bioavailability 60–100%, terminal half-life: t½ 1.5–2.5 h
- *Metabolism:* hepatic degradation into active (aminophenylacetic acid) and inactive metabolites, renal excretion of unchanged drug (1%) and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, neutropenia, thrombocytopenia with standard dose (see below) usually only moderate
- *Pulmonary:* pulmonary fibrosis (rare), especially with cumulative dose > 2,000 mg
- *Gastrointestinal:* mild nausea / vomiting, loss of appetite
- *Liver:* transient elevation of transaminases, severe hepatotoxicity (very rare)
- *Skin:* erythema, urticaria, alopecia
- *Nervous system:* rarely, peripheral / central neurotoxicity
- *Other:* infertility (especially with cumulative dose > 400 mg), fever, cystitis (rare)

Ci: Pre-existing myelosuppression, acute infections

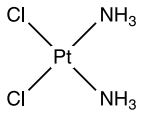
Th: *Approved indications:* CLL, NHL, Hodgkin's disease
Other areas of use: multiple myeloma, Waldenström's macroglobulinemia, ovarian cancer, breast cancer, testicular tumors, trophoblastic tumors

Dosage and Administration

- Standard dose: oral administration, once a day with food, various protocols, e.g.:
  - 0.05–0.2 mg/kg body weight/day p.o. for 3–6 weeks, thereafter daily maintenance dose of 2 mg absolute p.o.
  - 0.4 mg/kg body weight/day p.o. on day 1, every 2–4 weeks
  - 18–30 mg/m²/day p.o. on day 1, every 2 weeks
  - 16 mg/m²/day p.o. on days 1–5, every 4 weeks
- ATTN: cumulative dose > 2,000 mg: increased risk of pulmonary fibrosis. Increased side effects with concurrent administration of phenylbutazone derivatives or phenobarbital
- BEFORE TREATMENT: full blood count, liver and renal function tests

Cisplatin (CDDP)

Chem: cis-Diamminedichloroplatinum(II), platinum derivative



MOA:
- Covalent binding of platinum complexes to DNA, RNA, and proteins, cross-linking
- Cell-cycle-specific: G1/S phases

Pkin:
- *Kinetics:* half-life: initial t½ 25–50 min, terminal t½ 60–90 h
- *Metabolism:* formation of reactive platinum complexes, renal excretion (90%) of unchanged drug and metabolites, biliary excretion (10%)

Se:
- *Bone marrow:* myelosuppression, leukopenia, thrombocytopenia, anemia
- *Cardiovascular:* arrhythmias (rare), heart failure
- *Gastrointestinal:* severe nausea / vomiting (prolonged, duration > 24 h), loss of appetite, mucositis, diarrhea, enteritis
- *Liver:* transient elevation of transaminases
- *Kidney:* electrolyte changes (Ca^{2+} ↓, Mg^{2+} ↓, K^+ ↓, Na^+ ↓), cumulative nephrotoxicity with renal tubular damage (dose-limiting), probably from inadequate hydration
- *Skin:* alopecia, dermatitis
- *Nervous system:* ototoxicity and peripheral neurotoxicity (dose-limiting, cumulative, with total doses > 100–200 mg/m²), dysgeusia, focal encephalopathy (rare), visual disturbances, optic neuritis, vertigo
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* infertility, allergic reactions (rare)

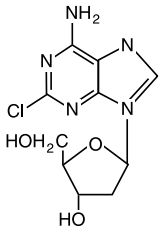
Ci: Impaired renal function, dehydration, hearing disorders, acute infections

Th: *Approved indications:* testicular tumors, ovarian cancer, bladder cancer
Other areas of use: solid tumors (head and neck region, lungs, esophagus, cervix, endometrium, prostate, osteosarcoma, melanoma), NHL

Dosage and Administration
- Standard dose: various protocols:
  - Low dose: 15–20 mg/m²/day i.v. on days 1–5, every 3–4 weeks
  - Medium dose: 50–75 mg/m²/day i.v. on days 1 + 8, every 3–4 weeks
  - High dose: 80–120 mg/m²/day i.v. on day 1, every 3–4 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: not to be given in combination with nephrotoxic drugs (aminoglycosides, NSAIDs, loop diuretics, etc.). Fluid replacement, aim: urine volume > 200 ml/h, with electrolyte replacement (K^+, Mg^{2+}) if necessary. Cumulative neurotoxicity and ototoxicity (with total dose > 100–200 mg/m²).
- BEFORE TREATMENT: full blood count, electrolytes, liver and renal function tests (creatinine clearance), audiometry and neurological evaluation, if necessary. Fluid administration 1,000–2,000 ml (with KCl and $MgSO_4$), osmotic diuresis

Cladribine (2-CDA)

Chem: 2-Chloro-deoxyadenosine, purine analog, antimetabolite



MOA:
- Inhibition of DNA polymerase β and ribonuclease reductase
- Induction of DNA strand breaks, depletion of NAD and ATP
- Cell cycle non-specific (including G0 phase)

Pkin:
- *Kinetics:* enters cerebrospinal fluid, half-life: initial t½ 35 min, terminal t½ 7 h
- *Metabolism:* intracellular formation of the active triphosphate derivative, 2-chlorodeoxy-ATP, by deoxycytidine kinase
- *Elimination:* renal excretion

Se:
- *Bone marrow:* myelosuppression dose-limiting, with neutropenia (30%) and thrombocytopenia, lymphopenia (100%)
- *Gastrointestinal:* moderate nausea / vomiting (15% of patients), diarrhea
- *Liver:* transient elevation of transaminases
- *Kidney:* impaired renal function, especially with inadequate fluid replacement
- *Skin:* erythema (rare), up to toxic epidermolysis
- *Nervous system:* peripheral or central neurotoxicity in 15% of patients
- *Other:* immunosuppression with T-cell deficiency (CD4+ ↓↓, CD8+ ↓), infections, fever (60%), tiredness (50%), headaches

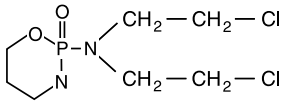
Ci: Severely impaired renal function

Th: *Approved indications:* hairy cell leukemia
Other areas of use: NHL, CLL, CML, acute leukemia, mycosis fungoides

Dosage and Administration
- Standard dose: usually given for one cycle only, no repeat. Various protocols:
  - 0.1 mg/kg body weight/day c.i.v., on days 1–7 (continuous infusion)
  - 0.14 mg/kg body weight/day i.v. on days 1–5 (2-h infusion)
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Cyclophosphamide

Chem: 2-[Bis(2-chloroethylamino)]-tetrahydro-2H-1,3,2-oxazaphosphine-2-oxide
Oxazaphosphorine, alkylating agent



MOA:
- DNA and RNA alkylation, DNA strand breaks, cross-linking, DNA synthesis ↓
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* oral bioavailability 90–100%, half-life: terminal t½ 4–8 h
- *Metabolism:* initial hepatic hydroxylation by the microsomal cytochrome P450 monooxygenase system, release of active metabolite (phosphoramide mustard) in plasma and tissue, hepatic degradation into inactive metabolites. Renal excretion of active and inactive metabolites, dialyzable

Se:
- *Bone marrow:* myelosuppression dose-limiting, leukopenia (nadir 8–14 days after administration) and thrombocytopenia, anemia
- *Cardiovascular:* in 5–10% of cases with high-dose therapy, acute myocarditis / pericarditis, heart failure, hemorrhagic myocardial necrosis
- *Pulmonary:* with high-dose therapy, pulmonary fibrosis (rare), pneumonitis
- *Gastrointestinal:* nausea, vomiting (especially with doses > 600 mg/m²/day), mucositis, stomatitis, loss of appetite
- *Liver:* transient elevation of transaminases, cholestasis (rare)
- *Kidney / genitourinary tract:* hemorrhagic cystitis (dose-limiting), especially with high-dose therapy, bladder fibrosis, impaired renal function
- *Skin:* alopecia, erythema, hyperpigmentation, nail changes, dermatitis
- *Nervous system:* with high-dose therapy: acute encephalopathy
- *Other:* infertility, immunosuppression, fever, allergic reactions

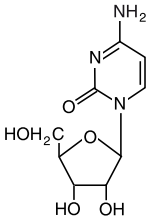
Ci: Severely impaired liver or renal function, acute infections, cystitis, urinary tract obstruction

Th: *Approved indications:* lymphomas, multiple myeloma, ovarian cancer, breast cancer
Other areas of use: leukemias, solid tumors, immunosuppression, severe autoimmune diseases

Dosage and administration
- Standard dose: oral or intravenous administration, various protocols:
  - 50–200 mg/m²/day p.o. on days 1–14 in the morning, every 28 days
  - 500–1,000 mg/m²/day i.v. on day 1 in the morning, every 21 days
- High-dose therapy: up to 16,000 mg/m²/day i.v. (*ATTN:* only in hematology / oncology centers)
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: prophylaxis of hemorrhagic cystitis starting with a dose of > 400 mg/m²/day: fluid replacement (urine volume > 200 ml/h), mesna. Effects enhanced by barbiturates (cytochrome P450 activation) and cimetidine
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Cytarabine (Cytosine Arabinoside, Arabinosylcytosine, AraC)

Chem: 4-Amino-1-β-D-ribofuranosyl-2(1H)-pyrimidinone, deoxycytidine analog, antimetabolite



MOA:
- Incorporated into DNA, inhibition of DNA polymerases, DNA synthesis ↓
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* Half-life: initial t½ 12 min, terminal t½ 2 h, enters cerebrospinal fluid
- *Metabolism:* intracellular phosphorylation to active ara-CMP and ara-CTP, hepatic degradation into inactive metabolites (ara-U, ara-UMP) by deamination, renal excretion of metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, leukopenia, thrombocytopenia, anemia
- *Pulmonary:* with high-dose therapy acute pulmonary toxicity, pulmonary edema, ARDS ("acute respiratory distress syndrome") → intensive care unit necessary
- *Gastrointestinal:* nausea / vomiting, mucositis, diarrhea, loss of appetite. Rarely with high-dose therapy, pancreatitis, ulcers, bowel necrosis, esophagitis
- *Liver:* transient elevation of transaminases, cholestasis
- *Skin:* alopecia, dermatitis, erythema, exanthema, keratitis
- *Nervous system:* peripheral and central neurotoxicity. Cerebral and cerebellar disorders, especially in older patients (> 60 years) and with high-dose therapy. With intrathecal administration: acute arachnoiditis, leukoencephalopathy
- *Other:* fever, myalgia, arthralgia, bone and muscle pain, flu-like symptoms, conjunctivitis

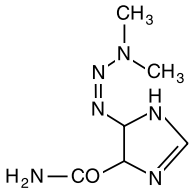
Ci: Severely impaired liver or renal function, pre-existing CNS disease

Th: *Approved indications:* AML, ALL, CML in blast crisis, NHL

Dosage and Administration
- Standard dose: various protocols:
  - Low-dose AraC: 10–20 mg/m²/day s.c. daily, for 21 days
  - Medium-dose AraC: 100 mg/m² twice a day i.v. on days 1–7 or 200 mg/m²/day c.i.v. on days 1–7
  - High-dose AraC: 1,000–3,000 mg/m² twice a day i.v. on days 1–6 (*ATTN:* only in hematology centers), with prophylactic administration of dexamethasone i.v. and as eye drops
  - Intrathecal (40–50 mg absolute) or intramuscular administration possible
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), neurological evaluation if necessary

Dacarbazine (DTIC)

Chem: 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide, tetrazine derivative, alkylating agent



MOA:
- DNA methylation and direct DNA toxicity, alkylating agent
- Cell cycle non-specific (including G0 phase)
- Inhibition of purine, RNA and protein synthesis

Pkin:
- *Kinetics:* half-life: initial t½ 20–80 min, terminal t½ 3–5 h
- *Metabolism:* hepatic activation (by microsomal oxidases) into MTIC (monomethyl triazeno imidazole carboxamide), renal excretion of unchanged drug (40%) and metabolites (50%), minor hepatobiliary and pulmonary excretion

Se:
- *Bone marrow:* myelosuppression dose-limiting, leukopenia, thrombocytopenia
- *Pulmonary:* pneumonitis (rare)
- *Gastrointestinal:* severe nausea / vomiting, loss of appetite, mucositis (rare), diarrhea
- *Liver:* transient elevation of transaminases, hepatic veno-occlusive disease (VOD, rare), hepatic necrosis
- *Kidney:* impaired renal function (rare)
- *Skin:* erythema, exanthema, photosensitivity, alopecia (rare)
- *Nervous system:* rarely central nervous system disorders (headache, visual disturbances, confusion, lethargy, seizures), paresthesias
- *Local toxicity* (extravasation ► Chap. 9.9): local thrombophlebitis, necrosis
- *Other:* rarely, flu-like symptoms (fever, chills, myalgia), allergic reactions, hypotension

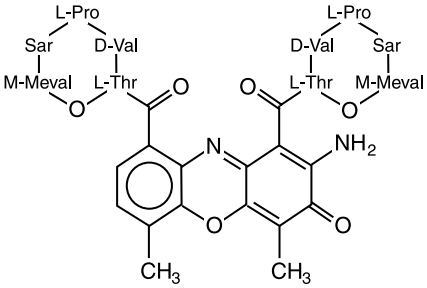
Ci: Severely impaired liver or renal function

Th: *Approved indications:* malignant melanoma, Hodgkin's disease
Other areas of use: soft tissue sarcoma, osteosarcoma, renal cell carcinoma

Dosage and Administration
- Standard dose: intravenous administration, with protection from light, various protocols:
  - 150–250 mg/m²/day i.v. on days 1–5, every 3–4 weeks
  - 375 mg/m²/day i.v. on days 1 + 15, every 3–4 weeks
  - 750–850 mg/m²/day i.v. on day 1, every 4 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: patients should avoid sunlight (photosensitivity). Antiemetic prophylaxis mandatory
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Dactinomycin (Actinomycin D)

Chem: Peptide antibiotic



MOA:
- DNA intercalation, inhibition of RNA and protein synthesis
- Inhibition of topoisomerase II

Pkin:
- *Kinetics:* strong tissue binding, half-life: terminal t½ 30–40 h
- *Metabolism:* hepatic degradation, renal and biliary excretion of unchanged drug (70%) and metabolites

Se:
- *Bone marrow:* prolonged myelosuppression (dose-limiting), neutropenia, thrombocytopenia, anemia
- *Gastrointestinal:* severe nausea / vomiting, mucositis, gastrointestinal ulcers, diarrhea, loss of appetite, dysphagia
- *Liver:* hepatitis (rare), impaired liver function, hepatomegaly, ascites
- *Kidney:* impaired renal function (rare)
- *Skin:* alopecia, acne, erythema, exanthema, desquamation, hyperpigmentation, delayed tissue reaction in a previously irradiated site ("radiation recall reaction"), rarely allergic reactions up to anaphylaxis
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* rarely, flu-like symptoms (fever, myalgia)

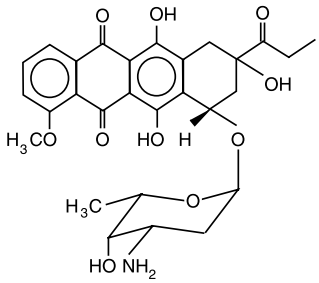
Ci:
- Severely impaired liver or renal function
- Acute infections (especially varicella, *Herpes zoster*)

Th: *Approved indications:* Wilms' tumor, soft tissue sarcomas, testicular cancer, choriocarcinoma, uterine cancer
Other areas of use: trophoblastic tumors, AML, osteosarcomas, melanomas, endometrial cancer, ovarian cancer

Dosage and Administration
- Standard dose: various protocols:
  - 0.25–0.6 mg/m²/day i.v. on days 1–5, every 3–5 weeks
  - 1.0–2.0 mg/m²/day i.v. on day 1, every 3–5 weeks
  - 35–50 µg/kg as an isolated limb perfusion
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Daunorubicin (DNR, Rubidomycin), Liposome-encapsulated Daunorubicin

Chem: Anthracycline, antineoplastic glycoside antibiotic



MOA:
- DNA intercalation, induction of DNA strand breaks, generation of free oxygen radicals, inhibition of topoisomerase II
- Cell-cycle-specific: S/G2 phases

Pkin:
- *Kinetics:* half-life: terminal t½ 15–48 h
- *Metabolism:* hepatic degradation to active (daunorubicinol) and inactive metabolites, aglycon formation, biliary (50%) and renal (< 20%) excretion

Se:
- *Bone marrow:* myelosuppression (dose-limiting), leukopenia and thrombocytopenia
- *Cardiovascular:* acute and chronic cardiotoxicity (dose-limiting)
  - *Acute:* ECG changes, arrhythmias, ischemia, infarction
  - *Chronic:* congestive cardiomyopathy with decreased left ventricular ejection fraction (LVEF)
  - *Risk factors:* pre-existing cardiac disorders, age < 15 or > 60 years, fast bolus injection, mediastinal radiation, total dose of > 500–600 mg/m². Liposome-encapsulated daunorubicin shows reduced cardiotoxicity
- *Gastrointestinal:* nausea, vomiting, mucositis, stomatitis, diarrhea (rare)
- *Liver:* transient elevation of transaminases
- *Skin:* exanthema, urticaria, alopecia, delayed tissue reaction in a previously irradiated site ("radiation recall reaction"), nail changes, hyperpigmentation (rare)
- *Local toxicity* (extravasation ► Chap. 9.9): causes severe necrosis
- *Other:* infertility, peripheral neuropathy (rare), red urine

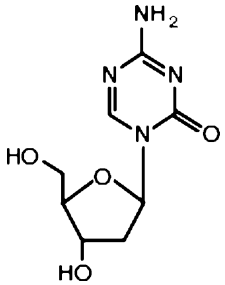
Ci:
- Cardiac disease (arrhythmias, myocardial infarction, coronary heart disease, heart failure)
- Severely impaired liver function, acute infections

Th: *Approved indications:* ALL, AML (daunorubicin), AIDS-associated Kaposi's sarcoma (liposome-encapsulated daunorubicin)
Other areas of use: NHL, CML, neuroblastoma

Dosage and Administration
- *Daunorubicin:* 45–60 mg/m²/day i.v. on days 1–3, every 4 weeks
- *Liposome-encapsulated daunorubicin:* 40 mg/m²/day i.v. every 2 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative threshold dose 500–600 mg/m² with daunorubicin
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), cardiac evaluation, echocardiogram / radionuclide ventriculography

Decitabine (5-aza-2′-deoxycytidine)

Chem: 4-Amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1H)-one, pyrimidine nucleoside analog



MOA:
- Inhibition of DNA methyltransferase after incorporation into DNA
- Causes demethylation and hypomethylation of DNA, potentially with functional changes of genes regulating differentiation, proliferation, and apoptosis

Pkin:
- *Kinetics:* terminal half-life t½ 0.5 ± 0.3 h
- *Elimination:* deamination by cytidine deaminase (liver, granulocytes, intestinal epithelia)

Se:
- *Bone marrow:* anemia, leucopenia, neutropenia, thrombocytopenia
- *Respiratory:* cough, dyspnea, respiratory tract infections, pneumonia, pharyngitis
- *Cardiovascular:* tachycardia, atrial fibrillation (rare), cardiac failure (rare), myocardial infarction (rare)
- *Gastrointestinal:* nausea / vomiting, diarrhea, constipation, anorexia, abdominal pain
- *Liver / pancreas:* transient elevation of liver enzymes, bilirubin ↑
- *Kidney:* dysuria (rare), impaired renal function, hypokalemia, hypomagnesemia
- *Skin:* erythema, rash, ecchymosis, pruritus, alopecia
- *Nervous system:* headache, dizziness, confusion, anxiety, depression, lethargy, insomnia
- *Other:* fever, infections, fatigue, weakness, rigors, arthralgia, back pain, edema, hyperglycemia

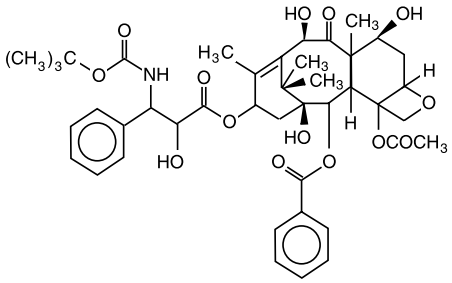
Ci:
- Known hypersensitivity to decitabine
- Uncontrolled active infection

Th: *Approved indications:* MDS (intermediate-1, intermediate-2, high-risk IPSS groups)
Other areas of use: AML, CML, sickle cell anemia

Dosage and Administration
- 15 mg/m²/day i.v. over 3 h every 8 h for 3 days, repeat every 6 weeks for a minimum of 4 cycles
- ATTN: decitabine may be embryotoxic, teratogenic, and mutagenic in humans. Appropriate precautions should be taken to avoid pregnancy and fathering. Monitoring of blood counts, liver enzymes, and renal function recommended
- BEFORE TREATMENT: full blood count, liver and renal function tests, electrolytes

Docetaxel

Chem: Taxane derivative, plant alkaloid, mitotic inhibitor



MOA:
- Stabilization of tubulin polymers, inhibition of spindle formation, mitotic arrest
- Cell-cycle-specific: M phase

Pkin:
- *Kinetics:* highly protein bound, half-life: terminal t½ 10–19 h
- *Metabolism:* hepatic degradation, cytochrome P450-dependent hydroxylation, biliary excretion (> 80–90%), renal excretion (< 10–20%)

Se:
- *Bone marrow:* myelosuppression dose-limiting, neutropenia, thrombocytopenia, anemia
- *Cardiovascular:* arrhythmias (rare), symptoms of ischemia
- *Gastrointestinal:* nausea / vomiting, mucositis, diarrhea, constipation
- *Liver:* transient elevation of transaminases, liver impairment (rare)
- *Skin:* alopecia, dermatotoxicity (50–75%): erythema, exanthema, pruritus, dysesthesia, nail changes, epidermolysis (rare)
- *Nervous system:* peripheral neurotoxicity (40–70%) with paresthesias and motor disturbances, paralytic ileus (rare), rarely central nervous system disorders (weakness, visual disturbances, seizures)
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* hypersensitivity reactions (flushing, urticaria, transient myalgia, hypotension (rare), bronchospasm, angioedema). Fatigue, reduced performance status, loss of appetite, fluid retention (increased capillary permeability) with weight gain, edema, hypotension, pleural effusion, ascites (especially with cumulative dose > 400 mg/m²)

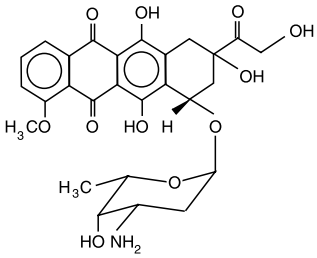
Ci: Severely impaired liver function, pre-existing cardiac disease

Th: *Approved indications:* lung cancer, breast cancer
Other areas of use: ovarian cancer, gastrointestinal tumors, bladder cancer, prostate cancer, head and neck tumors, sarcomas

Dosage and Administration
- Standard dose: 60–100 mg/m²/day i.v. on day 1, every 3 weeks or 35 mg/m²/day, weekly for 6 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: fluid retention with cumulative dose > 400 mg/m²
- BEFORE TREATMENT: full blood count, electrolytes, liver and renal function tests, cardiac evaluation. Premedication with dexamethasone; H1 blockers, H2 blockers, and diuretics may be given if required

Doxorubicin (DXR, Adriamycin, ADR), Liposome-encapsulated Doxorubicin

Chem: Anthracycline, hydroxydaunorubicin, antineoplastic glycoside antibiotic



MOA:
- DNA intercalation, induction of DNA strand breaks, generation of free oxygen radicals, inhibition of topoisomerase II
- Cell-cycle-specific: S/G2 phases

Pkin:
- *Kinetics:* 70% plasma protein-bound, half-life: triphasic pattern, terminal t½ 21–90 h
- *Metabolism:* hepatic degradation to active (doxorubicinol) and inactive metabolites, aglycon formation. Biliary (50%) and renal (< 10%) excretion

Se:
- *Bone marrow:* myelosuppression (dose-limiting), leukopenia, thrombocytopenia
- *Cardiovascular:* cardiotoxicity (dose-limiting)
  - *Acute cardiotoxicity:* ECG changes, arrhythmias, ischemia, infarction
  - *Chronic cardiotoxicity:* congestive cardiomyopathy with decreased LVEF
  - *Risk factors:* pre-existing cardiac disorders, age < 15 or > 60 years, rapid bolus injection, mediastinal radiation, total dose of 400–550 mg/m²
- *Gastrointestinal:* nausea / vomiting, mucositis, stomatitis, diarrhea (rare)
- *Skin:* exanthema, urticaria, alopecia, delayed tissue reaction in a previously irradiated site ("radiation recall reaction"), nail changes, hyperpigmentation (rare); reversible erythrodysesthesia with liposome-encapsulated doxorubicin
- *Local toxicity* (extravasation ► Chap. 9.9): causes severe necrosis
- *Other:* fever, allergic reactions, red urine

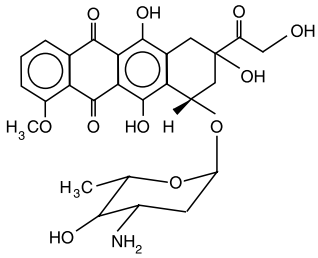
Ci:
- Cardiac disease (arrhythmias, myocardial infarction, coronary heart disease, heart failure)
- Severely impaired liver function, acute infections

Th: *Approved indications:* solid tumors (e.g., small cell lung cancer, breast cancer, ovarian cancer, endometrial cancer, bladder cancer, thyroid cancer, sarcomas, Wilms' tumor), malignant lymphomas (e.g., Hodgkin's disease, multiple myeloma, NHL), AML, ALL

Dosage and Administration
- Doxorubicin: 45–75 mg/m²/day every 21–28 days, 10–20 mg/m²/day i.v. weekly
  High-dose therapy: 90–150 mg/m²/day (*ATTN:* only in transplant centers)
- Liposome-encapsulated doxorubicin: 20–50 mg/m²/day i.v. every 3–4 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative threshold dose 400–550 mg/m² with doxorubicin
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance). Cardiac evaluation with echocardiography or radionuclide ventriculography

Epirubicin (EPI)

Chem: Anthracycline, antineoplastic glycoside antibiotic



MOA:
- DNA intercalation, induction of DNA strand breaks, generation of free oxygen radicals, inhibition of topoisomerase II
- Cell-cycle-specific: S/G2 phases

Pkin:
- *Kinetics:* half-life: triphasic pattern, terminal t½ 18–45 h
- *Metabolism:* hepatic degradation, glucuronidation, biliary (50%) and renal (< 10%) excretion

Se:
- *Bone marrow:* myelosuppression (dose-limiting), leukopenia and thrombocytopenia
- *Cardiovascular:* less cardiotoxic than daunorubicin or doxorubicin:
  - *Acute cardiotoxicity:* ECG changes, arrhythmias, ischemia, infarction
  - *Chronic cardiotoxicity:* congestive cardiomyopathy with decreased LVEF
  - *Risk factors:* pre-existing cardiac disorders, age < 15 or > 60 years, rapid bolus injection, mediastinal radiation, cumulative dose > 900–1,000 mg/m²
- *Gastrointestinal:* nausea / vomiting, mucositis, stomatitis, diarrhea (rare)
- *Skin:* exanthema, urticaria, delayed tissue reaction in a previously irradiated site ("radiation recall reaction"), nail changes, hyperpigmentation (rare). Moderate alopecia
- *Local toxicity* (extravasation ► Chap. 9.9): causes severe necrosis
- *Other:* infertility, allergic reactions, red urine

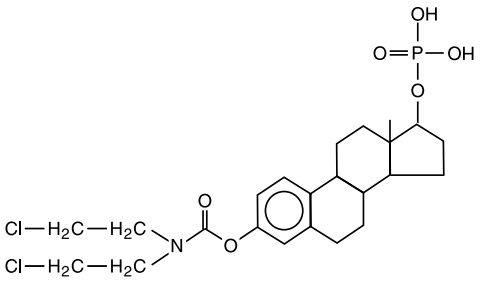
Ci:
- Cardiac disease (arrhythmias, myocardial infarction, coronary heart disease, heart failure)
- Severely impaired liver function

Th: *Approved indications:* solid tumors: (lung cancer, breast cancer, ovarian cancer, gastrointestinal tumors, prostate cancer, soft tissue sarcoma), lymphomas

Dosage and Administration
- Standard dose: 40–100 mg/m²/day i.v. every 3–4 weeks or 15–30 mg/m²/day i.v. weekly
- High-dose therapy: 120–180 mg/m²/day (*ATTN:* only in transplant centers)
- Topical administration: intravesical instillation in bladder cancer
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative threshold dose 900–1,000 mg/m²
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance). Cardiac evaluation with echocardiogram or radionuclide ventriculography

Estramustine Phosphate

Chem: Estra-1,3,5(10)-triene-3,17-diol(17beta)-, 3-[bis(2-chloroethyl)carbamate]
Combination molecule with estradiol and alkylating moieties



MOA:
- Estrogen-like effect, antigonadotropic effect
- Alkylating agent: DNA and RNA alkylation, DNA strand breaks, cross-linking
- Interaction with tubulin, interference with formation of microtubules, mitotic arrest

Pkin:
- *Kinetics:* oral bioavailability 75%, absorption inhibited by calcium-rich beverages / foods (milk, etc.). Half-life: initial t½ 90 min, terminal t½ 20–24 h
- *Metabolism:* dephosphorylation, cleavage of carbamide bond with release of estrogen moiety and bifunctional alkylating agent, biliary and renal excretion of metabolites

Se:
- *Bone marrow:* moderate myelosuppression (rare)
- *Cardiovascular:* cardiovascular disorders in 10–25% of patients: phlebitis, thromboembolism, angina pectoris symptoms, ischemia, heart failure, edema
- *Gastrointestinal:* nausea / vomiting, loss of appetite, diarrhea (rare)
- *Liver:* transient elevation of transaminases, cholestasis (rare)
- *Skin:* erythema, skin irritation, pruritus, alopecia
- *Local toxicity* (extravasation ► Chap. 9.9): local phlebitis
- *Other:* gynecomastia (50% of patients, prophylactic breast irradiation possible before therapy). Loss of libido, impotency (20–50%), paresthesia in perineum or prostatic area. Allergic reactions

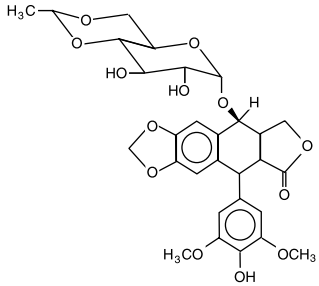
Ci:
- Thrombophilia, thromboembolism, cardiovascular disease
- Impaired liver function, gastrointestinal ulcers, *Herpes zoster*

Th: *Approved indications:* prostate cancer

Dosage and Administration
- *Intravenous administration:* 350–450 mg/day i.v. daily, for 5–10 days
- *Oral administration:* 3 × 280 mg/day for 28 days. With response, continue treatment with 2 × 280 mg/day
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: reduced absorption with oral intake of calcium-containing foods or beverages (milk, calcium-containing water, etc.)
- BEFORE TREATMENT: full blood count, liver and renal function tests, cardiac evaluation

Etoposide (VP-16), Etoposide Phosphate

Chem: 4'-Demethylepipodophyllotoxin 9-(4,6-0-ethylidene-beta-D-glucopyranoside)
Epipodophyllotoxin derivative, plant alkaloid, topoisomerase II inhibitor. Etoposide phosphate is a water-soluble phosphate ester of the plant alkaloid etoposide.



MOA:
- Inhibition of topoisomerase II → mitotic arrest → DNA strand breaks
- Cell-cycle-specific: G2/S/M phases

Pkin:
- *Kinetics:* oral bioavailability 30–70%, half-life: terminal t½ 4–14 h. Etoposide phosphate is phosphorylated to etoposide with t½ 7 min
- *Metabolism:* hepatic degradation, renal and biliary excretion of unchanged drug and metabolites

Se:
- *Bone marrow:* myelosuppression (dose-limiting), neutropenia, thrombocytopenia
- *Cardiovascular:* arrhythmias (rare), hypotension with intravenous administration, ischemia
- *Gastrointestinal:* nausea / vomiting (mainly with oral administration), mucositis, dysphagia, diarrhea, constipation, loss of appetite
- *Liver:* transient elevation of transaminases
- *Skin:* moderate alopecia, erythema (rare), hyperpigmentation, pruritus
- *Nervous system:* rarely peripheral neuropathy or central nervous systems disorders
- *Other:* infertility, allergic reactions (fever, chills, bronchospasm, skin reactions), anaphylaxis

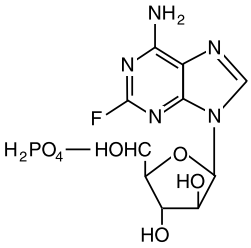
Ci:
- Severely impaired liver or renal function, neurological disorders
- Pre-existing cardiac disease (especially angina pectoris / coronary heart disease)

Th: *Approved indications:* lung cancer, testicular cancer, ovarian cancer, choriocarcinoma, Hodgkin's disease, NHL, AML
Other areas of use: gastrointestinal tumors, sarcomas, breast cancer

Dosage and Administration
- *Etoposide:* 50 mg/m²/day p.o. on days 1–21, or 50–120 mg/m²/day i.v. on days 1–5, every 3–4 weeks
  - High-dose therapy: 500 mg/m²/day i.v. on days 1–3 (*ATTN:* only in transplant centers)
- *Etoposide phosphate:* 100 mg etoposide is equivalent to 113.6 mg etoposide phosphate
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: calcium antagonists may enhance etoposide cytotoxicity
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Fludarabine (2-Fluoro-ara-AMP, Fludarabine Phosphate)

Chem: 9-β-D-Arabinosyl-2-fluoroadenine, purine analog, antimetabolite



MOA: Incorporated into DNA and RNA, inhibition of DNA polymerase α, ribonucleotide reductase, DNA primase and ligase

Pkin:
- *Kinetics:* half-life: initial t½ 0.6–2 h, terminal t½ 7–20 h
- *Metabolism:* dephosphorylation in plasma, intracellular rephosphorylation by deoxycytidine kinase, formation of active triphosphate derivative F-Ara-ATP, renal excretion

Se:
- *Bone marrow:* myelosuppression dose-limiting, leukopenia, thrombocytopenia, anemia
- *Cardiovascular:* acute cardiotoxicity with arrhythmias (rare), hypotension
- *Pulmonary:* acute pulmonary toxicity (rare), dyspnea, interstitial infiltrates
- *Gastrointestinal:* nausea / vomiting (rare), mucositis, loss of appetite, diarrhea
- *Liver:* transient elevation of transaminases, cholestasis (rare)
- *Skin:* moderate alopecia (rare), erythema (rare), dermatitis
- *Nervous system:* peripheral neuropathy with paresthesias (15% of patients), central nervous system disorder with somnolence, weakness, confusion, delayed CNS toxicity with higher doses, demyelination, visual disturbances, seizures, coma
- *Other:* immunosuppression with T-cell deficiency (CD4+ ↓↓, CD8+ ↓) and increased incidence of opportunistic infections. Fever, myalgia. Isolated cases of tumor lysis syndrome (► Chap. 9.6)

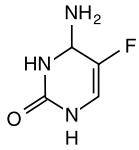
Ci: Severely impaired renal function

Th: *Approved indications:* B-CLL
Other areas of use: other low malignant NHL, cutaneous T-cell lymphomas, Hodgkin's disease. High-dose therapy before stem cell transplantation

Dosage and Administration
- Standard dose: 20–30 mg/m²/day i.v. on days 1–5, repeat every 3–4 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), exclude pre-existing neuropathy

Fluorouracil (5-FU)

Chem: 5-Fluoro-2,4(1H, 3H)-pyrimidinedione, pyrimidine analog, antimetabolite



MOA:
- Inhibition of thymidylate synthetase by FdUMP → thymidine synthesis ↓, incorporated into RNA, inhibition of RNA synthesis by FUTP
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* enters cerebrospinal fluid, half-life: initial t½ 8–14 min, terminal t½ 5 h
- *Metabolism:* intracellular activation and phosphorylation (formation of FdUMP, FUTP etc.). Degradation in liver and intestinal mucosa by dihydropyrimidine dehydrogenase (DPD). Metabolic elimination (90%), renal excretion (10%)

Se:
- *Bone marrow:* myelosuppression dose-limiting, mainly with bolus administration, leukopenia, thrombocytopenia, anemia
- *Cardiovascular:* acute cardiotoxicity with arrhythmias (rare), angina pectoris, ischemia up to myocardial infarction in isolated cases
- *Gastrointestinal:* nausea / vomiting, loss of appetite, in some cases severe mucositis / diarrhea (delayed toxicity), dose-limiting, especially following continuous infusion
- *Skin:* conjunctivitis, lacrimation ↑, dermatitis, erythema, palmar-plantar erythrodysesthesia, hyperpigmentation, moderate alopecia
- *Nervous system:* rarely central nervous system disorder (somnolence, confusion), reversible cerebellar disorder (ataxia, vertigo, tiredness, speech disorders)
- Other: allergic reactions, thrombophlebitis, fever

Ci:
- Severely impaired liver function, pre-existing stomatitis / diarrhea
- DPD deficiency

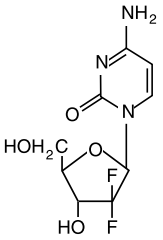
Th: *Approved indications:* gastrointestinal tumors, breast cancer
Other areas of use: ovarian cancer, cervical cancer, prostate cancer, bladder cancer, head and neck tumors. Topical application: solar keratoses, Bowen's disease, basal cell carcinoma

Dosage and Administration
- Standard dose: various protocols:
  - 400–1,000 mg/m²/day i.v. on days 1–5, every 2–4 weeks
  - 600–1,000 mg/m²/day i.v. on day 1, every 7–14 days
  - Continuous infusion 2,600 mg/m²/week c.i.v.
  - Intra-arterial administration as regional chemotherapy (e.g., liver perfusion)
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Folinic Acid (Calcium Folinate):
- Folinic acid increases cytotoxic effect of 5-FU
- Combination therapy 5-FU + folinic acid: always administer folinic acid before 5-FU

Gemcitabine (DFDC)

Chem: 2',2'-Difluorodeoxycytidine, pyrimidine analog, antimetabolite



MOA:
- Inhibition of ribonucleotide reductase, inhibition of deoxycytidine deaminase, incorporated into DNA by DNA polymerases, induction of DNA strand breaks
- Cell-cycle-specific: G1/S phases

Pkin:
- *Kinetics:* negligible plasma protein binding, half-life: initial t½ 8 min, terminal t½ 14 h
- *Metabolism:* intracellular activation by phosphorylation. Deamination in plasma. Metabolized into cytostatically inactive metabolite 2'-deoxydifluorouridine in liver, kidney, and other tissues. Renal (10%) and metabolic (90%) excretion

Se:
- *Bone marrow:* pronounced myelotoxicity (dose-limiting) with neutropenia in 25% of patients, thrombocytopenia (rare) in 25% of patients, anemia
- *Pulmonary:* pulmonary edema (rare)
- *Gastrointestinal:* nausea, vomiting (15%), diarrhea (rare), mucositis (rare)
- *Liver:* transient elevation of transaminases
- *Kidney:* moderate proteinuria / hematuria, hemolytic uremic syndrome (rare)
- *Skin:* erythema, pruritus, alopecia (rare), edema
- *Other:* peripheral edema, flu-like symptoms (may be treated with paracetamol); in rare cases infusion reactions (flushing, dyspnea, facial edema, headache, hypotension)

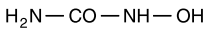
Ci: Severely impaired liver and renal function

Th: *Approved indications:* non-small cell lung cancer, breast cancer, pancreatic cancer, bladder cancer, ovarian cancer, lymphoma
Other areas of use: testicular tumors

Dosage and Administration
- Standard dose: 1,000 mg/m²/day i.v. on days 1, 8, 15, repeat on day 29
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests

Hydroxyurea (Hydroxycarbamide)

Chem: Hydroxycarbamide, antimetabolite



MOA:
- Inhibition of ribonucleotide reductase, inhibition of DNA synthesis
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* oral bioavailability 80–90%, enters cerebrospinal fluid, half-life: t½ 2–5 h
- *Metabolism:* rapid hepatic inactivation, predominantly renal excretion of unchanged drug (50%) and inactive metabolites (50%)

Se:
- *Bone marrow:* myelosuppression dose-limiting with leukopenia, thrombocytopenia, anemia, megaloblastosis in bone marrow
- *Pulmonary:* acute pulmonary toxicity with diffuse pulmonary infiltration (rare), pulmonary edema
- *Gastrointestinal:* moderate nausea, vomiting, loss of appetite. In rare cases mucositis, diarrhea, constipation
- *Liver:* transient elevation of transaminases, cholestasis (rare)
- *Kidney:* renal function disorders (rare) with proteinuria, hyperuricemia
- *Skin:* exanthema, erythema (especially face and neck), hyperpigmentation (rare), nail changes, alopecia, delayed tissue reaction in a previously irradiated site ("radiation recall reaction")
- *Nervous system:* peripheral / central neurotoxicity (rare)
- *Other:* flu-like symptoms (rare), fever

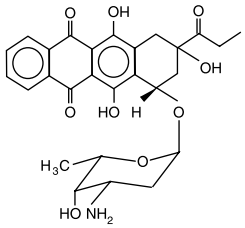
Ci: Severely impaired liver or renal function

Th: *Approved indications:* CML
Other areas of use: myeloproliferative syndromes, cervical cancer, prostate cancer

Dosage and Administration
- Standard dose: 500–1,000 mg/m²/day (or 15–30 mg/kg body weight/day) daily p.o.; with long-term therapy, dose is adjusted according to leukocyte count
- With solid tumors: 2,000–3,000 mg/m²/day (or 60–80 mg/kg body weight/day) every third day
- Dose modification ► Chap. 3.2.4
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Idarubicin (IDA)

Chem: 4-Demethoxydaunorubicin, anthracycline, antineoplastic glycoside antibiotic



MOA:
- DNA intercalation, induction of DNA strand breaks, generation of free oxygen radicals, inhibition of topoisomerase II
- Cell-cycle-specific: S/G2 phases

Pkin:
- *Kinetics:* oral bioavailability 30–35%, enters cerebrospinal fluid, half-life: triphasic pattern, terminal t½ 6–25 h
- *Metabolism:* hepatic degradation, active (idarubicinol) and inactive metabolites, aglycon formation, biliary (50%) and renal (10%) excretion

Se:
- *Bone marrow:* myelosuppression (dose-limiting), leukopenia and thrombocytopenia
- *Cardiovascular:* less cardiotoxic than other anthracyclines:
  - *Acute cardiotoxicity:* ECG changes, arrhythmias, ischemia, infarction
  - *Chronic cardiotoxicity:* congestive cardiomyopathy (rare)
  - *Risk factors:* pre-existing cardiac disorders, age < 15 or > 60 years, rapid bolus injection, mediastinal radiation, cumulative dose > 150–290 mg/m²
- *Gastrointestinal:* nausea, vomiting (80%), mucositis, stomatitis, diarrhea (rare)
- *Liver:* transient elevation of transaminases
- *Skin:* dermatitis, exanthema, urticaria, alopecia, delayed tissue reaction in a previously irradiated site ("radiation recall reaction"), palmar-plantar erythrodysesthesia (rare)
- *Local toxicity* (extravasation ► Chap. 9.9): causes severe necrosis
- *Other:* infertility, fever, allergic reactions, red urine

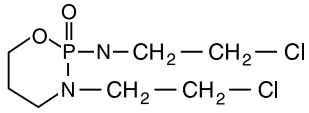
Ci:
- Severe cardiac disorders (arrhythmias, myocardial infarction, coronary heart disease, heart failure, etc.)
- Severely impaired liver and renal function, acute infections

Th: *Approved indications:* AML, ALL
Other areas of use: breast cancer, CML in blast crisis

Dosage and Administration
- Standard dose: 10–12 mg/m² i.v. or 35–50 mg/m² p.o. on days 1–3, every 3–4 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative threshold dose of 150–290 mg/m²
- BEFORE TREATMENT: full blood count, liver and renal function tests. Cardiac evaluation, echocardiogram or radionuclide ventriculography if risk factors present

Ifosfamide

Chem: N,3-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide
Oxazaphosphorine, bifunctional alkylating agent



MOA:
- DNA and RNA alkylation, DNA strand breaks, DNA intercalation, DNA synthesis ↓
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* half-life: terminal t½ 5–6 h
- *Metabolism:* slow hepatic hydroxylation by microsomal cytochrome P450 oxidase, release of active metabolite (isophosphoramide mustard) in plasma and tissue, hepatic degradation into inactive metabolites, renal excretion of unchanged drug (15–55%) and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, leukopenia and thrombocytopenia
- *Gastrointestinal:* acute and delayed nausea (50%), vomiting, mucositis, diarrhea, loss of appetite
- *Liver:* transient elevation of transaminases, cholestasis (rare)
- *Genitourinary:* hemorrhagic cystitis, impaired renal function
- *Skin:* alopecia (80%), erythema (rare), urticaria (rare), nail changes, hyperpigmentation, dermatitis
- *Nervous system:* acute encephalopathy and cerebellar neurotoxicity, especially in the presence of impaired renal function or acidosis: confusion, psychosis, ataxia, seizures, somnolence, coma (prophylaxis: sodium carbonate, treatment: methylene blue)
- *Other:* infertility, fever

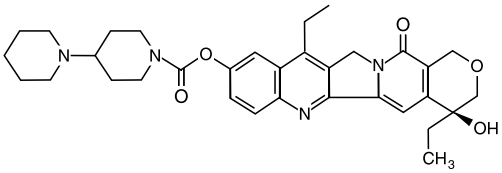
Ci:
- Severely impaired liver or renal function, acute infections
- Cystitis, urinary tract obstruction

Th: *Approved indications:* testicular tumor, lung cancer, ovarian cancer, cervical cancer, pancreatic cancer, soft tissue sarcomas, lymphomas
Other areas of use: breast cancer, osteosarcoma

Dosage and Administration
- Standard dose: various protocols:
  - 1,200–2,400 mg/m²/day i.v. mornings, for 3–5 days
  - 4,000–8,000 mg/m²/day c.i.v. for 24 h
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: prophylaxis of hemorrhagic cystitis: fluid replacement (aim: urine volume > 200 ml/h), administration of mesna. Effects enhanced by barbiturates (cytochrome P450 activation) and cimetidine
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance); alkalinization

Irinotecan (CPT-11)

Chem: Camptothecin analog, topoisomerase I inhibitor



MOA:
- Inhibition of topoisomerase I, DNA religation ↓↓ → DNA strand breaks and DNA intercalation
- Cell-cycle-specific: G2/M phases

Pkin:
- *Kinetics:* ubiquitous distribution, enters cerebrospinal fluid, third space fluid accumulation (pleural effusions, ascites), half-life: t½ 14–18 h
- *Metabolism:* intracellular activation by carboxylesterase to active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin), hepatic degradation to inactive metabolites, biliary and renal excretion of active and inactive metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, neutropenia, eosinophilia, thrombocytopenia, anemia
- *Cardiovascular:* thromboembolic events (rare)
- *Gastrointestinal:* nausea, vomiting, loss of appetite, delayed and in some cases severe diarrhea with mucositis (5–10 days after administration) in 10–20% of patients
- *Liver:* transient elevation of transaminases
- *Kidney:* reversible decrease of renal function, microscopic hematuria
- *Hematology:* alopecia, erythema
- *Other:* acute cholinergic syndrome (acute diarrhea, salivation, lacrimation, etc. within 24 h of administration) especially with doses > 300 mg/m^2; treat with atropine 0.25–1 mg. Fever, weakness, reduced performance status.

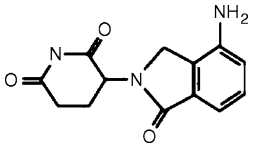
Ci: Pre-existing diarrhea, acute infections

Th: *Approved indications:* metastatic colorectal cancer
Other areas of use: gastrointestinal tumors, lung cancer, ovarian cancer, cervical cancer

Dosage and Administration
- Standard dose: various protocols:
  - 250–350 mg/m^2/day i.v. on day 1, every 3 weeks
  - 100–125 mg/m^2/day i.v. on days 1, 8, 15, 22, every 6 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: for severe delayed diarrhea, loperamide may be given. With diarrhea in the neutropenic phase, increased risk of gram-negative sepsis
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Lenalidomide

Chem: 3-(4-Amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione, thalidomide analog



MOA: Mechanism of action not fully characterized. Proposed mechanisms include:
- Immunomodulation: immunosuppressive properties, proinflammatory cytokines ↓, anti-inflammatory cytokines ↑, tumor necrosis factor ↓, cyclooxygenase-2 (COX-2) ↓
- Anti-angiogenic properties
- Direct antineoplastic / cytotoxic activity in cells of lymphatic origin

Pkin:
- *Kinetics:* rapid oral absorption, peak plasma concentration after 0.6–1.5 h, protein binding 30%, half-life t½ 3 h
- *Metabolism:* renal excretion (> 65% as unchanged drug)

Se:
- *Bone marrow:* severe myelosuppression (80%), with leukopenia, neutropenia (59%), thrombocytopenia (62%), anemia
- *Pulmonary:* cough, dyspnea, upper respiratory tract infections, pneumonia
- *Cardiovascular:* edema, chest pain, atrial fibrillation, cardiac failure, myocardial infarction, hypertension, thromboembolic events, pulmonary embolism
- *Gastrointestinal:* nausea / vomiting, diarrhea, anorexia, constipation, abdominal pain
- *Hepatic:* transient increase of liver enzymes, hyperbilirubinemia
- *Kidney:* dysuria, serum creatinine ↑, hypokalemia, hypomagnesemia
- *Skin:* erythema, pruritus, rash, dry skin, ecchymosis, petechiae, sweating
- *Nervous system:* headache, dizziness, confusion, depression, insomnia, peripheral neuropathy
- *Other:* fever, fatigue, infections, arthralgia, myalgia, back pain, asthenia, hypothyroidism

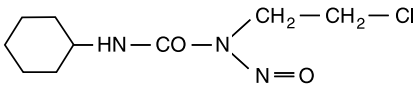
Ci:
- Pregnant women or women capable of becoming pregnant. Female patients must use two different methods of contraception. Male patients must use condoms.
- Hypersensitivity to lenalidomide

Th: *Approved indications:* MDS with deletion 5q- and transfusion-dependent anemia, multiple myeloma
Other areas of use: MDS (non-5q-)

Dosage and Administration
- Standard dose: 10 mg p.o. daily
- ATTN: potential for life-threatening human birth defects. Appropriate precautions should be taken to avoid pregnancy and fathering. In order to avoid fetal exposure to lenalidomide, in the US the drug is only available under a special restricted distribution program. Hematological toxicity (neutropenia, thrombocytopenia) requires weekly monitoring. Significantly increased risk of deep venous thrombosis and pulmonary embolism
- BEFORE TREATMENT: full blood count, liver and renal function tests, electrolytes, thyroid function tests, pregnancy test (in women of childbearing potential)

Lomustine (CCNU)

Chem: 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea, alkylating agent



MOA:
- DNA and RNA alkylation (O^6 position of guanine), DNA strand breaks, cross-linking, inhibition of DNA polymerase and RNA synthesis
- Cell cycle non-specific (including G0 phase)

Pkin:
- *Kinetics:* high oral availability, lipophilic compound, enters cerebrospinal fluid, half-life: t½ 2 h, t½ of the metabolites 5–72 h
- *Metabolism:* hepatic hydroxylation (cytochrome P450) to active metabolites, spontaneous degradation to inactive metabolites, renal excretion of unchanged drug and metabolites

Se:
- *Bone marrow:* prolonged and cumulative myelosuppression (dose-limiting), leukopenia and thrombocytopenia after 4–6 weeks, anemia
- *Pulmonary:* pulmonary infiltrates and pulmonary fibrosis (cumulative)
- *Gastrointestinal:* nausea / vomiting (within 6–24 h), mucositis, diarrhea, loss of appetite
- *Liver:* transient elevation of transaminases
- *Kidney:* impaired renal function (cumulative nephrotoxicity)
- *Skin:* erythema, pruritus, moderate alopecia, dermatitis, hyperpigmentation
- *Nervous system:* peripheral and central neurotoxicity, psychotic organic brain syndrome, optic neuritis, confusion, ataxia
- *Other:* infertility, amenorrhea, fatigue

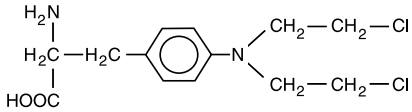
Ci:
- Pre-existing bone marrow dysfunction, acute infections
- Severely impaired liver or renal function

Th: *Approved indications:* Hodgkin's disease, CNS tumors, melanomas, lung cancer
Other areas of use: brain metastases, NHL, multiple myeloma, breast cancer, ovarian cancer, colorectal cancer

Dosage and Administration
- Standard dose: 80–130 mg/m²/day p.o. on day 1, every 6–8 weeks
- Dose modification ► Chap. 3.2.4
- ATTN: cumulative, delayed and prolonged myelotoxicity. Cumulative nephrotoxicity and pulmonary toxicity (with doses > 1,200–1,500 mg/m²)
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), pulmonary function tests

Melphalan (MPL)

Chem: 4-[Bis(2-chloroethyl)amino]-L-phenylalanine
L-phenylalanine mustard (L-PAM), alkylating agent



MOA:
- DNA and RNA alkylation, DNA strand breaks, cross-linking
- Cell-cycle-specific: S/G2 phases

Pkin:
- *Kinetics:* oral bioavailability, interindividual variation (20–90%), half-life: initial t½ 6–8 min, terminal t½ 1–4 h
- *Metabolism:* spontaneous degradation by hydrolysis to inactive dechlorinated metabolites, renal excretion of unchanged drug (10–15%) and metabolites

Se:
- *Bone marrow:* delayed myelosuppression (dose-limiting), leukopenia, thrombocytopenia, lasting up to 4–6 weeks, hemolytic anemia (rare)
- *Pulmonary:* pulmonary fibrosis (rare), pneumonitis, especially with high-dose therapy
- *Gastrointestinal:* nausea, vomiting, mucositis, loss of appetite, diarrhea, especially after high-dose therapy
- *Liver:* hepatic veno-occlusive disease (VOD) after high-dose therapy
- *Skin:* alopecia (rare), exanthema, erythema, urticaria, pruritus, edema
- *Other:* infertility (amenorrhea, oligospermia). Allergic reactions/anaphylaxis (rare). Inadequate ADH secretion syndrome (rare), hyponatremia

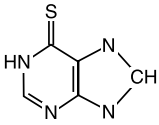
Ci: Severely impaired renal function

Th: *Approved indications:* multiple myeloma, ovarian cancer
Other areas of use: breast cancer, thyroid cancer, testicular tumors, limb perfusion (melanoma), high-dose therapy before stem cell transplantation

Dosage and Administration
- Standard dose: various protocols:
  - 0.1–0.2 mg/kg body weight/day (8–10 mg/m²/day) p.o., for 4–5 days
  - 0.25 mg/kg body weight/day (10–15 mg/m²/day) p.o. for 4–7 days, every 4–6 weeks
- High-dose therapy: 140–200 mg/m²/day i.v. on day 1 (*ATTN:* only in transplant centers)
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Mercaptopurine (6-MP, Purinethol)

Chem: 1,7-dihydro-6H-purine-6-thione, purine analog (hypoxanthine analog), antimetabolite



MOA:
- Inhibition of de novo purine synthesis and purine conversion, chromosome breaks
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* oral bioavailability 5–35% (interindividual variation), first-pass hepatic metabolism, half-life: terminal t½ 0.5–3 h
- *Metabolism:* intracellular activation with formation of various active metabolites (ribonucleotide derivatives). Hepatic degradation by xanthine oxidase (→ half-life prolonged if xanthine oxidase inhibitors given, e.g., allopurinol), biliary (80–85%) and renal (5–20%) excretion

Se:
- *Bone marrow:* myelotoxic (dose-limiting), leukopenia, thrombocytopenia, anemia
- *Gastrointestinal:* moderate nausea, vomiting, loss of appetite in 25% of patients, mucositis, diarrhea, abdominal pain
- *Liver:* transient elevation of transaminases, cholestasis in 30% of patients, severe liver impairment in isolated cases, hepatic veno-occlusive disease (VOD)
- *Kidney:* reversible decrease of renal function, hyperuricemia
- *Skin:* dermatitis (rare), exanthema, hyperpigmentation, moderate alopecia
- *Other:* fever, immunosuppression

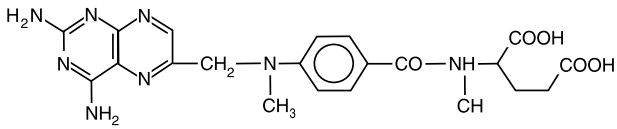
Ci: Severely impaired liver function

Th: *Approved indications:* ALL
Other areas of use: AML, CML, NHL, polycythemia vera, chronic inflammatory diseases

Dosage and Administration
- Standard dose: 70–100 mg/m²/day p.o. daily (1.5–2.5 mg/kg body weight/day)
- Dose modification ► Chap. 3.2.4
- ATTN: reduce dose to 25% with concurrent administration of allopurinol
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Methotrexate (MTX, Amethopterin)

Chem: 4-Amino-10-methylfolic acid derivative, antimetabolite



MOA:
- Dihydrofolate reductase ↓ → tetrahydrofolic acid formation ↓ → DNA synthesis ↓
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* 50–70% plasma protein-bound, half-life: terminal t½ 8–10 h
- *Metabolism:* hepatic inactivation by 7-hydroxylation (20–45%), renal and biliary excretion of unchanged drug (80%) and metabolites (20%)

Se:
- *Bone marrow:* myelosuppression (dose-limiting), leukopenia, thrombocytopenia
- *Pulmonary:* pneumonitis (rare), pulmonary fibrosis
- *Gastrointestinal:* pronounced mucositis (dose-limiting), moderate nausea / vomiting, diarrhea, gastrointestinal bleeding (rare)
- *Liver:* impaired liver function, elevated transaminases
- *Kidney:* renal tubular damage (dose-limiting), especially with acidic urine (pH < 7.0)
- *Skin:* dermatitis, erythema, exanthema, pruritus, conjunctivitis, alopecia (rare), palmar-plantar erythrodysesthesia
- *Nervous system:* reversible acute encephalopathy, leukoencephalopathy, confusion, motor and sensory disturbances, seizures, coma
- *Other:* allergic reactions, anaphylaxis, vasculitis

Ci:
- "Third space" fluid deposits: pleural effusions, ascites, etc.
- Impaired renal and liver function, gastrointestinal ulcers

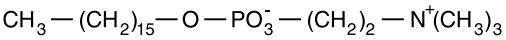
Th: *Approved indications:* leukemias, malignant lymphomas, meningeal leukemia, solid tumors, psoriasis vulgaris, rheumatoid arthritis
Other areas of use: immunosuppression with allogeneic stem cell transplantation

Dosage and Administration
- Low-dose: 20–60 mg/m²/day i.v. weekly or 4–6 mg/m²/day p.o. on days 1–3
- Medium-high dose: 500 mg/m²/day i.v. every 2–3 weeks with leucovorin rescue
- High-dose: up to 12,000 mg/m² i.v. with leucovorin rescue. ATTN: only at hematology/oncology centers. High risk of severe side effects
- May be administered intrathecally (maximum 15 mg absolute), orally or intramuscularly
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: not to be given in combination with nephrotoxic drugs. Not to be given in combination with acetylsalicylic acid, penicillin, sulfonamides, phenytoin (renal excretion ↓). Accumulates in fluid-filled spaces (pleural effusions, ascites) → t½ ↑↑ → toxicity ↑↑
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance). Fluid replacement (urine volume > 200 ml/h), alkalinization (urine pH > 7.4)

Folinic Acid (Calcium Folinate, Leucovorin):
- Folinic acid is an antidote for medium-high dose and high-dose methotrexate therapy
- Folinic acid is usually started 24 h after methotrexate and given for at least 36 h (with close monitoring of the serum methotrexate level)

Miltefosine

Chem: 2-(Hexadecoxy-oxido-phosphoryl)oxyethyl-trimethyl-ammonium
Alkylphosphocholine



MOA:
- Inhibition of the membrane-based enzyme systems

Pkin:
- Topical application → no evidence of effective systemic levels

Se:
- *Skin:* with local application: pruritus, erythema, tense feeling in skin, skin dryness, desquamation, burning

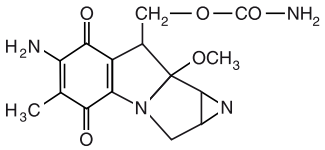
Ci:
- Concurrent radiotherapy
- Large nodular / deep-seated metastases with simultaneous skin involvement

Th: *Approved indications:* cutaneous metastases of breast cancer

Dosage and Administration
- Standard dose: 1 × /day in the first week to the involved skin area, thereafter twice a day, 1–2 drops per 10 cm^2, not more than 5 ml/day in total
- Hormone therapy or chemotherapy may be given concurrently

Mitomycin C (MMC)

Chem: Antineoplastic antibiotic, aziridine derivative, bifunctional alkylating agent



MOA:
- DNA alkylation, cross-linking, DNA depolymerization, generation of free radicals → strand breaks
- Cell-cycle-specific: G1/S phases

Pkin:
- *Kinetics:* half-life: initial t½ 8 min, terminal t½ 50 min
- *Metabolism:* intracellular activation by opening of the aziridine ring, hepatic degradation to inactive metabolites, renal excretion of unchanged drug (25%) and metabolites

Se:
- *Bone marrow:* cumulative myelosuppression (dose-limiting), often severe and prolonged leukopenia and thrombocytopenia (lasting up to 6–8 weeks). In rare cases microangiopathic hemolytic anemia (MAHA)
- *Cardiovascular:* heart failure (rare), ischemia
- *Pulmonary:* pulmonary toxicity (pneumonitis, fibrosis) in up to 10% of patients
- *Gastrointestinal:* moderate nausea / vomiting, loss of appetite, mucositis
- *Liver:* impaired liver function (rare), transient elevation of transaminases
- *Kidney:* impaired renal function (rare), hemolytic uremic syndrome
- *Skin:* alopecia, erythema, photosensitivity
- *Nervous system:* headache (rare), visual disturbances, paresthesia
- *Local toxicity* (extravasation ► Chap. 9.9): local phlebitis, necrosis
- *Other:* fever (rare), allergic reactions, fatigue

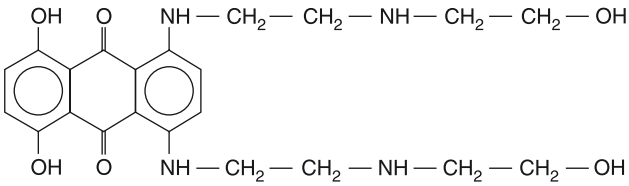
Ci:
- Severely impaired liver or renal function
- Pre-existing cardiac or pulmonary disease (coronary heart disease, COPD, etc.)

Th: *Approved indications:* gastric cancer, pancreatic cancer
Other areas of use: head and neck tumors, gastrointestinal tumors, lung cancer, bladder cancer, breast cancer, prostate cancer, cervical cancer

Dosage and Administration
- Standard dose: various protocols:
  Monotherapy: 10–20 mg/m²/day i.v. on day 1, every 6–8 weeks
  Polychemotherapy: 5–10 mg/m²/day i.v. on day 1, every 6 weeks
- Topical use: bladder instillation: 20–40 mg absolute
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), cardiopulmonary evaluation

Mitoxantrone

Chem: 1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthraquinone dihydrochloride
Dihydroxyanthracenedione, synthetic anthracycline analog



MOA:
- DNA intercalation, induction of DNA strand breaks, inhibition of topoisomerase II
- Cell-cycle-specific: S/G2 phases

Pkin:
- *Kinetics:* enters cerebrospinal fluid, tissue accumulation, half-life: terminal t½ 40–190 h
- *Metabolism:* hepatic degradation, side chain oxidation, renal and biliary excretion of unchanged drug and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, especially leukopenia
- *Cardiovascular:* chronic cardiotoxicity: cardiomyopathy, heart failure (less pronounced in comparison to doxorubicin) from total cumulative dose > 160 mg/m²
- *Gastrointestinal:* moderate nausea / vomiting, mucositis, gastrointestinal bleeding (rare), abdominal pain, diarrhea
- *Liver:* transient elevation of transaminases, cholestasis (rare)
- *Kidney:* transient disturbances of renal function
- *Skin:* moderate alopecia, allergic reactions, dermatitis, pruritus, blue discoloration of sclera / finger nails / injection site and urine (reversible after 48 h)
- *Other:* infertility, headache, allergic reactions (rare)

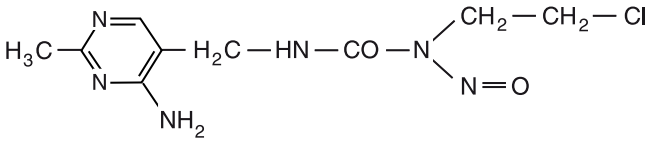
Ci:
- Severely impaired liver and renal function, acute infections
- Pre-existing cardiac disease, myocardial impairment, previous anthracycline administration at the maximum tolerated cumulative dose

Th: *Approved indications:* prostate cancer, AML
Other areas of use: CML, NHL, cerebral tumors, lung cancer, breast cancer, hepatocellular cancer, high-dose therapy before stem cell transplantation

Dosage and Administration
- Standard dose: various protocols:
  - Solid tumors: 12–14 mg/m²/day i.v. on day 1, every 3 weeks
  - Acute leukemia (in combination with cytarabine): 10–12 mg/m²/day i.v. on days 1–5
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative threshold dose 160 mg/m² (increased risk of cardiotoxicity)
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance). Cardiac evaluation, echocardiogram / radionuclide ventriculography if risk factors present

Nimustine (ACNU)

Chem: 1-(4-Amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea
Alkylating agent



MOA:
- DNA and RNA alkylation (O^6 position of guanine), DNA strand breaks, cross-linking, inhibition of DNA polymerase and RNA synthesis
- Cell cycle non-specific (including G0 phase)

Pkin:
- *Kinetics:* lipophilic compound, enters cerebrospinal fluid, half-life: t½ 30–60 min
- *Metabolism:* spontaneous degradation into inactive metabolites, renal excretion of unchanged drug and metabolites

Se:
- *Bone marrow:* prolonged and cumulative myelosuppression (dose-limiting), leukopenia and thrombocytopenia, with slow recovery
- *Gastrointestinal:* nausea / vomiting, mucositis, diarrhea
- *Liver:* transient elevation of transaminases
- *Kidney:* impaired renal function (rare)
- *Skin:* alopecia, dermatitis, hyperpigmentation
- *Nervous system:* peripheral and central neurotoxicity
- *Other:* infertility

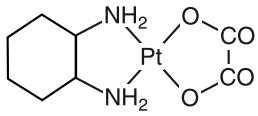
Ci:
- Pre-existing bone marrow dysfunction, acute infections
- Severely impaired liver or renal function

Th: *Approved indications:* malignant gliomas, cerebral metastases, lung cancer, breast cancer, gastric cancer, colorectal cancer, CML, Hodgkin's disease, NHL

Dosage and Administration
- Standard dose: 90–100 mg/m²/day (or 2–3 mg/kg body weight/day) i.v. on day 1, every 4–8 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative, delayed and prolonged myelotoxicity
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Oxaliplatin

Chem: Trans-1-diaminocyclohexane oxalato-platinum, platinum derivative



MOA:
- Platinum-DNA adduct with inhibition of DNA synthesis, DNA intercalation, cross-links, inhibition of RNA synthesis, inhibition of DNA repair mechanisms
- Cell cycle non-specific (including G0 phase)

Pkin:
- *Kinetics:* highly protein bound (70–95%), half-life: terminal t½ 9 days
- *Metabolism:* spontaneous formation of active metabolites, predominantly renal excretion of platinum and oxaliplatin metabolites

Se:
- *Bone marrow:* moderate myelosuppression, neutropenia
- *Gastrointestinal:* nausea, vomiting, diarrhea
- *Liver:* transient elevation of transaminases
- *Kidney:* reversible decrease of renal function (rare)
- *Skin:* moderate alopecia (rare)
- *Nervous system:* acute (< 1%): peripheral paresthesias and acute laryngeal / pharyngeal dysesthesia with a feeling of suffocation, induced / exacerbated by exposure to cold. Chronic (45%): cumulative peripheral sensory neuropathy (dose-limiting) with dysesthesia, paresthesia of the limbs, after total dose > 900–1,000 mg/m², exacerbated by exposure to cold, reversible after a few months in some cases
- *Local toxicity* (extravasation ► Chap. 9.9): causes necrosis
- *Other*: allergic reactions, fatigue, arthralgia

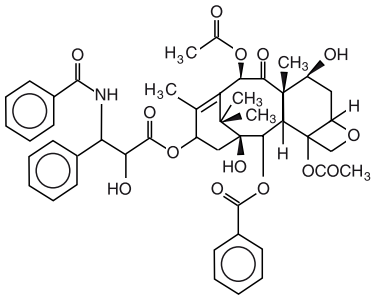
Ci:
- Severely impaired renal function
- Pre-existing bone marrow dysfunction
- Pre-existing peripheral sensory neuropathy
- Known intolerance to platinum

Th: *Approved indications:* colorectal carcinoma
Other areas of use: lung cancer, esophageal cancer, ovarian cancer, head and neck tumors

Dosage and Administration
- Standard dose: various protocols:
  - 100–130 mg/m²/day i.v. on day 1, every 3 weeks
  - 85–100 mg/m²/day i.v. on day 1, every 2 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: cumulative, dose-limiting peripheral neurotoxicity with total cumulative dose > 1,000 mg/m²
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), neurological evaluation

Paclitaxel

Chem: Taxane derivative, plant alkaloid, mitotic inhibitor



MOA:
- Stabilization of tubulin polymers, inhibition of the spindle function, mitotic arrest
- Cell-cycle-specific: M phase

Pkin:
- *Kinetics:* highly protein-bound, half-life: initial t½ 20 min, terminal t½ 6 h (paclitaxel) to 27 h (protein-bound paclitaxel)
- *Metabolism:* hepatic degradation, cytochrome P450-dependent hydroxylation, biliary excretion (25%), renal excretion (< 10%)

Se:
- *Bone marrow:* myelosuppression dose-limiting, especially neutropenia, moderate thrombocytopenia, anemia
- *Cardiovascular:* cardiac conduction disorders (rare), arrhythmias, ischemia
- *Gastrointestinal:* nausea / vomiting, mucositis / diarrhea (rare)
- *Liver:* transient elevation of transaminases, hepatic impairment (rare)
- *Skin:* alopecia, erythema, nail changes
- *Nervous system:* peripheral neurotoxicity with paresthesias (especially with single doses > 175 mg/m²/day or total cumulative dose > 1,000 mg/m²), paralytic ileus (rare), in rare cases central nervous system disorders (headache, weakness, visual disturbances, seizures)
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* hypersensitivity reactions in 1–3% of patients (flushing, urticaria, transient myalgia / arthralgia, hypotension (rare), bronchospasm, angioedema, anaphylaxis), fatigue, reduced performance status, loss of appetite

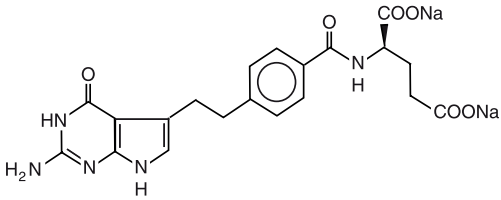
Ci: Severely impaired liver function, pre-existing cardiac disease, neuropathy

Th: *Approved indications (paclitaxel):* breast cancer, ovarian cancer, lung cancer, Kaposis's sarcoma
Approved indications (protein-bound paclitaxel): metastatic breast cancer
Other areas of use: esophageal cancer, gastric cancer, bladder cancer, cervical cancer, prostate cancer, head and neck tumors, melanomas

Dosage and Administration
- Monotherapy: 175–200 mg/m²/day i.v. on day 1 every 21 days or 80–100 mg/m²/day i.v. on day 1 weekly
- Polychemotherapy: 135–185 mg/m²/day i.v. on day 1 every 21 days or 60–100 mg/m²/day i.v. on day 1 weekly
- Protein-bound paclitaxel: 260 mg/m²/day i.v. on day 1 every 3 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: administration sequence important: always administer paclitaxel prior to cisplatin / carboplatin, but after anthracyclines (doxorubicin / epirubicin)
- BEFORE TREATMENT: full blood count, urea and electrolytes, liver and renal function tests (creatinine clearance), cardiac evaluation. Premedication with steroids (dexamethasone), H1/H2 inhibitors (clemastine, famotidine), diuretics if necessary

Pemetrexed

Chem: L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]-benzoyl], folic acid antagonist, antimetabolite



MOA:
- Inhibition of thymidylate synthetase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase → inhibition of RNA synthesis
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* half-life: terminal t½ 20 h
- *Metabolism:* negligible hepatic degradation, renal excretion of unchanged drug (70–90%) and metabolites

Se:
- *Bone marrow:* myelosuppression with neutropenia, thrombocytopenia, anemia
- *Cardiovascular:* pericarditis (rare)
- *Gastrointestinal:* nausea / vomiting (35%), mucositis, diarrhea, loss of appetite
- *Liver:* transient elevation of transaminases, hepatic impairment/hepatitis (rare)
- *Skin:* alopecia, erythema, palmar-plantar erythrodysesthesia (hand-foot syndrome)
- *Nervous system:* sensory peripheral neuropathy and acute neurotoxicity from functional folate deficiency → folic acid / vitamin B_{12} prophylaxis
- *Other:* fatigue, reduced performance status

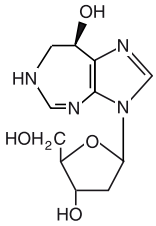
Ci: Pre-existing neurological disorders

Th: *Approved indications:* pleural mesothelioma, lung cancer (NSCLC)
Other areas of use: breast cancer, colon cancer, pancreatic cancer, head and neck tumors

Dosage and Administration
- Standard dose: 500 mg/m²/day i.v. on day 1, every 3 weeks
- Dose modification ► Chap. 3.2.4
- BEFORE TREATMENT: full blood count, liver and renal function tests. Prophylactic administration of folic acid 350–1,000 µg (starting 5 days before therapy and until 21 days after therapy) and vitamin B12 1,000 µg i.m. (1 week before therapy, as well as after every 3rd therapy cycle)

Pentostatin (DCF)

Chem: 2'-Deoxycoformycin, purine analog, antimetabolite



MOA:
- Inhibition of adenosine deaminase, inhibition of ribonucleotide reductase → inhibition of DNA synthesis
- Inhibition of homocysteine hydrolase, lymphocytotoxic effects

Pkin:
- *Kinetics:* half-life: initial t½ 9 min, terminal t½ 5–14 h
- *Metabolism:* intracellular degradation to nucleotides, renal excretion (> 90%)

Se:
- *Bone marrow:* myelosuppression dose-limiting, pronounced leukopenia, lymphopenia, thrombocytopenia, anemia
- *Cardiovascular:* arrhythmias (rare), ECG changes, heart failure
- *Pulmonary:* cough, dyspnea, pulmonary infiltrates (rare)
- *Gastrointestinal:* moderate nausea / vomiting (50%), diarrhea (rare) / mucositis, dysgeusia
- *Liver:* transient elevation of transaminases, hepatitis (rare)
- *Kidney:* decreased renal function (increased incidence with inadequate hydration), renal tubular damage (rare), renal failure
- *Skin:* erythema / exanthema (25%), with increased photosensitivity in some cases, pruritus, exfoliative dermatitis, keratoconjunctivitis, periorbital edema
- *Nervous system:* central nervous system disorders (headache, tiredness, etc.), progressive encephalopathy (rare), seizures, coma
- *Other:* immunosuppression with T-cell deficiency, peripheral edema, fever, myalgia, headache, allergic reactions

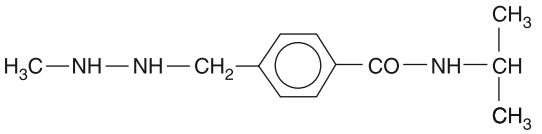
Ci:
- Impaired renal function (creatinine clearance < 60 ml/min)
- Skin changes, central nervous system disorders

Th: *Approved indications:* hairy cell leukemia
Other areas of use: cutaneous T-cell lymphomas, NHL

Dosage and Administration
- Standard dose: 4 mg/m²/day i.v. every 14 days
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: due to the risk of decreased renal function, adequate fluid replacement necessary (1,000–2,000 ml). Not to be given in combination with fludarabine or cytarabine (pneumotoxic)
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Procarbazine

Chem: N-Isopropyl-alpha-(2-methylhydrazino)-p-toluamide



MOA:
- DNA alkylation and depolymerization, methylation, inhibition of DNA, RNA and protein synthesis
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* oral bioavailability 95–100%, enters cerebrospinal fluid, half-life: t½ 7 min, initial t½ 30–90 min, terminal t½ 60 min
- *Metabolism:* hepatic cytochrome P450-dependent activation, degradation to inactive metabolites, renal excretion

Se:
- *Bone marrow:* delayed myelosuppression (dose-limiting), nadir after 3–5 weeks
- *Cardiovascular:* tachycardia, hypotension
- *Gastrointestinal:* nausea / vomiting, mucositis (rare), dysphagia, diarrhea, loss of appetite
- *Liver:* transient elevation of transaminases
- *Skin:* alopecia (rare), erythema, exanthema, photosensitivity, hyperpigmentation, allergic reactions
- *Nervous system:* central nervous system disorders (headache, somnolence, agitation, depression, visual disturbances, hallucinations, ataxia, nystagmus, seizures) or mild reversible peripheral neurotoxicity
- *Other:* flu-like symptoms (fever, chills, myalgia, arthralgia), gynecomastia, infertility (amenorrhea, azoospermia)

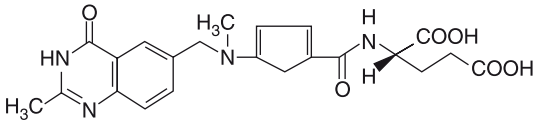
Ci:
- Severely impaired liver or renal function
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Th: *Approved indications:* Hodgkin's disease, NHL
Other areas of use: plasmacytoma, CNS tumors, lung cancer, melanoma, polycythemia vera

Dosage and Administration
- Standard dose: 100 mg/m²/day p.o. on days 1–14, every 21–28 days
- Dose modification ► Chap. 3.2.4
- ATTN: Procarbazine is a monoamine oxidase inhibitor; interactions:
  - Alcohol: intolerance, flushing, tachycardia, neurological disorders
  - Antihistamines, barbiturates, phenothiazines, narcotics: synergistic effects, overdosage
  - Tricyclic antidepressants, L-dopa, sympathomimetics, tyramine-containing foods (milk products, red wine, etc.): hypertension, hypertensive crisis, coma
- BEFORE TREATMENT: full blood count, liver and renal function tests

Raltitrexed

Chem: Folate analogue, quinazoline derivative



MOA:
- Inhibition of thymidylate synthetase → de novo thymidine synthesis ↓ → DNA synthesis ↓ DNA fragmentation
- Cell cycle specific: S phase

Pkin:
- *Kinetics*: 93% plasma protein-bound, half-life: terminal t½ 168 h
- *Metabolism*: intracellular conversion to polyglutamate forms, long-term intracellular retention
- *Elimination*: predominantly renal (>50%)

Nw:
- *Bone marrow*: myelosuppression dose-limiting, especially neutropenia, mostly mild to moderate
- *Gastrointestinal*: nausea, vomiting, anorexia, less frequently mucositis, diarrhea
- *Liver*: reversible increase in transaminases
- *Skin*: alopecia, dermatitis, erythema
- *Other*: asthenia, fever

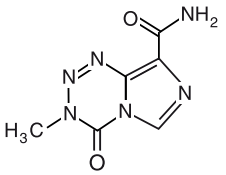
Ci: Severe hepatic and renal impairment

Th: *Approved indications*: colorectal cancer

Dosage and Administration
- Standard dose: 3 mg/m²/day i.v. on day 1, every 3 weeks
- Dose modification ► Chap. 2.2.4, incompatibility ► Chap. 2.2.7, stability ► Chap. 2.2.8
- ATTN: folic acid, folinic acid or vitamin preparations must not be given immediately prior to or during drug administration
- BEFORE TREATMENT: full blood count, liver and renal function tests

Temozolomide

Chem: 3,4-Dihydro-3-methyl-4-oxoimidazo(5,1-d)-as-tetrazine-8-carboxamide
Methazolastone, alkylating agent



MOA: Alkylating drug, DNA methylation at O^6 and N^7 positions of guanine, DNA strand breaks

Pkin:
- *Kinetics:* enteric absorption after protonation in the stomach, 100% bioavailability, enters cerebrospinal fluid, half-life: t½ 90–130 min
- *Metabolism:* activation to monomethyl triazeno imidazole carboxamide (MTIC), hepatic degradation, renal excretion of unchanged drug and metabolites, minor hepatobiliary and pulmonary excretion

Se:
- *Bone marrow:* myelosuppression dose-limiting, with leukopenia, lymphopenia, thrombocytopenia, anemia
- *Gastrointestinal:* nausea, vomiting, loss of appetite, constipation, mucositis (rare), diarrhea
- *Liver:* transient elevation of transaminases
- *Skin:* erythema, exanthema, photosensitivity, alopecia (rare)
- *Nervous system:* rarely, central nervous system disorders: headache, fatigue, vertigo, dysgeusia, paresthesias, seizures
- *Other:* fever, edema (rare)

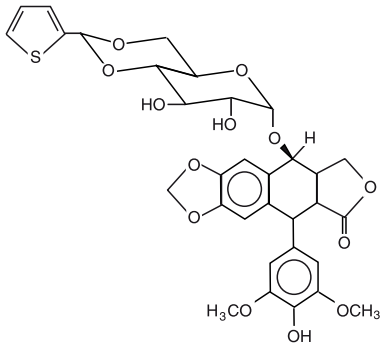
Ci: Severe myelosuppression

Th: *Approved indications:* malignant gliomas: glioblastoma multiforme, anaplastic astrocytoma
Other areas of use: cerebral tumors, melanomas

Dosage and Administration
- Standard dose: 200 mg/m²/day p.o. on days 1–5, repeat after 4 weeks
- For patients who have previously received chemotherapy, initial dose is 150 mg/m²/day on days 1–5 with repeat after 4 weeks, increasing dose to 200 mg/m²/day
- Dose modification ► Chap. 3.2.4
- ATTN: avoid sunlight
- BEFORE TREATMENT: full blood count, liver and renal function tests

Teniposide (VM-26)

Chem: 4'-Demethylepipodophyllotoxin 9-(4,6-O-2-thenylidene-beta-D-glucopyranoside)
Epipodophyllotoxin derivative, plant alkaloid, topoisomerase II inhibitor



MOA:
- Inhibition of topoisomerase II → DNA strand breaks → mitotic arrest
- Cell-cycle-specific: G2 / S / M phases

Pkin:
- *Kinetics:* > 95% protein-bound, half-life: terminal t½ 5–14 h
- *Metabolism:* cytochrome P450 hepatic degradation (90%), renal excretion (10%)

Se:
- *Bone marrow:* myelosuppression dose-limiting, especially neutropenia, anemia (rare) and thrombocytopenia (rare)
- *Cardiovascular:* hypotension with rapid intravenous administration
- *Gastrointestinal:* nausea / vomiting (25%), mucositis (rare), diarrhea, gastrointestinal / perforation (rare)
- *Liver:* transient elevation of transaminases, hepatic veno-occlusive disease (VOD, rare)
- *Skin:* moderate alopecia, erythema (rare), hyperpigmentation
- *Nervous system:* rarely, peripheral neuropathy (paresthesias) or central nervous system disorders (headache, confusion, weakness, fatigue, seizures)
- *Other:* infertility, allergic reactions (fever, chills, bronchospasm, skin reactions), anaphylaxis

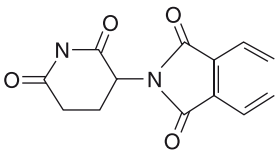
Ci: Severely impaired liver or renal function, pre-existing neurological disorders

Th: *Approved indications:* ALL, lymphomas, CNS tumors
Other areas of use: small cell lung cancer

Dosage and Administration
- Standard dose: various protocols:
  - 20–60 mg/m²/day i.v. on days 1–5, every 2–3 weeks
  - 100–250 mg/m²/day i.v. on day 1, weekly for 4–8 weeks
  - 165 mg/m²/day i.v. on days 1 + 4, weekly for 4 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6
- BEFORE TREATMENT: full blood count, liver and renal function tests

Thalidomide

Chem: Alpha-(N-phthalimido)glutarimide



MOA: Mechanism of action not fully characterized. Proposed mechanisms include:
- Immunomodulation: immunosuppressive properties, proinflammatory cytokines ↓, anti-inflammatory cytokines ↑, tumor necrosis factor α ↓, leukocyte migration ↓
- Anti-angiogenic properties, endothelial cell proliferation ↓

Pkin:
- *Kinetics:* oral bioavailability 90%, peak plasma concentration reached after 2.9–5.7 h, protein binding 55–66%, half-life t½ 5.5–7.3 h
- *Metabolism:* non-enzymatic hydrolysis in plasma

Se:
- *Bone marrow:* leukopenia, neutropenia
- *Pulmonary:* cough, dyspnea, upper respiratory tract infections, pneumonia
- *Cardiovascular:* edema, chest pain, atrial fibrillation, cardiac failure, myocardial infarction, tachycardia, bradycardia, orthostatic hypotension, thromboembolic events, pulmonary embolism
- *Gastrointestinal:* nausea, anorexia, constipation, abdominal pain
- *Hepatic:* transient increase of liver enzymes, hyperbilirubinemia
- *Kidney:* dysuria, hypocalcemia
- *Skin:* erythema, pruritus, rash, alopecia, Stevens-Johnson syndrome / toxic epidermal necrolysis (rare)
- *Nervous system:* headache, dizziness, drowsiness, somnolence, anxiety, tremor, confusion, peripheral neuropathy, seizures (rare)
- *Other:* fever, fatigue, infections, arthralgia, myalgia, back pain, asthenia, hypothyroidism

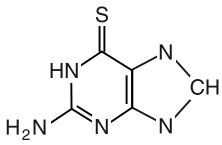
Ci:
- Pregnant women or women capable of becoming pregnant. Female patients must use two different methods of contraception. Male patients must use condoms.
- Hypersensitivity to thalidomide

Th: *Approved indications:* multiple myeloma (newly diagnosed, first line with dexamethasone), erythema nodosum leprosum (ENL)
Other areas of use: MDS, Crohn's disease, graft-versus-host disease (GvHD)

Dosage and Administration
- Standard dose: 100–800 mg p.o. daily
- ATTN: potential for life-threatening human birth defects. Appropriate precautions should be taken to avoid pregnancy and fathering. In order to avoid fetal exposure to thalidomide, in the US the drug is only available under a special restricted distribution program. Significantly increased risk of deep venous thrombosis and pulmonary embolism. Avoid concomitant use of alcohol, CNS depressants, and medications associated with peripheral neuropathy
- BEFORE TREATMENT: full blood count, liver and renal function tests, electrolytes, thyroid function, neurological status, pregnancy test (in women of childbearing potential)

6-Thioguanine (6-TG)

Chem: 2-Aminopurine-6(1H)-thione, purine analog (guanine analog), antimetabolite



MOA:
- Inhibition of de novo purine synthesis and purine conversion, chromosome breaks
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* oral bioavailability variable (10–60%), interindividual variation in absorption over 8–12 h, half-life: terminal t½ 1.5–11 h
- *Metabolism:* intracellular activation and formation of various effective metabolites (ribonucleotide and deoxyribonucleotide derivatives), hepatic degradation, biliary excretion of metabolites

Se:
- *Bone marrow:* myelotoxicity dose-limiting, leukopenia, thrombocytopenia, anemia (rare)
- *Gastrointestinal:* mild nausea, vomiting, loss of appetite, mucositis, diarrhea, intestinal perforation in isolated cases
- *Liver:* transient elevation of transaminases, cholestasis (rare), hepatic veno-occlusive disease (VOD) in isolated cases
- *Kidney:* impaired renal function (rare), renal failure (rare)
- *Skin:* erythema (rare), dermatitis
- *Nervous system:* loss of vibration sensitivity, gait disorders

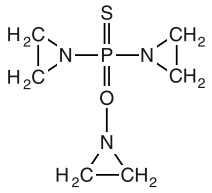
Ci: Severely impaired liver function

Th: *Approved indications:* ALL, AML, CML

Dosage and Administration
- Standard dose: 80–200 mg/m²/day (2–3 mg/kg body weight/day) p.o. daily, for 5–20 days, to be taken on an empty stomach with fluids
- Dose modification ► Chap. 3.2.4
- BEFORE TREATMENT: full blood count, liver function tests

Thiotepa

Chem: Tris(1-aziridinyl)phosphine sulfide, aziridine, alkylating agent



MOA:
- DNA, RNA and protein alkylation, DNA strand breaks, cross-linking, inhibition of nucleic acid synthesis and protein synthesis
- Cell-cycle-specific: S / G2 phases

Pkin:
- *Kinetics:* readily enters cerebrospinal fluid, half-life: initial t½ 8 min, terminal t½ 2–3 h
- *Metabolism:* rapid decay in plasma, formation of bifunctional alkylating metabolites (main metabolite is TEPA, i.e., triethylenephosphoramide), renal excretion of unchanged drug (< 10%) and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, cumulative, leukopenia, thrombocytopenia and anemia (rare)
- *Gastrointestinal:* nausea, vomiting, mucositis, loss of appetite, diarrhea, enteritis, especially after high-dose therapy
- *Liver:* transient elevation of transaminases
- *Genitourinary:* impaired renal function (especially with high-dose therapy); with intravesical instillation: abdominal pain, hematuria, dysuria, ureteric obstruction
- *Skin:* erythema, dermatitis, alopecia (rare) after high-dose therapy, hyperpigmentation
- *Nervous system:* central neurotoxicity (headache, confusion, paresthesias, muscle weakness, somnolence, coma), especially with cumulative doses > 1,100 mg/m²
- *Other:* infertility, hyperuricemia, fever (rare), allergic reactions

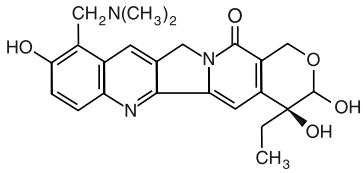
Ci: Severely impaired liver or renal function

Th: *Approved indications:*
- *Systemic:* breast cancer, ovarian cancer, chronic leukemias, lymphomas
- *Local:* bladder tumors, condylomata, malignant effusions

Dosage and Administration
- Due to good local tolerance, intravenous, intra-arterial, subcutaneous, intravesical, intrathecal, and intracavitary (intrapleural, intraperitoneal) administration possible
- Standard dose:
  - Systemic: 12–16 mg/m²/day i.v. on day 1 weekly or every 2–4 weeks
  - Local application: instillation of 15–60 mg absolute weekly, for 4 weeks
- High-dose therapy regimens: 125–150 mg/m²/day i.v. for 4 days on days 1–4 (*ATTN:* only in transplant centers)
- Incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Topotecan

Chem: Camptothecin analog, topoisomerase I inhibitor



MOA:
- Inhibition of topoisomerase I, DNA religation ↓↓ → DNA strand breaks and intercalation
- Cell-cycle-specific: G2 / M phases

Pkin:
- *Kinetics:* ubiquitous distribution, enters cerebrospinal fluid, accumulates in "third space" fluid deposits (pleural effusions, ascites), half-life: terminal t½ 2–6 h
- *Metabolism:* plasma degradation, renal excretion of unchanged drug (40–50%) and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, leukopenia (80%) and thrombocytopenia, anemia
- *Gastrointestinal:* diarrhea (30%), nausea, vomiting (10%), loss of appetite, mucositis
- *Liver:* transient elevation of transaminases, hyperbilirubinemia
- *Kidney:* impaired renal function, microscopic hematuria
- *Skin:* alopecia, erythema, urticaria (rare), pruritus
- *Nervous system:* headache, peripheral neurotoxicity (rare)
- *Other:* fever, fatigue, reduced performance status, dyspnea (rare), arthralgia (rare), myalgia

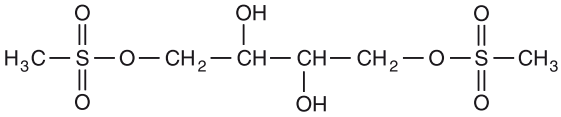
Ci:
- Acute infection
- "Third space" fluid deposits (ascites, pleural effusions)

Th: *Approved indications:* ovarian cancer, small cell lung cancer, cervical carcinoma
Other areas of use: AML, NHL, cerebral metastases

Dosage and Administration
- Standard dose: 1.5 mg/m²/day i.v. on days 1–5, every 3 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: with combination therapy regimens, topotecan must be administered prior to cisplatin. Dose must be increased with concurrent administration of anticonvulsive therapy
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance)

Treosulfan

Chem: L-Threitol-1,4-bis (methanesulfonate), bifunctional alkylating agent



MOA:
- DNA and RNA alkylation (N^7 position of guanine), DNA strand breaks, cross-linking
- Cell-cycle-specific: S / G2 phases

Pkin:
- *Kinetics:* oral bioavailability 90%, half-life: terminal t½ 1.5–2 h
- *Metabolism:* spontaneous activation in plasma, degradation to inactive metabolites, renal excretion of unchanged drug (15%) and metabolites

Se:
- *Bone marrow:* myelosuppression dose-limiting, long neutropenic phase, thrombocytopenia
- *Pulmonary:* pulmonary fibrosis (rare), allergic alveolitis, pneumonia
- *Gastrointestinal:* moderate nausea / vomiting, mucositis, diarrhea
- *Liver:* transient disturbances of liver function, cholestasis
- *Skin:* erythema, urticaria, pruritus, hyperpigmentation, alopecia
- *Nervous system:* paresthesias
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* hemorrhagic cystitis (rare), allergic reactions, flu-like symptoms

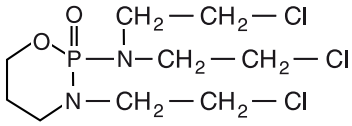
Ci: Pulmonary function disorders, pre-existing bone marrow dysfunction

Th: *Approved indications:* ovarian tumors
Other areas of use: lung cancer (NSCLC), esophageal cancer, head and neck tumors

Dosage and Administration
- Standard dose: various protocols:
  - *Intravenously:* 5,000–8,000 mg/m²/day i.v. on day 1, every 21–28 days
  - *Orally:* 750–1,250 mg/day p.o. on days 1–28, every 56 days to be taken with food
- Incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- BEFORE TREATMENT: full blood count, liver and renal function tests, pulmonary function evaluation

Trofosfamide

Chem: N,N,3-Tris(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide
Oxazaphosphorine, alkylating agent



MOA:
- DNA and RNA alkylation, DNA strand breaks, cross-linking, inhibition of DNA synthesis
- Cell-cycle-specific: S phase

Pkin:
- *Kinetics:* oral bioavailability > 95%, half-life: terminal t½ 4–8 h
- *Metabolism:* hepatic hydroxylation by microsomal cytochrome P450 monooxygenase to 4-hydroxytrofosfamide, active metabolites released in plasma and tissues, hepatic degradation, renal excretion of unchanged drug (5–15%) and metabolites

Se:
- *Bone marrow:* Myelosuppression dose-limiting, leukopenia and thrombocytopenia
- *Gastrointestinal:* moderate nausea / vomiting, loss of appetite
- *Liver:* transient elevation of transaminases
- *Genitourinary:* hemorrhagic cystitis with high-dose therapy or prolonged treatment (dose-limiting)
- *Skin:* alopecia
- *Other:* moderate immunosuppression

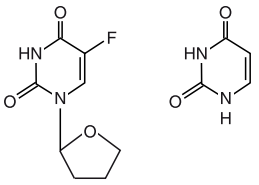
Ci:
- Severely impaired liver or renal function, acute infections
- Cystitis, urinary tract obstruction

Th: *Approved indications:* maintenance therapy for hematological neoplasms (e.g., CLL, Hodgkin's disease, NHL, plasmacytoma, Waldenström's macroglobulinemia) and solid tumors (e.g., ovarian cancer, breast cancer, small cell lung cancer, seminoma)

Dosage and Administration
- Oral administration with plenty of fluids, standard dose:
  - Initial therapy: 150–200 mg/m²/day p.o.
  - Maintenance dose: 25–100 mg/m²/day p.o.
- Dose modification ► Chap. 3.2.4
- ATTN: enhances the effects of sulfonylureas. Effects enhanced by barbiturates (cytochrome P450 activation) and cimetidine
- BEFORE TREATMENT: full blood count, liver and renal function tests

UFT (Tegafur-Uracil)

Chem: Tegafur: 5-fluoro-1-tetrahydro-2-furanyl-2,4(1H,3H)-pyrimidinedione
Uracil: 2,4(1H,3H)-pyrimidinedione



Tegafur Uracil

MOA:
- Tegafur (Ftorafur) is metabolized in vivo to 5-FU. Uracil inhibits further degradation of 5-FU → t½ prolonged
- Inhibition of thymidylate synthetase by FdUMP → thymidine synthesis ↓
- Incorporated into RNA, inhibition of RNA synthesis by FUTP
- Cell-cycle-specific: S phase

Pkin:
- *Metabolism:* Conversion to 5-FU, intracellular activation and phosphorylation (formation of FdUMP, FUTP, etc.). Degradation in liver and intestinal mucosa by dihydropyrimidine dehydrogenase is reduced by uracil, metabolic (90%), renal (10%) excretion

Se:
- *Bone marrow:* mild myelosuppression
- *Cardiovascular:* rarely acute cardiotoxicity with arrhythmias, ischemia, myocardial infarction in isolated cases
- *Gastrointestinal:* nausea, vomiting, diarrhea, abdominal pain
- *Liver:* elevated transaminases, bilirubin ↑ (rare)
- *Kidney:* proteinuria (rare) and hematuria
- *Skin:* erythema, pruritus, dermatitis, pigmentation disorders, alopecia (especially with long-term use), palmar-plantar erythrodysesthesia
- *Nervous system:* in rare cases central nervous system changes (headache, vertigo, somnolence, confusion), dysgeusia
- *Other:* fever, fatigue, reduced performance status, arthralgia

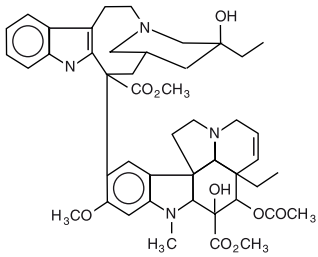
Ci:
- Severely impaired liver function
- Pre-existing stomatitis / diarrhea / myelosuppression
- CyP2A6 deficiency

Th: *Approved indications:* colorectal cancer
Other areas of use: gastrointestinal tumors, breast cancer, other solid tumors

Dosage and Administration
- Standard dose: 300 mg/m²/day p.o. for 28 days, then no therapy for 7 days
- Dose modification ► Chap. 3.2.4, stability 2 years at room temperature
- BEFORE TREATMENT: full blood count, liver and renal function tests

Vinblastine

Chem: Vincaleukoblastine, alkaloid extracted from *Vinca rosea*, mitotic inhibitor



MOA:
- Binds to tubulin → formation of mitotic spindle microtubules ↓ → mitotic arrest
- Inhibition of DNA-dependent RNA polymerases → RNA synthesis ↓
- Cell-cycle-specific: G2 / M phases

Pkin:
- *Kinetics:* half-life: initial t½ < 5 min, terminal t½ 20–64 h
- *Metabolism:* hepatic activation (deacetylation), hepatic metabolism (cytochrome P450-dependent), biliary (30%) and renal (25%) excretion

Se:
- *Bone marrow:* myelosuppression dose-limiting, neutropenia, thrombocytopenia (rare) / anemia
- *Cardiovascular:* cardiovascular disorders, hypertension, hypotension
- *Pulmonary:* pulmonary toxicity with acute interstitial pneumonitis / bronchospasm when given in combination with mitomycin
- *Gastrointestinal:* mild nausea / vomiting, diarrhea, mucositis, constipation (in severe cases paralytic ileus), intestinal spasm (rare), gastrointestinal bleeding (rare)
- *Skin:* moderate alopecia, erythema, exanthema, photosensitivity
- *Nervous system:* moderate peripheral neurotoxicity (cumulative) with paresthesias, motor disturbances (rare), less pronounced than with vincristine or vindesine
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* muscle spasms in mandible/ neck / back / limbs

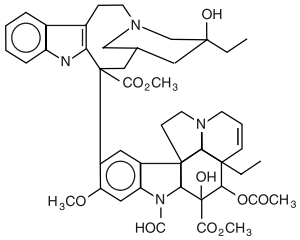
Ci: Impaired liver function, hepatic radiation, neuropathies, acute infections

Th: *Approved indications:* malignant lymphomas, testicular cancer, breast cancer, choriocarcinoma, Kaposi's sarcoma
Other areas of use: other solid tumors, CML

Dosage and Administration
- Standard dose: various protocols:
  - *Polychemotherapy:* 6 mg/m²/day i.v. on day 1 every 7–14 days
  - Monotherapy: 4 mg/m²/day i.v. on day 1 every 7 days, gradually increase by 2 mg/m²/day each week up to a maximum of 18 mg/m²/day
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: Cumulative neurotoxicity, enhanced by cisplatin, etoposide, paclitaxel. Regular neurological examination. Increased risk of paralytic ileus with administration of opiates
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), neurological evaluation. Constipation prophylaxis

Vincristine

Chem: 22-Oxovincaleukoblastine, alkaloid extracted from *Vinca rosea*, mitotic inhibitor



MOA:
- Binds to tubulin → formation of mitotic spindle microtubules ↓ → mitotic arrest
- Inhibition of DNA-dependent RNA polymerases → RNA synthesis ↓
- Cell-cycle-specific: G2 / M phases

Pkin:
- *Kinetics:* half-life: initial t½ < 5 min, terminal t½ 23–85 h
- *Metabolism:* hepatic metabolism, biliary excretion (> 70–80%), minor renal excretion

Se:
- *Bone marrow:* mild myelosuppression, especially neutropenia
- *Cardiovascular:* cardiovascular disorders, hypertension, hypotension
- *Pulmonary:* interstitial pneumonitis / bronchospasm (esp. when given in combination with mitomycin C)
- *Gastrointestinal:* constipation / ileus, nausea / vomiting, mucositis
- *Kidney:* polyuria (ADH secretion ↓), dysuria, urinary retention (bladder atony)
- *Skin:* moderate alopecia, erythema
- *Nervous system:* peripheral neurotoxicity (cumulative, dose-limiting), autonomic neurotoxicity, in some cases cranial nerve deficits and central nervous system disorders: hypesthesia, paresthesias, motor disorders, areflexia, in rare cases paralysis, ataxia, ileus, optic atrophy / blindness, seizures
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* muscle spasms / pain in mandible / neck / back / limbs, fever (rare), pancreatitis (rare)

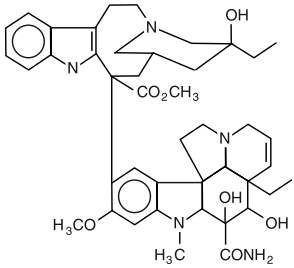
Ci: Impaired liver function, hepatic radiation, manifest neuropathies, constipation

Th: *Approved indications:* lymphomas, leukemias, solid tumors (e.g., breast cancer, lung cancer, sarcomas, Wilms' tumor, neuroblastoma)
Other areas of use: other solid tumors

Dosage and Administration
- Standard dose: 1.0–1.4 mg/m²/day i.v. on day 1, maximum single dose 2 mg (1 mg in patients over 65 years)
- Dose modification ► Chap. 3.2.4, incompatibility► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: regular neurological examination. Cumulative neurotoxicity (especially with total doses > 20 mg). Neurotoxicity enhanced by cisplatin, etoposide, paclitaxel. Increased risk of ileus with administration of opiates
- BEFORE TREATMENT: full blood count, liver and renal function tests (creatinine clearance), neurological evaluation. Constipation prophylaxis

Vindesine

Chem: 3-Carbamoyl-4-deacetyl-3-de(methoxy-carbonyl) vincaleukoblastine sulfate
Mitotic inhibitor



MOA:
- Binds to tubulin → formation of mitotic spindle microtubules ↓ → mitotic arrest
- Inhibition of DNA-dependent RNA polymerases → RNA synthesis ↓
- Cell-cycle-specific: G2 / M phases

Pkin:
- *Kinetics:* half-life: initial t½ < 5 min, terminal t½ 20–24 h
- *Metabolism:* hepatic metabolism (cytochrome P450-dependent), biliary excretion (> 80–90%) and renal excretion (10–15%)

Se:
- *Bone marrow:* myelosuppression (dose-limiting), especially neutropenia
- *Cardiovascular:* cardiovascular disorders, hypertension, hypotension
- *Pulmonary:* interstitial pneumonitis / bronchospasm (esp. when given in combination with mitomycin C)
- *Gastrointestinal:* constipation, nausea / vomiting (rare), mucositis
- *Skin:* alopecia (more pronounced than with vincristine), erythema
- *Nervous system:* peripheral, autonomic and central neurotoxicity similar to vincristine, but less pronounced: hypesthesia, paresthesias, motor disorders, areflexia
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* muscle spasms / pain in mandible / neck / back / limbs, fever (rare), pancreatitis (rare)

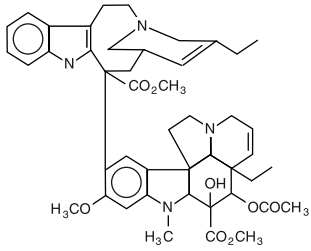
Ci: Impaired liver function, hepatic radiation, neuropathies, constipation

Th: *Approved indications:* leukemias, lymphomas, melanoma, lung cancer, breast cancer, esophageal cancer, testicular tumors, head and neck tumors
Other areas of use: other solid tumors, plasmacytoma

Dosage and Administration
- Standard dose: various protocols:
  - 3–4 mg/m²/day i.v. on day 1, every 7–14 days, maximum single dose: 5 mg absolute
  - 1.0–1.3 mg/m²/day i.v. for 5–7 days, every 3 weeks
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: regular neurological examination. Cumulative neurotoxicity enhanced by cisplatin, etoposide, paclitaxel. Risk of ileus with administration of opiates
- BEFORE TREATMENT: full blood count, liver and renal function tests, neurological evaluation. Constipation prophylaxis

Vinorelbine

Chem: 3',4'-Didehydro-4'-deoxy-8'-norvincaleukoblastine, mitotic inhibitor



MOA:
- Binds to tubulin → formation of mitotic spindle microtubules ↓ → mitotic arrest
- Inhibition of DNA-dependent RNA polymerases → RNA synthesis ↓
- Cell-cycle-specific: G2 / M phases

Pkin:
- *Kinetics:* oral bioavailability 20–40%, half-life: initial t½ < 5 min, terminal t½ 18–49 h
- *Metabolism:* hepatic metabolism to active and inactive metabolites, biliary excretion (35–80%), minor renal excretion (15–30%)

Se:
- *Bone marrow:* myelosuppression dose-limiting, neutropenia, thrombocytopenia / anemia (rare)
- *Gastrointestinal:* nausea / vomiting / diarrhea / mucositis / constipation (rare)
- *Skin:* moderate alopecia
- *Nervous system:* peripheral neurotoxicity (cumulative) with paresthesias, motor disorders (rare), less pronounced than with vincristine or vindesine
- *Local toxicity* (extravasation ► Chap. 9.9): phlebitis, necrosis
- *Other:* muscle spasms / pain in mandible / neck / back / limbs (rare)

Ci: Impaired liver function, radiotherapy, neuropathies

Th: *Approved indications:* non-small cell lung cancer, breast cancer
Other areas of use: other solid tumors

Dosage and Administration
- Standard dose: 30 mg/m²/day i.v. on day 1, weekly
- Dose modification ► Chap. 3.2.4, incompatibility ► Chap. 3.2.6, stability ► Chap. 3.2.7
- ATTN: regular neurological examination. Cumulative neurotoxicity, enhanced by cisplatin, etoposide, paclitaxel. Risk of paralytic ileus with administration of opiates
- BEFORE TREATMENT: full blood count, liver and renal function tests, neurological evaluation. Constipation prophylaxis

3.2.2 Check List Cytostatic Treatment

D.P. Berger

Def: Every cytostatic treatment carries the risk of adverse and potentially life-threatening effects. Therefore, it is imperative to observe general treatment guidelines as well as specific precautions for certain cytostatics.

Meth: The procedures listed below are mandatory in all patients before and during cytostatic treatment. However, this list is not exhaustive. Additional measures may be indicated, depending on the patient's general condition, pre-existing disorders, and the disease situation.

Recommended procedures / check-ups in cytostatic therapy

Compounds	Procedures / tests
All cytostatics	Case history, clinical examination; exhaustive patient counseling and obtaining of informed consent before treatment; information on sperm / oocyte preservation (► Chaps. 4.10.1, 4.10.2), and potentially necessary supportive measures (transfusion therapy, antiemesis, etc.) Blood count, liver / renal function tests, inflammation parameters
• Anthracyclines, amsacrine, mitoxantrone	Serum bilirubin, ECG, with suspected cardiopathies / cardiac insufficiency: echocardiography or radionuclide ventriculography
• Asparaginase	Blood glucose, lipase, coagulation status, neurostatus
• Bleomycin, busulfan	Pulmonary function, chest x-rays
• Carmustine, lomustine	Pulmonary function, chest x-rays, neurostatus
• Cisplatin	Creatinine clearance, serum magnesium, neurostatus, possibly audiometry, fluid therapy, osmotic diuresis
• Cladribine, fludarabine, pentostatin	Lymphocyte subpopulations (especially CD4- / CD8-positive T-cells), neurostatus
• Cyclophosphamide, ifosfamide	Fluid therapy, mesna, alkalization
• Methotrexate	Creatinine clearance, rule out ascites and pleural effusion, fluid therapy, alkalization, possibly leucovorin rescue, methotrexate serum levels
• 6-Mercaptopurine	Dose reduction in case of simultaneous administration of allopurinol
• Pemetrexed	Prophylactic administration of folic acid and vitamin B_{12}
• Taxanes	Cardiac check-up, neurostatus, premedication with steroids and H1/H2 blocker
• Vinca alkaloids	Serum bilirubin, neurostatus, constipation prophylaxis

Ref:

1. Ginsberg JP, Womer WB. Preventing organ-specific chemotherapy toxicity. Eur J Cancer 2005;41:2690–700
2. Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003;349:474–85

Web:

1. http://www.druginfonet.com/ Drug information
2. http://www.meds.com/DChome.html Information on Cytostatics

3.2.3 Drug Dosage Calculation Based on Body Surface Area (BSA)

C.I. Müller, D.P. Berger, M. Engelhardt

Def: Many important pharmacokinetic parameters (e.g., renal function, liver function) correlate particularly with the body surface area (BSA). Therefore, dosage recommendations for cytostatics are generally based on the patient's body surface area (in m^2). Height and weight are used to calculate BSA.

Meth:

Normal-weight Patients

Body surface area (BSA) calculation is based on empirical formulas:

Body Surface Area Calculation by Mosteller

$$\text{Body Surface Area } (m^2) = \left(\text{Height (cm)} \times \text{Weight (kg)} / 3{,}600 \right)^{0.5}$$

Body Surface Area Calculation by Gehan and George

$$\text{Body Surface Area } (m^2) = 0.0235 \times \text{Height (cm)}^{0.42245} \times \text{Weight (kg)}^{0.51456}$$

Simplified formulas are not sufficiently accurate for clinical use and should not be used for calculating the dosage of cytostatics. Sufficiently accurate alternatives used in everyday clinical practice are slide charts, BSA tables, or so called nomograms. Alternatively, many internet pages provide online body surface area calculations or offer BSA calculators for download.

Obese Patients

In obese patients, various cytostatic dosages have to be adapted to the body weight.
Rule of thumb:

- With palliative indication: limiting of body surface area-based cytostatic dosage to a maximum of 2 m^2
- With curative indication: dosage calculation based on "ideal body weight" (IBW) or "adapted IBW" (► Chap. 3.2.4)

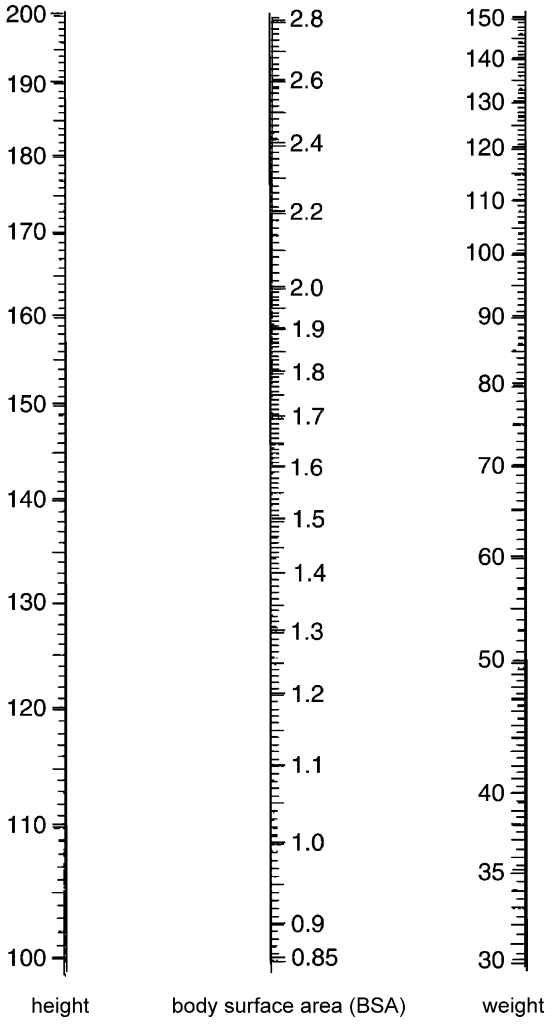
Ref:

1. Bailey BJ, Briars GL. Estimating the surface area of the human body. Stat Med 1996;15:1325–32
2. Baker SD, Verweij J, Rowinsky EK et al. Role of body surface area in dosing of investigational anticancer agents in adults, 1991-2001. J Natl Cancer Inst 2002;94:883–8
3. Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemother Rep 1970;54:225–35
4. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098
5. Reilly JJ, Workman P. Normalization of anti-cancer drug dosage using body weight and surface area: is it worthwhile? Cancer Chemother Pharmacol 1993;32:411–8

Web:

1.	http://www.halls.md/body-surface-area/refs.htm	BSA, Formulas and Comments
2.	http://www.halls.md/body-surface-area/bsa.htm	BSA Calculation
3.	http://www.ultradrive.com/bsac.htm	BSA Calculation

Nomogram for determination of the body surface area of an adult



3.2.4 Dose Adjustment of Cytostatic Drugs

W. Digel

The individual doses of cytostatic drugs should be adapted to the current status of the patient. Primarily, the following parameters should be taken into consideration: hematological situation, liver function, renal function, performance status, expected toxicity (e.g., cardiotoxicity, oto- / neurotoxicity, mucosal toxicity) and comorbidities.

Phys: ***Renal Parameters: Creatinine Clearance***

Calculation

$$\text{Creatinine Clearance (ml/min)} = \frac{\text{Creatinine}_{\text{Urine}}\ \text{(mg/dl)} \times \text{Urine Volume (ml)}}{\text{Creatinine}_{\text{Serum}}\ \text{(mg/dl)} \times \text{Time (min)}}$$

Estimation

$$\text{♂ Creatinine Clearance (ml/min)} = \frac{\text{Body Weight (kg)} \times (140 - \text{Age})}{\text{Creatinine}_{\text{Serum}}\ \text{(mg/dl)} \times 72}$$

$$\text{♀ Creatinine Clearance (ml/min)} = \frac{\text{Body Weight(kg)} \times (120 - \text{Age})}{\text{Creatinine}_{\text{Serum}}\ \text{(mg/dl)} \times 72}$$

Liver Parameters

The following parameters are used to evaluate liver function:

- Bilirubin, alkaline phosphatase
- Transaminases (AST, ALT), γGT
- Synthetic capacity (coagulation parameters, Quick's test score)

Bone Marrow Function

Generally, bone marrow toxicity is the dose-limiting side effect of cytostatic treatment (exceptions: bleomycin, vincristine, L-asparaginase).

ATTENTION:

- Whether dose adjustment is necessary or whether it is preferable to extend the treatment interval, has to be decided in each individual case.
- In cases of prolonged neutropenia after chemotherapy, the administration of hematopoietic growth factors (e.g., G-CSF) should be considered.
- If bone marrow damage / suppression of normal hematopoiesis can be attributed to the primary disease (leukemia, lymphoma with bone marrow involvement, etc.), dose reduction based on blood count parameters is not indicated.

Recommended dose adjustment according to bone marrow function

Leukocyte count (/µl)	Thrombocyte count (/µl)	Dose (%)
> 3,500	> 100,000	100
3,000–3,500	75,000–100,000	75
2,500–3,000	50,000–75,000	50
< 2,500	< 50,000	0

Body Weight and Chemotherapy

In obese patients, dose adjustment of cytostatics to body weight is required. This is of particular importance for cyclophosphamide and etoposide / VP-16 in the frame of high-dose chemotherapy.

- In these cases, dose should be based on the "ideal body weight" (IBW).
- If the IBW is more than 15 kg below the real body weight (which is usually the case with highly obese patients), dose adjustment should be based on the "adapted ideal body weight" (AIBW).

Ideal Body Weight (IBW)

♂ $$IBW = 50\ kg + 2.3 \times \left(\frac{\text{Height in cm}}{2.53} - 60 \right)$$

♀ $$IBW = 45.5\ kg + 2.3 \times \left(\frac{\text{Height in cm}}{2.53} - 60 \right)$$

Adjusted Ideal Body Weight (AIBW)

$$AIBW = IBW + 0.4 \times (\text{Actual Body Weight} - IBW)$$

Dose Modification Table

General rules of cytostatic drug dose adjustment based on hepatic and renal functions are given in the table below. Manufacturers' recommendations and relevant literature have been incorporated. Since data can vary considerably, the cytostatic dosage should be determined discerningly, taking into consideration the patient's general status.
All data are percentages of the standard dosages specified in the respective therapy protocols.

Ref:

1. Canal P, Chatelut E, Guichard S. Practical treatment guide for dose individualisation in cancer chemotherapy. Drugs 1998;56:1019–38
2. Donelli MG, Zucchetti M, Munzone E et al. Pharmacokinetics of anticancer agents in patients with impaired liver function. Eur J Cancer 1998;34:33–46
3. Ibrahim S, Honig P, Huang SM et al. Clinical pharmacology studies in patients with renal impairment: past experience and regulatory perspectives. J Clin Pharmacol 2000;40:31–8
4. Lichtman SM, Villani G. Chemotherapy in the elderly: pharmacologic considerations. Cancer Control 2000;7:548–56
5. Marx GM, Blake GM, Galani E et al. Evaluation of the Cockroft-Gault, Jelliffe and Wright formulae in estimating renal function in elderly cancer patients. Ann Oncol 2004;15:291–5
6. Stevens LA, Coresh J, Greene Tet al. Assessing kidney function – measured and estimated glomerular filtration rate. N Engl J Med 2006; 354:2473–83

Web:

1.	http://www.druginfonet.com/	Drug Information (with specialist information)
2.	http://chemfinder.camsoft.com/	Data Base of Chemical Compounds
3.	http://www.meds.com/DChome.html	Information on Cytostatics
4.	http://www.manuelsweb.com/IBW.htm	IBW calculator
5.	http://medcal3000.com/CreatinineCl.htm	Creatinine Clearance Calculator
6.	http://nephron.com/	GFR calculator

Dose modification table: recommended dose adjustment of cytostatics in case of reduced organ function

Compound	Dose modification with renal dysfunction			Dose modification with liver dysfunction		
	Parameter	Limit	Dose	Bilirubin (mg/dl)	AST (IU/l)	Dose
Altretamine (HMM)	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		
Amsacrine	$Crea_{Serum}$ (mg/dl)	> 1.5	75%	< 1.5	< 60	100%
				1.5–3.0	60–180	50%
				> 3.0	>180	Relative CI
Asparaginase		None		Use cautiously in patients with liver dysfunction		
Bendamustine	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		
Bleomycin	GFR (ml/min)	> 60	100%	Use cautiously in patients with liver dysfunction		
		10–60	75–50%			
		< 10	50–25%			
	No reduction when given twice weekly					
Capecitabine	GFR (ml/min)	> 50	100%	Use cautiously in patients with liver dysfunction		
		30–50	75%			
		< 30	Not specified			
Carboplatin	GFR (ml/min)	≥ 60	100%	Use cautiously in patients with liver dysfunction		
		41–59	60%			
		16–40	40%			
		≤ 15	Relative CI			
Carmustine	GFR (ml/min)	> 10	100%	< 1.5	< 60	100%
		< 10	Relative CI	1.5–3.0	60–180	75%
				3.1–5.0	> 180	50%
				> 5.0		Relative CI
Cisplatin	GFR (ml/min)	> 60	100%	Use cautiously in patients with liver dysfunction		
		< 60	Absolute CI			
Cladribine (2-CDA)	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		

[a]With alkaline phosphatase > 2.5 × upper normal value
[b]With alkaline phosphatase > 6 × upper normal value
AST aspartate transaminase, *CI* contraindication, *Crea* creatinine, *GFR* glomerular filtration rate

Dose modification table: recommended dose adjustment of cytostatics in case of reduced organ function *(continued)*

Compound	Dose modification with renal dysfunction			Dose modification with liver dysfunction		
	Parameter	Limit	Dose	Bilirubin (mg/dl)	AST (IU/l)	Dose
Cyclophosphamide	GFR (ml/min)	> 60 10–60 < 10	100% 75% 50%	< 3.0 3.1–5.0 > 5.0	< 180 > 180 > 180	100% 75% Relative CI
Cytarabine	GFR (ml/min)	<10	50–75%	Possible dose reduction (incomplete data)		
Dacarbazine	GFR (ml/min)	> 60 10–60 < 10	100% 75% 50%	< 1.5 1.5–3.0 3.1–5.0 > 5.0	< 60 60–180 > 180	100% 75% 50% Relative CI
Dactinomycin	GFR (ml/min)	< 10	75%	Use cautiously in patients with liver dysfunction		
Daunorubicin	$Crea_{Serum}$ (mg/dl)	> 3.0	50%	< 1.5 1.5–3.0 3.1–5.0 > 5.0	< 60 60–180 > 180	100% 75% 50% Relative CI
	NOTE: dose reduction recommended in geriatric patients					
Docetaxel	No dose adjustment (insignificant renal elimination)			– – > 1.5	< 30 30–60[a] > 60[b]	100% 75% Relative CI
Doxorubicin	GFR (ml/min)	< 10	75%	< 1.5 1.5–3.0 3.1–5.0 > 5.0	< 60 60–180 > 180	100% 50% 25% Relative CI
Epirubicin	Dose reduction in patients with major renal dysfunction			< 1.5 1.5–3.0 3.1–5.0 > 5.0	< 60 60–180 > 180	100% 50% 25% Relative CI
Estramustine	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		

[a]With alkaline phosphatase > 2.5 × upper normal value
[b]With alkaline phosphatase > 6 × upper normal value
AST aspartate transaminase, *CI* contraindication, *Crea* creatinine, *GFR* glomerular filtration rate

Dose modification table: recommended dose adjustment of cytostatics in case of reduced organ function *(continued)*

Compound	Dose modification with renal dysfunction			Dose modification with liver dysfunction		
	Parameter	Limit	Dose	Bilirubin (mg/dl)	AST (IU/l)	Dose
Etoposide	GFR (ml/min)	> 60 10–60 < 10	100% 75% 50%	< 1.5 1.5–3.0 3.1–5.0 > 5.0	< 60 60–180 > 180 –	100% 75% 50% Relative CI
Fludarabine	GFR (ml/min)	< 50 < 10	75% Relative CI		Not specified	
Fluorouracil	GFR (ml/min)	> 10 < 10	100% 50–75%	< 5.0 > 5.0	– –	100% Relative CI
Gemcitabine	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		
Hydroxyurea	GFR (ml/min)	> 50 10–50 < 10	100% 50% 25%	> 5.0	–	Relative CI
Idarubicin	Use cautiously in patients with renal insufficiency			>2.5 2.5–5.0 >5.0	– – –	100% 50% Relative CI
Ifosfamide	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		
Irinotecan	Use cautiously in patients with renal insufficiency			> 1.5	–	Absolute CI
Lomustine	GFR (ml/min)	> 50 10–50 < 10	100% 75% 50%	Use cautiously in patients with liver dysfunction		
Melphalan	GFR (ml/min)	> 60 10–60 < 10	100% 50% 25%	Use cautiously in patients with liver dysfunction		
Mercaptopurine	GFR (ml/min)	> 60 10–60 < 10	100% 10–50% Relative CI	< 1.5 1.5–3.0 3.1–5.0 > 5.0	60–180 > 180 –	100% 50% 25% Relative CI

[a]With alkaline phosphatase > 2.5 × upper normal value
[b]With alkaline phosphatase > 6 × upper normal value
AST aspartate transaminase, *CI* contraindication, *Crea* creatinine, *GFR* glomerular filtration rate

Dose modification table: recommended dose adjustment of cytostatics in case of reduced organ function *(continued)*

Compound	Dose modification with renal dysfunction			Dose modification with liver dysfunction		
	Parameter	Limit	Dose	Bilirubin (mg/dl)	AST (IU/l)	Dose
Methotrexate (low dose)	GFR (ml/min)	> 60 10–60 < 10	100% 10–50% Relative CI	Use cautiously in patients with liver dysfunction		
Methotrexate (high dose)	GFR (ml/min)	< 60	Absolute CI	1.0–3.0 3.1–5.0 > 5.0	60–180 > 180 –	100% 75% Relative CI
Mitomycin C	$Crea_{Serum}$ (mg/dl)	> 1.5 > 1.7	Follow-up Relative CI	Contraindicated in patients with severe liver dysfunction		
Mitoxantrone	With mild to medium renal dysfunction, no dose reduction necessary			< 1.5 1.5–3.0 3.1–5.0 > 5.0	< 60 60–180 > 180 –	100% 50% 25% Relative CI
Nimustine	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		
Oxaliplatin	GFR (ml/min)	< 30	Relative CI	Use cautiously in patients with liver dysfunction		
Paclitaxel	With mild to medium renal dysfunction, no dose reduction necessary (renal elimination < 10%)			< 3.0 > 3.0	– –	100% 50%
Pemetrexed	GFR (ml/min)	≥ 45 < 45	100% Relative CI	Use cautiously in patients with liver dysfunction		
Pentostatin	GFR (ml/min) Positive correlation between pentostatin clearance and creatinine clearance	< 60	Relative CI	Use cautiously in patients with liver dysfunction		
Procarbazine	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		
Temozolomide	Use cautiously in patients with renal insufficiency			Use cautiously in patients with liver dysfunction		

[a]With alkaline phosphatase > 2.5 × upper normal value
[b]With alkaline phosphatase > 6 × upper normal value
AST aspartate transaminase, *CI* contraindication, *Crea* creatinine, *GFR* glomerular filtration rate

Dose modification table: recommended dose adjustment of cytostatics in case of reduced organ function *(continued)*

Compound	Dose modification with renal dysfunction			Dose modification with liver dysfunction		
	Parameter	Limit	Dose	Bilirubin (mg/dl)	AST (IU/l)	Dose
Teniposide	Use cautiously in patients with renal insufficiency			< 1.5	< 60	100%
				1.5–3.0	60–180	75%
				3.1–5.0	> 180	50%
				> 5.0	–	Relative CI
6-Thioguanine	Use cautiously in patients with renal insufficiency			Contraindicated in patients with severe liver dysfunction		
Topotecan	GFR (ml/min)	> 40	100%	< 10	No dose adjustment	
		20–40	50%			
		< 20	Absolute CI			
Trofosfamide	Contraindicated in patients with severe renal dysfunction			Use cautiously in patients with liver dysfunction		
UFT (tegafur-uracil)	Use cautiously in patients with renal insufficiency			Contraindicated in patients with severe liver dysfunction		
Vinblastine	GFR (ml/min)	> 10	100%	< 1.5	< 60	100%
		< 10	75%	1.5–3.0	60–180	50%
				3.1–5.0	> 180	25%
				> 5.0	–	Relative CI
Vincristine	GFR (ml/min)	> 10	100%	< 1.5	< 60	100%
		< 10	75%	1.5–3.0	60–180	50%
				3.1–5.0	> 180	25%
				> 5.0	–	Relative CI
Vindesine	No dose reduction necessary			< 1.5	< 60	100%
				1.5–3.0	60–180	50%
				3.1–5.0	> 180	25%
				> 5.0	–	Relative CI
Vinorelbine	No dose reduction necessary			< 2.0	–	100%
				2.1–3.0	–	50%
				> 3.0	–	25%

[a]With alkaline phosphatase > 2.5 × upper normal value
[b]With alkaline phosphatase > 6 × upper normal value
AST aspartate transaminase, *CI* contraindication, *Crea* creatinine, *GFR* glomerular filtration rate

3.2.5 Chemotherapy During Pregnancy and Lactation

H. Henß

Def: Antineoplastic treatment during pregnancy or lactation.

Ep: Chemotherapy in pregnant or breastfeeding women is indicated in rare cases. The most common tumor types are:

- Breast cancer
- Cervical carcinoma
- Lymphoma
- Malignant melanoma

Prg: Risks of malignancies in pregnant women:

- Threat to the mother's life
- Threat to the child's life
- Spread of disease to the child
- Side effects of treatment on mother and child

Beside medical aspects, ethical and psychosocial considerations are to be taken into account when determining whether antineoplastic chemotherapy in pregnant / breastfeeding women is indicated. Of paramount importance is the interdisciplinary cooperation of the chemotherapist with the obstetrician, pediatrician, and, if necessary, with the medical ethicist.

Th:

Principles of Therapy

Decisions on chemotherapy during pregnancy have to be taken on an individual patient basis. The patient and her relatives are to be included in the decision-making process. Of practical importance are, in particular:

- Stage of pregnancy
- Stage / prognosis of malignancy
- Patient's general health / secondary disorders
- Therapeutic options
- Postchemotherapy fertility / urgency of wanting a child

First to 20th Week of Gestation (WOG)

Cytostatic chemotherapy up to the 20th WOG bears a high risk of fetal malformation (15–20%). Termination of pregnancy should therefore be seriously considered. In deciding between abortion and deferment of chemotherapy, the therapeutic situation of both mother and child needs to be taken into consideration. Treatment is absolutely indicated when, due to expected rapid progression (acute leukemia, highly malignant lymphoma), it is unlikely that the mother will survive until the earliest possible delivery date.

Curative Therapeutic Intention

- As far as possible, deferment of curative chemotherapy should be avoided.
- Immediate initiation of treatment after termination of pregnancy.
- If the parents object to an abortion, chemotherapy should nonetheless be started immediately (*ATTN:* with highly elevated risk of malformation). Through frequent sonographic monitoring, malformations can be detected before the 24th WOG and the pregnancy can subsequently be terminated. It is important to inform the patient of the risk of non-detection of malformations by ultrasound examination.

Palliative Therapeutic Intention

- Immediate initiation of treatment after termination of pregnancy.
- If in light of the palliative situation immediate treatment is not desired, deferment until completion of organogenesis may be considered. The possible risks for both mother (tumor progression) and child (transplacental tumor metastasis into fetus) must be pointed out.

Twentieth to 32nd Week of Gestation (WOG)

Chemotherapy between the 20th and 32nd WOG rarely leads to fetal malformation. The main therapeutic risks are organ toxicity, intrauterine growth retardation (IUGR) and preterm delivery. Precautions:

- Monitoring of pregnancy at a perinatal center
- Planning of early delivery
- Consideration of possible myelosuppression in both mother and child
- Consideration of prenatal surfactant therapy to enhance pulmonary maturation

Curative Therapeutic Intention

Immediate initiation of chemotherapy.

Palliative Therapeutic Intention

Possible deferment of antineoplastic therapy until infant is viable. Postpartum initiation of treatment. Patient information on risks and possible consequences of therapy delay for both mother (tumor progression) and child (risk of metastasis).

From 32nd Week of Gestation (WOG)

Usually, the fetus is viable from the 32nd WOG on → delivery before initiation of chemotherapy.

Lactation

Infants should be weaned before chemotherapy is initiated. For the majority of cytostatic drugs, the transfer into breast milk is not specified. However, potential damage to the child can not be ruled out completely.

Ref:

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2. Giacalone PL, Laffargue F, Benos P. Chemotherapy for breast carcinoma during pregnancy. A French national survey. Cancer 1999;86:2266–72
3. Loibl S, von Minckwitz G, Gwyn K et al. Breast carcinoma during pregnancy. Cancer 2006; 106:237–46
4. Partridge AH, Garber JE. Long-term outcomes of children exposed to antineoplastic agents in utero. Semin Oncol 2000;27:712–26
5. Salooja N, Szydio RM, Socie G et al. Pregnancy outcomes after peripheral blood or marrow transplantation: a retrospective survey. Lancet 2001;358:271–6
6. Williams SF, Schilsky RL. Antineoplastic drugs administered during pregnancy. Semin Oncol 2000;27:618–22

Web:

1. http://www.cancer.gov/cancertopics/pdq/treatment/breast-cancer-and-pregnancy/ NCI Cancernet
2. http://www.sogc.org/guidelines/public/111E-CPG-February2002.pdf SOGC Guideline

3.2.6 Selected Cytostatic Drug Incompatibilities

A. Göbel, B. Lubrich

Def: Physicochemical incompatibility of antineoplastic compounds may lead to, e.g., precipitation, discoloration, decomposition. These processes can be triggered by even brief contact with other compounds, e.g., when using the same infusion pump, injection via a Y-piece, or parallel infusion via a manifold set.

Prevention of Drug Incompatibility

In principle, mixing different cytostatic drug solutions as well as mixing cytostatics with parenteral nutrition solutions should be avoided. When using complex therapeutic regimens, manufacturers' recommendations and drug incompatibility databases should be consulted.

Incompatibility Table

- Cytostatic drugs and substances listed below are physicochemically incompatible.
- Consecutive administration of incompatible compounds without changing the infusion pump or injection via a Y-piece has to be avoided.
- Incompatibilities are negligible if the infusion set is replaced before each drug administration or flushed with 0.9% saline or 5% glucose solution.
- Drugs not listed in this table cannot generally be seen as compatible. In case of incompatibility questions, the responsible pharmacy should be contacted.

Physicians and nurses administrating chemotherapy have the obligation to regularly and carefully check infusions for incompatibilities.

Cytostatic	Incompatible with:
Amsacrine	Saline and other chlorine solutions, acyclovir, amphotericin B, aztreonam, ceftazidime, ceftriaxone, cimetidine, furosemide, ganciclovir, heparin, methylprednisolone-21-hydrogen succinate, metoclopramide, ondansetron, sargramostim
Asparaginase	Not specified
Bleomycin	Aminophylline, amino acids, ascorbic acid, carbenicillin, cefalotin, cefazolin, dexamethasone, diazepam, furosemide, 5% glucose, hydrocortisone-21-hydrogen succinate, methotrexate, mitomycin, nafcillin, penicillin G, riboflavin, sulfhydryl-containing drugs (e.g., glutathione), terbutaline, divalent and trivalent cations
Carboplatin	Aluminum (e.g., in infusion cannulas), 5-FU, mesna, sodium bicarbonate
Carmustine	Alkaline solutions, allopurinol, sodium bicarbonate, PVC (infusion container and application set)
Cisplatin	Amino acids, water for injection, alkaline solutions, aluminum (e.g., in infusion cannulas), amifostine, cefepime, chelating agents (e.g., penicillamine), 5-FU, gallium nitrate, 5% glucose, mesna, metoclopramide, sodium bicarbonate, sodium bisulfite-, -hydrogen sulfite- and -thiosulfate-containing drugs, piperacillin / tazobactam, thiotepa
Cladribine	5% glucose
Cyclophosphamide	Aluminum (e.g., in infusion cannulas), amphotericin B, benzyl alcohol

Cytostatic	Incompatible with:
Cytarabine	Allopurinol, carbenicillin, cefalotin, 5-FU, gallium nitrate, ganciclovir, gentamicin, heparin, hydrocortisone-21-hydrogen succinate, insulin, methotrexate, nafcillin, penicillin G, methylprednisolone-21-hydrogen succinate, oxacillin
Dacarbazine	Alkaline solutions, allopurinol, cefepime, heparin, hydrocortisone-21-hydrogen succinate, L-cysteine, mercaptoethanol, methoxypsoralen, sodium bicarbonate, piperacillin sodium / tazobactam
Dactinomycin	Benzyl alcohol, cellulose ester (in filter), filgrastim, paraben, riboflavin
Daunorubicin	Allopurinol, aluminum, aztreonam, cefepime, dexamethasone, fludarabine, 5-FU, furosemide, heparin, methotrexate, piperacillin sodium / tazobactam, pH < 4.0 or pH > 7.0
Daunorubicin liposomal	Benzyl alcohol or other bacteriostatics, dexamethasone, heparin, solvents other than 5% glucose, detergents and similar substances, electrolyte-containing solvents and drugs
Docetaxel	Amphotericin B, liposomal doxorubicin, methylprednisolone sodium succinate, nalbuphine
Doxorubicin	Alkaline solutions, allopurinol, aluminum (e.g., in infusion cannulas), aminophylline, amino acids, cefalotin, cefepime, dexamethasone, diazepam, 5-FU, furosemide, gallium nitrate, ganciclovir, heparin, hydrocortisone-21-hydrogen succinate, pH < 4.0 or pH > 7.0, methotrexate, sodium bicarbonate, piperacillin sodium / tazobactam, vincristine
Doxorubicin liposomal	Amphotericin B, benzyl alcohol / other bacteriostatics, docetaxel, mannitol, metoclopramide, mitoxantrone, morphine, sodium bicarbonate, detergents, electrolyte-containing solvents and drugs
Epirubicin	Alkaline solutions, 5-FU, heparin, ifosfamide, methotrexate, mesna
Estramustine	0.9% saline and other infusion solutions (other than 5% glucose), calcium-containing preparations
Etoposide	ABS synthetics, solutions with pH > 6, cefepime, filgrastim, gallium nitrate, idarubicin, sodium bicarbonate, PVC (infusion container and application set)
Etoposide phosphate	pH > 7, amphotericin B, cefepime, chlorpromazine, imipenem-cilastatin, methylprednisolone sodium succinate, mitomycin
Fludarabine	Acyclovir, amphotericin B, chlorpromazine, daunorubicin, ganciclovir, hydroxyzine, miconazole, prochlorperazine edisylate, pH < 4.5 or pH > 8
Fluorouracil	Calcium folinate, carboplatin, chlormethine, chlorpromazine, cisplatin, cytarabine, daunorubicin, diazepam, droperidol, doxorubicin, epirubicin, etoposide, fentanyl, filgrastim, folinic acid, gallium nitrate, leucovorin calcium, methotrexate, metoclopramide, morphine sulfate, ondansetron, spirogermanium, sulfobenzoic penicillin, vincristine, vinorelbine
Gemcitabine	Acyclovir, amphotericin B, furosemide, ganciclovir, irinotecan, methotrexate, methylprednisolone sodium succinate, mitomycin
Idarubicin	Acyclovir, alkaline solutions, allopurinol, ampicillin/sulbactam, cefazolin, cefepime, ceftazidime, clindamycin, dexamethasone-21-hydrogen phosphate, etoposide, furosemide, gentamicin, heparin, hydrocortisone-21-hydrogen succinate, imipenem, cilastin, lorazepam, methotrexate, mezlocillin, sodium bicarbonate, pethidine, piperacillin sodium / tazobactam, sargramostim, teniposide, vancomycin, vincristine
Ifosfamide	Benzyl alcohol, cefepime, methotrexate, mesna
Irinotecan	Alkaline solutions, gemcitabine, sodium folinate

ABS: Acrylnitril Butadien Styrol Polymer

Cytostatic	Incompatible with:
Melphalan	Amphotericin B, chlorpromazine, 5% glucose
Methotrexate	Aluminum, bleomycin, chlormethine, chlorpromazine, cytarabine, daunorubicin, dexamethasone, doxorubicin, droperidol, 5-FU, gemcitabine, heparin, hydrocortisone-21-hydrogen succinate, idarubicin, ifosfamide, metoclopramide, methotrexate, midazolam, nalbuphine, prednisolone-21-dihydrogen phosphate, promethazine, propofol, ranitidine, vancomycin
Mitomycin	Aztreonam, bleomycin, cefepime, etoposide phosphate, filgrastim, gemcitabine, 5% glucose, piperacillin sodium / tazobactam, sargramostim, vinorelbine
Mitoxantrone	Alkaline solutions, amino acid-containing solutions, aztreonam, cefepime, heparin, hydrocortisone-21-dihydrogen phosphate, paclitaxel, piperacillin sodium / tazobactam, propofol, thiotepa
Nimustine	Not specified
Oxaliplatin	0.9% saline
Paclitaxel	Amphotericin B, chlorpromazine, liposomal doxorubicin, hydroxyzine, methylprednisolone-21-hydrogen succinate, mitoxantrone, PVC (infusion container and application set)
Pentostatin	Acidic solutions
Teniposide	ABS synthetics, heparin, idarubicin, PVC (infusion container and giving set), solvents other than 0.9% saline and 5% glucose
Thiotepa	Cisplatin, filgrastim, minocycline, mitoxantrone, acidic solutions, vinorelbine
Topotecan	Not specified
Treosulfan	Alkaline solutions
Vinblastine	Cefepime, furosemide, heparin, pH < 3.5 or pH > 5
Vincristine	Cefepime, doxorubicin, furosemide, idarubicin, sodium bicarbonate, pH < 3.5 or pH > 5
Vindesine	5-FU, sodium bicarbonate, pH < 3.5 or pH > 5
Vinorelbine	Acyclovir, alkaline solutions, allopurinol, aminophylline, amphotericin B, ampicillin, cefazolin, cefoperazone, ceforanide, cefotaxime, cefotetan, ceftriaxone, cefuroxime, 5-FU, furosemide, ganciclovir, methylprednisolone-21-hydrogen succinate, mitomycin, sodium bicarbonate, piperacillin, thiotepa, trimethoprim / sulfamethoxazole

ABS: Acrylnitril Butadien Styrol Polymer

Ref:

1. Trissel LA. Handbook on Injectable Drugs, 14th edn. American Society of Health-System Pharmacists, Bethesda, 2007.

Web:

1. http://www.druginfonet.com/ Drug Information (with specialist information)
2. http://chemfinder.camsoft.com/ Database of Chemical Compounds
3. http://rxlist.com Internet Drug Index
4. http://www.meds.com/DChome.html Information on Cytostatics

3.2.7 Preparation and Stability of Cytostatics

B. Lubrich, A. Göbel

Def: Precautions for the safe handling of cytostatics involve preparation, use, and disposal. Of particular importance is systemic exposure of staff to cytostatics via inhalation, ingestion, and cutaneous absorption. Potential threats include:

- Local and systemic toxicity
- Acute and chronic toxicity
- Genotoxicity / teratogenicity / mutagenicity

Meth:

Proper and Safe Handling of Cytostatics: Minimum Requirements

- Staff safety, occupational health and safety
- Patient safety
- Product safety
- Environmental protection

Occupational Safety

Cytostatics must be prepared and used by trained staff only.

Preparation and Use of Cytostatics

Cytostatic drug solutions are prepared in the pharmacy in accordance with the pharmaceutical law, pharmacy rules, and approved principles of pharmaceutical science.
Preparations for the use of cytostatics are the responsibility of the physician and are carried out by him-/herself or by members of staff based on approved principles of medical science.

Facilities

Cytostatic drug solutions should be prepared at a central location, e.g., in the hospital pharmacy:

- In rooms separated from other sectors, with limited access for authorized staff only.
- There must be no eating, drinking, or smoking in the designated rooms.
- There must be no other activities taking place in the room during preparation of cytostatics.
- Doors and windows must be kept closed during preparation: draft-free work environment.

Safety Cabinets

Preparation must be carried out in category 2 safety cabinets.

- Safety cabinets are to be regularly inspected in accordance with current policies. Inspections are to be documented in a log book.
- A user manual must be provided for work at the cabinets.
- The user manual must contain directives for cleaning and disinfection of all work surfaces.
- Supply and exhaust air in the preparation room must correspond with the cabinet. The exhaust air ventilation system must be ducted outside.
- Air flow modification during work (e.g., covering of ventilation slots, addition of voluminous or large numbers of items to the cabinet, vigorous movements) is to be avoided as it could negatively influence the retention capacity / product safety / entrainment prevention.

Protective Clothing

- Protective clothing is mandatory to avoid direct contact between skin or mucous membranes and cytostatics.
- Liquid-proof, long-sleeved, high-necked, non-fuzzing gowns with fitting cuffs. Suitable clothing includes liquid-proof disposable gowns or textile disposable gowns with liquid-proof gauntlets.
- Gowns must only be worn within the designated rooms.
- Gowns must be changed at least on a daily basis.

Gloves

- Liquid-proof disposable gloves, e.g., latex and/or nitrile gloves of at least 0.2 mm thickness and of documented quality (double gloving recommended).

- Gloves must be long enough to remain tight above the cuff during work.
- In the event of visible contamination or leakage and after working with amsacrine, carmustine, irinotecan, mitoxantrone, and thiotepa, gloves must be changed immediately.

Protective Glasses with Side Shields

When handling cytostatics outside the safety cabinet, e.g., to remove a major spillage of cytostatics, protective glasses with side shields must be worn.

Inhalation Protection

When handling cytostatics outside the safety workbench, e.g., to remove a major spillage of cytostatics, a particle filtration half-mask must be worn.

Textile Aids

For easy removal of contamination, cytostatics should be prepared on a liquid-proof absorbent mat. In addition:

- Use compresses when opening ampoules.
- When retracting cannulas from piercable rubber stoppers or removing residual air from syringes, use compresses or gauze swabs in order to avoid contamination from spraying or aerosol formation.

Technical Aids

- As far as possible, choose cytostatics in "cytosafe packaging."
- Strict use of disposable syringes and needles with Luer-Lok connections.
- Use pressure release devices with filters (spikes) for venting injection bottles.
- Cytostatics should be dissolved in a closed system. Cytostatics and solvents or vehicles are transferred between containers using transfer caps or needles, providing internal pressure equalization. That way, containers can be disconnected without pressure differences, preventing splashing or release of cytostatic aerosols.

Transport

Drug solutions must be transported in shatter-proof, water-proof, and sealable containers.

Storage and Stability of Cytostatics

The following factors impact cytostatic drug storage and stability:

- Expiry date of primary product (dry substance or solution)
- Physicochemical stability of cytostatic stock solution
- Physicochemical stability of the ready-prepared cytostatic compound
- Hygienic aspects, i.e., microbiological fitness
- Cool storage or storage at room temperature
- Light protection
- Shelf-life of prepared solution

Storage limits and conditions for compounds prepared in the pharmacy are to be specified by the responsible pharmacy and stated on the drug label. Cytostatic drug solutions must be stored according to these specifications. After expiry, compounds must be discarded.

Details on physicochemical stability of common cytostatic solutions are given in the table below.

Preparation and Administration of Cytostatic Infusions and Injections

- When connecting, changing, venting, or removing an infusion system, contamination of staff members must be avoided (e.g., by wearing protective gloves), as well as contamination of the room and aerosol formation.
- For this purpose, technical aids (pressure release systems with aerosol filters) should be used.
- Vent the infusion system only with carrier solution.

Dispensing of Cytostatics for Oral Application

When dispensing drugs into containers designated for patients (e.g., dispenser), certain precautions have to be observed, e.g.:

- Wearing of protective gloves
- Use of tweezers or spoons
- Splitting of tablets, pulverization, etc. should be carried out using suitable aids (closed systems) and with particular care (preparation usually in the pharmacy).
- When cleaning and handling containers and items used for dispensing drugs, contamination of staff members must be avoided. Full details should be given in a user manual.

Administration of Liquid and Semisolid Cytostatic Formulations

Use suitable protective gloves or applicators.

Spillage

Spilled cytostatics must be removed immediately and carefully and in compliance with the preventive measures specified for the preparation of cytostatics:

- When lifting contaminated broken glass use an extra pair of gloves to prevent physical risks. Preferably, lift shards with tongs.
- Use dry disposable cloths to soak up spilled solutions.
- Use wet disposable cloths for spilled powder.
- Afterwards, clean with soapy water.
- Dispose of all contaminated materials using a leak-proof single-use container.
- Sets of the necessary equipment (protective gown, safety goggles, gloves and masks, cellulose, waste container, scoop) – including instructions – should be held ready.

Skin Contamination

Areas of skin contaminated with cytostatics must be irrigated immediately with copious quantities of cold water.

Eye Contamination

In case of eye contamination, irrigate with copious quantities of water or isotonic saline solution for 10 min. Then, consult an ophthalmologist.

Disposal of Cytostatics

Cytostatics are collected and disposed of according to local regulations.

- Collection and disposal of cytostatic residue requires particular supervision and is to be carried out in accordance with waste regulations and the Hazardous Substances Ordinance using labeled, robust, and leak-proof containers.
- Collection should be separate and in a central location. Disposal should be carried out in hazardous waste incinerators.
- Materials contaminated with cytostatics (textile aids, disposable gowns, applicators, etc.) can be treated as household waste.
- Contaminated reusable clothes or reusable textile materials must be changed, collected without further manipulation, and laundered.
- Cytostatics-containing excrements are not regarded hazardous but should be disposed of on the ward in compliance with hygiene guidelines and health and safety regulations.

Ref:

1. ASCO. Criteria for facilities and personnel for the administration of parenteral systemic antineoplastic therapy. J Clin Oncol 2004;22:4613–5
2. Connor TH, McDiarmid MA. Preventing occupational exposures to antineoplastic drugs in health care settings. CA Cancer J Clin 2006;56:354–65
3. Trissel LA. Handbook on Injectable Drugs, 14th edn. American Society of Health-System Pharmacists, Betherda, 2007

Web:

1. http://www.druginfonet.com/ Drug Information
2. http://www.meds.com/DChome.html Information on Cytostatics

Physicochemical stability of ready-prepared cytostatic and antibody preparations

Cytostatics	Stock solution			Solution for application			
	Solvent	Concentration	Stability / temperature	Carrier	Stability at RT	Stability at 2–8°C	Storage / details
Alemtuzumab		10 mg/ml	28 d / cool	Saline or G5	24 h	24 h	Cool, protect from light
Amsacrine	Lactic acid 0.035m	5 mg/ml	48 h / RT	G5 (!)	72 h	Unspecified	RT
L-Asparaginase	Water for injection	2,500 U/ml	5 d / cool	Saline	8 h	24 h	Cool, avoid vigorous shaking (!)
Bendamustine	Water for injection	3 mg/ml	Dilute in 0.9% saline immediately after reconstitution	Saline (!)	9 h	5 d	Cool
Bevacizumab	–	25 mg/ml	5 d / cool	Saline	–	48 h	Cool, protect from light
Bleomycin	Saline (!)	3 mg/ml	28 d / cool	Saline (!)	14 d	28 d	Cool, protect from light
Bortezomib	Saline	1 mg/ml	8 h / cool	Dilution not recommended; application of stock solution			
Busulfan	–	6 mg/ml	28 d / cool	Saline	8 h	15 h	Cool, stability details are for concentrations 0.5 mg/ml, use plastic material free of polycarbonate
Carboplatin	–	10 mg/ml	28 d / cool	G5 (!)	14 d	28 d	Cool
Carmustine	1. Absolute ethanol 2. Water for injection	3.33 mg/ml	24 h / cool	G5 (!)	6 h	48 h	Cool, protect from light adsorption on synthetics (except PE)
Cetuximab	–	2 mg/ml	24h / cool	–	24 h	28 d	Cool, protect from light, use special inline-filters
Cisplatin	–	0.5 mg/ml	28 d / cool	Saline (!)	21 d	21 d	Cool, protect from light
	–	1 mg/ml	28d / cool	Saline	21 d	21 d	Cool protect from light; dilute not more than 1:2 with saline

RT room temperature, *d* day, *h* hour, *G5* 5% glucose, *Saline* 0.9% saline, *(!)* compulsory. Solvents in *brackets* refer to the relevant dry substance. These specifications are applicable for parenteral application and conditions of microbiologically validated central preparation of cytostatics

Physicochemical stability of ready-prepared cytostatic and antibody preparations *(continued)*

Cytostatics	Stock solution			Solution for application			
	Solvent	Concentration	Stability / temperature	Carrier	Stability at RT	Stability at 2–8°C	Storage / details
Cladribine	–	1 mg/ml	7 d / cool	Saline (!)	28 d	28 d	Cool, protect from light
Cyclophosphamide	Saline	20 mg/ml	28 d / cool	Saline or G5	4–7 d	28 d	Cool
Cytarabine	Saline	50 or 100 mg/ml	14 d / cool	Saline or G5	7 d	28 d	Cool
Dacarbazine	(Water for injection)	10 mg/ml	72 h / cool	Saline or G5	8 h	24 h	Cool, protect from light
Dactinomycin	Water for injection	0.5 mg/ml	28 d / cool	Saline or G5	72 h	72 h	Cool, protect from light
Daunorubicin	Saline or G5	2 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light
Daunorubicin, liposomal	–	50 mg/ml	–	G5	–	6 h < 0.5 mg/ml 24 h 0.5–1 mg/ml	Cool, protect from light
Docetaxel	Special solvent	10 mg/ml	28 d / RT or cool	Saline or G5	28 d	28 d	RT, protect from light
Doxorubicin	(G5)	2 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light, pH 5
Doxorubicin, liposomal (PEGylated)	–	2 mg/ml	28 d / cool	G5 (!)	48 h	7 d	Cool, protect from light
Doxorubicin, liposomal (non-PEGylated)	–	2 mg/ml	5 d / cool	G5 (!)	24 h	24 h	Cool, protect from light
Epirubicin	(G5)	2 mg/ml	28 d/cool	G5	28 d	28 d	Cool, protect from light, pH 5
Erwinia-asparaginase	Saline	5,000 IU/ml	20 d / cool	Saline or G5	7 d	7 d	Cool
Estramustine	Water for injection	37.5 mg/ml	10 d / cool	G5 (!)	24 h	48 h	Cool, avoid vigorous shaking (!)

RT room temperature, *d* day, *h* hour, *G5* 5% glucose, *Saline* 0.9% saline, *(!)* compulsory. Solvents in *brackets* refer to the relevant dry substance. These specifications are applicable for parenteral application and conditions of microbiologically validated central preparation of cytostatics

Physicochemical stability of ready-prepared cytostatic and antibody preparations *(continued)*

Cytostatics	Stock solution			Solution for application			
	Solvent	Concentration	Stability / temperature	Carrier	Stability at RT	Stability at 2–8°C	Storage / details
Etoposide	–	20 mg/ml	28 d / cool	Saline or G5	96 h (0.2 mg/ml) 48 h (0.4 mg/ml) 24 h (0.5 mg/ml)	–	RT
Etoposide phosphate	Water for injection	10 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light
Fludarabine phosphate	Water for injection	25 mg/ml	16 d / cool	Saline or G5	16 d	16 d	Cool
5-Fluorouracil	–	50 mg/ml	28 d / RT	Saline or G5	28 d	28 d	Cool if diluted solutions, RT if concentration > 40 mg/ml
Gemcitabine	Saline	28 mg/ml	28 d / RT (!)	Saline	28 d	28 d	Cool, protect from light
Idarubicin	Saline	1 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light
Ifosfamide	Water for injection	40 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool
Irinotecan	–	20 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light
Melphalan	Added solvent	5 mg/ml	19 h / RT	Saline (!)	3 h	24 h	Cool (!)
Methotrexate	–	25 or 100 mg/ml	28 d / cool	Saline or G5	7 d	28 d	Cool, protect from light, risk of crystallization in G5
Mitomycin	Water for injection	0.5 mg/ml	7 d / cool	Saline	48 h	5 d	Cool, pH 7 (!)
Mitoxantrone	–	2 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, risk of crystallization
Nimustine	Water for injection	5 mg/ml	72 h / cool	Saline or G5	7 h	6 d	Cool, protect from light

RT room temperature, *d* day, *h* hour, *G5* 5% glucose, *Saline* 0.9% saline, *(!)* compulsory. Solvents in *brackets* refer to the relevant dry substance. These specifications are applicable for parenteral application and conditions of microbiologically validated central preparation of cytostatics

Physicochemical stability of ready-prepared cytostatic and antibody preparations *(continued)*

Cytostatics	Stock solution			Solution for application			
	Solvent	Concentration	Stability / temperature	Carrier	Stability at RT	Stability at 2–8°C	Storage / details
Oxaliplatin	Water for injection	2 mg/ml	28 d / cool	G5 (!)	28 d	28 d	Cool, protect from light
Paclitaxel	–	6 mg/ml	28 d / cool	Saline or G5	72 h	72 h	RT, prepare in polypropylene or glass containers only, avoid PVC
PEG-asparaginase	–	750 IU/ml	10 d / cool	Saline or G5	4 h	96 h	Cool
Pemetrexed	Saline	50 mg/ml	72 h /cool	Saline	24 h	72 h	Cool, protect from light
Pentostatin	Saline	2 mg/ml	96 h / cool	Saline (!)	48 h	96 h	Cool
Rituximab	–	10 mg/ml	28 d / cool	Saline or G5	24 h	24 h	Cool, concentration 1–4 mg/ml
Thiotepa	Water for injection	10 mg/ml	28 d / cool	G5	3 d (> 5 mg/ml) 8 h (< 0.5 mg/ml)	15 d 8 h	Cool
Topotecan	Water for injection	1 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light
Trastuzumab	Water for injection	21 mg/ml	28 d / cool	Saline (!)	24 h	24 h	Cool
Treosulfan	Water for injection	50 mg/ml	5 d / RT	Dilution not recommended, infusion of stock solution			
Vinblastine	Saline	1 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light
Vincristine	Saline	1 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light
Vindesine	Saline	1 mg/ml	28 d / cool	Saline or G5	21 d	21 d	Cool, protect from light
Vinorelbine	–	10 mg/ml	28 d / cool	Saline or G5	28 d	28 d	Cool, protect from light

RT room temperature, *d* day, *h* hour, *G5* 5% glucose, *Saline* 0.9% saline, *(!)* compulsory. Solvents in *brackets* refer to the relevant dry substance. These specifications are applicable for parenteral application and conditions of microbiologically validated central preparation of cytostatics

3.3 Hormone Therapy

H. Henß, R. Engelhardt

Def: Use of hormones and hormonally active compounds (stimulating or inhibiting) in tumor therapy.
Areas of application:
- Antineoplastic therapy
- Supportive or substitution therapy

Pharm: **Hormone therapy**

Type	Mode of action
GnRH Analogs	
Buserelin, goserelin, leuprolide	Inhibition of gonadotropin secretion by continuous stimulation of the pituitary gland → release of gonadotropins (LH, FSH) ↓ → estrogen ↓, testosterone ↓
Antiestrogens, SERM	
Tamoxifen, raloxifene	Estrogen receptor competitive binding → inhibition of estradiol-specific effects, estradiol ↓, TGFβ ↑, TGFα ↓, EGF receptor expression ↓, IL-2 secretion ↑
Aromatase Inhibitors	
Unspecific: aminoglutethimide *Specific:* fadrozole, exemestane, vorozole, anastrozole, letrozole	Inhibition of aromatization of androstenedione to estrone → cellular estrogen biosynthesis ↓
Gestagens	
Megestrol acetate, medroxyprogesterone acetate	Estrogen level ↓, estrogen receptor synthesis ↓, pituitary secretion of LH / FSH / ACTH ↓ → cortisol / androstenedione / testosterone / estrone / estradiol and estrone sulfate levels ↓, dihydrotestosterone synthesis ↓
Antiandrogens	
Unspecific: cyproterone acetate *Specific:* flutamide, nilutamide, bicalutamide	Blockade of androgen receptors → inhibition of androgenic proliferative stimulation of prostatic epithelia

ACTH adrenocorticotropic hormone, *EGF* epidermal growth factor, *FSH* follicle-stimulating hormone, *GnRH* gonadotropin-releasing hormone, *IL* interleukin, *LH* luteinizing hormone, *SERM* selective estrogen receptor modulators, *TGF* tumor growth factor

Antineoplastic Therapy

MOA:

Hormone Therapy

Specific hormonal effects following interaction with cell-surface receptors, e.g., estrogen / progesterone / steroid receptors.

Antihormonal Therapy

Inhibition of specific hormonal effects via:
- Administration of hormonally active compounds → suppression of endocrine regulatory systems
- Application of specific inhibitors (e.g., competitive inhibition of hormone receptors)

Ind: ***Areas of Application***

Hormone-sensitive neoplasias (verified receptor expression):

- Breast cancer (antiestrogens, gestagens, LHRH analogs)
- Prostate cancer (estrogens, antiandrogens, LHRH analogs)
- Carcinoma of the uterine corpus (antiestrogens)
- Thyroid carcinoma (thyroxine for TSH suppression, also: substitution therapy)
- Lymphomas, multiple myeloma (corticosteroids)
- Carcinoid tumors (octreotide)

Th: For therapy details, see respective chapters.

Substitution Therapy

Ma: Use of hormones to replace hormone production which has completely or partially ceased as a result of antineoplastic therapy.

Ind:

- Estrogen / gestagen preparations in cases of premature menopause following chemotherapy
- Testosterone after bilateral orchiectomy
- Thyroxine after thyroidectomy
- Cortisone after bilateral adrenalectomy (e.g., due to bilateral adrenal tumors)

Estrogen Substitution in Premature Menopause

Pphys: In women, chemotherapy and high-dose chemotherapy in particular, can lead to gonadal damage with subsequent estrogen deficiency and premature menopause. Risks include:

- Menopausal symptoms
- Osteoporosis
- Cardiovascular complications

Ind: Estrogen substitution may be indicated in women with early menopausal symptoms and evidence of reduced hormone levels (estrogen).

Ci: ATTENTION: Continuous estrogen and combined (estrogen + gestagen) therapy constitutes an increased risk of breast cancer and cardiovascular events in healthy menopausal women (WHI study). Treatment should only be initiated after careful evaluation of risks and benefits as well as detailed patient information.

Se: Side effects of long-term estrogen substitution:

- Thrombosis, thromboembolism, cardiovascular events
- Increased breast tissue density → reduced sensitivity for mammography
- Increased risk for relapse of breast cancer and endometrial carcinoma

Th: Alternatives to estrogen substitution:

- Osteoporosis: bisphosphonates, tamoxifen, selective estrogen receptor modulators (e.g., raloxifene)
- Cardiovascular prevention: increased physical activity, dietary measures, tobacco abstinence, lipid-lowering compounds (statins) where indicated
- Menopausal symptoms: oral or transdermal clonidine, gabapentin against hot flushes, topical estrogen application (creams) against vaginal dryness (attention: systemic resorption if used long-term)
- In severe cases: gabapentin

Testosterone Replacement After Bilateral Orchiectomy

Pphys: Testicular carcinoma initially requires unilateral orchiectomy. Loss of the contralateral testicle due to unrelated causes or a second metachronous testicular carcinoma results in anorchia with subsequent testosterone deficiency.

Ind: Testosterone therapy has no influence on prognosis and progression of testicular carcinoma → long-term testosterone replacement after bilateral orchiectomy definitely indicated.

Ci: Prostate cancer

Thyroxine Replacement After Thyroidectomy in Thyroid Carcinoma

Pphys: Thyroid carcinoma commonly requires total thyroidectomy with life-long thyroid hormone replacement (L-thyroxine).

Ind: Administration of high dose of L-thyroxine (175–250 µg/d). Treatment goals:
- Substitution of thyroid hormones
- Suppression of TSH (thyroid-stimulating hormone): TSH can stimulate growth of thyroid carcinomas → L-thyroxine inhibits TSH secretion of pituitary gland

Ref:

1. Boekhout AH, Beijnen JH, Schellens JHM. Symptoms and treatment in cancer therapy-induced early menopause. Oncologist 2006;11:641–54
2. Miller WR. Aromatase inhibitors: mechanism of action and role in the treatment of breast cancer. Semin Oncol 2003;30(suppl 14):3–11
3. Smith RE. A review of Selective Estrogen Receptor Modulators and National Surgical Adjuvant Breast and Bowel Projects clinical trials. Semin Oncol 2003;30(suppl 16):4–13
4. Writing Group for the Women's Health Initiative (WHI) Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002;288:321–33
5. Zlotta AR, Schulman CC. Neoadjuvant and adjuvant hormone therapy for prostate cancer. World J Urol 2000;18:179–82

Web:

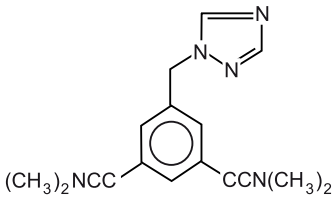
1.	http://www.prostateinfo.com/	Hormone Therapy in Prostate Cancer
2.	http://www.acor.org/TCRC/tclinks6.html	Hormone Therapy in Testicular Tumors
3.	http://www.aace.com/	American Association of Clinical Endocrinologists
4.	http://www.duj.com/Article/Hellstrom2/Hellstrom2.html	Testosterone Replacement Therapy

3.3.1 Characterization of Hormone Treatments in Oncology

H. Henß

Anastrozole

Chem: a,a,α,α-Tetramethyl-5-[(1,2,4-triazol-1-yl)methyl]benzol-1,3-diacetonitrile, non-steroidal aromatase inhibitor



MOA:
- Competitive aromatase inhibition → conversion of androgens into estrogens ↓ → estradiol serum level ↓
- No gestagenic, androgenic, or estrogenic effect

Pkin:
- *Kinetics:* good oral resorption (85%), independent of food intake, half-life: t½ 50 h
- *Metabolism:* hepatic degradation, dealkylation, glucuronidation, predominantly renal elimination of original compound (10%) and metabolites (90%)

Se:
- *Cardiovascular:* vasodilatation (25%), peripheral edema, infrequent hypertension, thromboembolic events (rare)
- *Lung:* dyspnea (rare)
- *Gastrointestinal:* moderate nausea, vomiting, diarrhea, loss of appetite
- *Liver:* increase of transaminases, hypercholesterolemia
- *Skin:* erythema, pruritus, mild alopecia
- *Nervous system:* headaches (10%), paresthesia, sleep disturbances
- *Other:* fatigue (15%), reduced performance, flush (20%), back pain, bone pain. In rare cases flu-like symptoms

Ci:
- Premenopause
- Pregnancy and breast feeding
- Liver dysfunction, renal failure

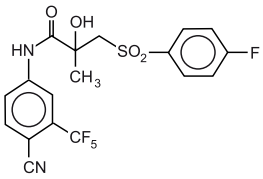
Th: *Approved indications:* advanced breast cancer in postmenopausal women. Adjuvant treatment of estrogen receptor positive breast cancer.

Dosage and Administration

Oral administration: 1 mg (1 tablet) daily

Bicalutamide

Chem: (RS)-N-[4-Cyan-3-(trifluormethyl)phenyl]-3-(4-fluorphenylsulfonyl)-2-hydroxy-2-methylpropanamide, non-steroidal antiandrogen



MOA:
- Competitive binding to androgen receptor → inhibition of testosterone effect on prostate cancer cells
- Binding to central androgen receptors (pituitary gland)

Pkin:
- *Kinetics:* slow oral resorption (independent of food intake), peak plasma level about 30 h following oral application, half-life: t½ 50 h
- *Metabolism:* hepatic degradation, biliary and renal excretion of original compound and metabolites

Se:
- *Bone marrow:* anemia (rare)
- *Cardiovascular:* hypertension (infrequent), edema
- *Lung:* dyspnea (rare)
- *Gastrointestinal:* nausea (10%), vomiting, diarrhea, constipation
- *Liver:* increase of transaminases, cholestasis
- *Skin:* occasional erythema, exanthema, perspiration, alopecia (rare)
- *Nervous system:* diminished libido, occasional vertigo, tiredness, somnolence
- *Other:* hot flushes (45%), gynecomastia (35%) impotence, pain syndromes (25–30%, thoracic region, back, pelvis), fatigue, reduced performance

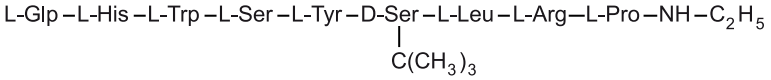
Ci: Not to be taken by women or children

Th: *Approved indications:* advanced prostate cancer, in combination with LHRH analogues ("total androgen blockade")

Dosage and Administration
- Oral administration, 50 mg daily
- Dose modification: use cautiously in patients with severe liver dysfunction
- ATTN: increase of effect of coumarin derivatives

Buserelin

Chem: 5-Oxo-*l*-prolyl- *l*-histidyl- *l*-tryptophyl- *l*-seryl- *l*-tyrosyl- *l*-*O*-tert-butyl-d-seryl- *l*-leucyl- *l*-arginyl- *N*-ethyl- *l*-prolinamide, GnRH-analog



MOA: GnRH / LHRH analog with continuous stimulation of pituitary receptors → desensitization of pituitary gland → LH / FSH secretion ↓ → estrogen / testosterone synthesis ↓ ("drug-induced castration")

Pkin:
- *Kinetics:* subcutaneous injection, slow-release drug with effective serum levels for 10–14 weeks
- *Metabolism:* hepatic degradation
- *Elimination:* degradation by peptidases, biliary and renal excretion

Se:
- *Gastrointestinal:* constipation, nausea, vomiting, loss of appetite
- *Liver:* transient increase of transaminases, hypercholesterolemia
- *Kidney:* hypercalcemia (rare)
- *Skin:* erythema, exanthema, perspiration, acne, seborrhea
- *Nervous system:* diminished libido, occasional vertigo, tiredness, somnolence
- *Other:* hot flushes (45%), gynecomastia (35%) impotence, pain syndromes (25–30%, thoracic region, back, pelvis), fatigue, reduced performance

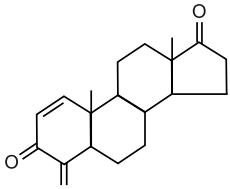
Ci: Hypersensitivity to buserelin

Th: *Approved indications:* advanced hormone responsive prostate cancer (not after bilateral orchiectomy)
Other areas of use: metastatic breast cancer

Dosage and Administration
- Subcutaneous injection every 3 months, one applicator with 9.45 mg (corresponding to 3 implant rods)
- ATTN: short initial stimulation of estrogen or testosterone excretion, prior to hormone blockage → simultaneous antiestrogen / antiandrogen treatment for initial 3–4 weeks recommended

Exemestane

Chem: 6-Methylenandrosta-1,4-diene-3,17-dione, steroidal aromatase inhibitor



MOA:
- Irreversible aromatase inhibition → conversion of androgens into estrogens ↓ → estradiol serum level ↓
- No effect on corticosteroid or aldosterone synthesis

Pkin:
- *Kinetics:* good oral resorption (> 80%), esp. with simultaneous food intake, half-life: t½ 24 h
- *Metabolism:* hepatic degradation (cytochrome P450 3A4), biliary and renal elimination of metabolites

Se:
- *Bone marrow:* lymphopenia (rare)
- *Cardiovascular:* hypertension (infrequent)
- *Lung:* dyspnea, cough
- *Gastrointestinal:* nausea (18%), occasional vomiting, diarrhea, loss of appetite, abdominal pain
- *Liver:* transient increase of transaminases
- *Skin:* erythema, perspiration, alopecia (infrequent)
- *Nervous system:* headaches, vertigo, sleep disturbances, depression
- *Other:* fatigue (20%), reduced performance, flushes (10%), back pain, bone pain. In rare cases flu-like symptoms

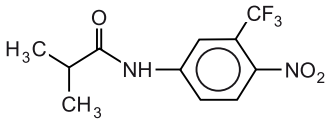
Ci:
- Premenopause
- Pregnancy and breast feeding

Th: *Approved indications:* breast cancer in postmenopausal women.
Other areas of use: prevention of prostate cancer

Dosage and Administration
- Oral administration, 25 mg (1 tablet) daily, following meal
- Dose reduction in severe liver or renal failure
- ATTN: induction of cytochrome P450 system (e.g., by phenytoin, rifampicin, barbiturates) reduces effect. Inhibition of cytochrome P450 system (e.g., itraconazole, cimetidine, macrolides) increases effect and toxicity

Flutamide

Chem: 4'-Nitro-3'-(trifluormethyl)isobutyranilide, non-steroidal antiandrogen



MOA:
- Competitive binding to androgen receptor → inhibition of testosterone effect on prostate cancer cells
- Binding to central androgen receptors (pituitary gland)

Pkin:
- *Kinetics:* good oral resorption (independent of food intake), peak plasma level 0.5–2 h following oral application, active metabolite 2-OH-flutamide, half-life: t½ 8–10 h
- *Metabolism:* hepatic degradation, hydroxylation, biliary and renal elimination of initial compound (50%) and metabolites

Se:
- *Bone marrow:* anemia (rare)
- *Cardiovascular:* hypertension, edema
- *Gastrointestinal:* nausea (10%), vomiting, diarrhea
- *Liver:* transient increase of transaminases, liver function disorders, cholestasis, hepatitis
- *Skin:* erythema
- *Nervous system:* vertigo, headaches
- *Other:* hot flushes (60%), diminished libido (35%), gynecomastia (prophylactic radiation of nipples with 10 Gy feasible), galactorrhea, impotence (10–35%) fatigue, reduced performance, cramps

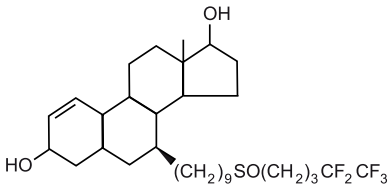
Ci:
- Not to be taken by women or children
- Liver function disorders

Th: *Approved indications:* advanced prostate cancer, in combination with LHRH analogues ("total androgen blockade")

Dosage and Administration
- Oral administration, 750 mg/day (3 × 1 tablet/day)
- ATTN: increased effect of coumarin derivatives

Fulvestrant

Chem: 7-Alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl) nonyl]estra-1,3,5-(10)-triene-3,17-beta-diol, estradiol analog, steroidal antiestrogen



MOA:
- Competitive binding to estrogen receptors without estrogen like activity → complete blocking of all estrogen effects, with simultaneous downregulation of estrogen receptors
- No cross-resistance to classic antiestrogens

Pkin:
- *Kinetics:* slow distribution following intramuscular injection, peak plasma level after 7–9 days, half-life: t½ 40 h
- *Metabolism:* hepatic degradation (in part by cytochrome P450 3A4 system), predominantly biliary elimination

Se:
- *Bone marrow:* anemia (10%)
- *Cardiovascular:* venous thrombosis (rare)
- *Lung:* dyspnea, pharyngitis, cough
- *Gastrointestinal:* nausea, vomiting, diarrhea, loss of appetite, up to 50% of patients
- *Liver:* transient increase of transaminases
- *Skin:* erythema, exanthema, angioneurotic edema, urticaria
- *Nervous system:* headaches (15%), vertigo, sleep disturbances, depression
- *Local toxicity:* injection site (reactions)
- *Other:* fatigue (65%), reduced performance, hot flushes (25%), back pain, arthralgia. In rare cases flu-like symptoms

Ci:
- Pregnancy and breast feeding
- Severe liver dysfunction

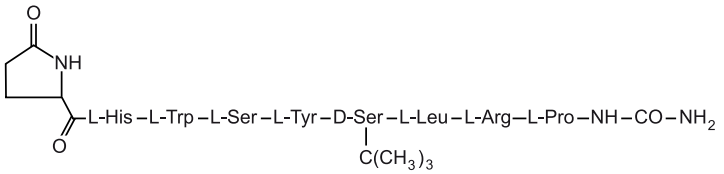
Th: *Approved indications:* estrogen receptor positive breast cancer in postmenopausal women

Dosage and Administration

Intramuscular injection of 250 mg (5 ml) monthly

Goserelin

Chem: 1-(5-Oxo-l-prolyl- l-histidyl- l-tryptophyl- l-seryl- l-tyrosyl- l-*O*-tert-butyl-d-seryl- l-leucyl- l-arginyl- l prolyl)semicarbazide, GnRH analog



MOA: GnRH / LHRH analog with continuous stimulation of pituitary receptors → desensitization of pituitary gland → LH / FSH secretion ↓ → estrogen / testosterone synthesis ↓ ("drug-induced castration")

Pkin:
- *Kinetics:* subcutaneous injection, slow-release drug with slow resorption for 27 days, half-life t½ 4–5 h
- *Metabolism:* renal elimination of original compound

Se:
- *Cardiovascular:* hypertension
- *Gastrointestinal:* constipation, nausea, vomiting, loss of appetite
- *Liver:* transient increase of transaminases, hypercholesterolemia
- *Kidney:* hypercalcemia
- *Skin:* erythema, exanthema, perspiration, acne, seborrhea, allergic reactions (rare)
- *Nervous system:* headaches (75%), vertigo, sleep disturbances, somnolence, depression
- *Bones:* osteoporosis, bone pain (rare)
- *Other:* fatigue, reduced performance. In men: hot flushes (60%), gynecomastia, impotence, loss of libido. In women: amenorrhea, uterine bleeding

Ci:
- Pregnancy and lactation
- Not for use in children

Th: *Approved indications:* advanced prostate cancer, endometriosis, metastatic breast cancer

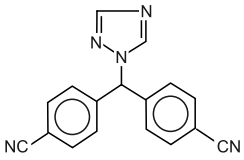
Dosage and Administration

Subcutaneous injection monthly 3.6 mg, or every 3 months 10.8 mg

ATTN: short initial stimulation of estrogen or testosterone excretion, prior to hormone blockage → simultaneous antiestrogen / antiandrogen treatment for initial 3–4 weeks recommended

Letrozole

Chem: 4,4'-(1H-1,2,4-Triazol-1-ylmethylene)dibenzonitrile, non-steroidal aromatase inhibitor



MOA:
- Competitive aromatase inhibition → conversion of androgens into estrogens ↓ → estradiol serum level ↓
- No gestagenic, androgenic, or estrogenic effect. No influence on corticosteroid or aldosterone synthesis

Pkin: *Kinetics:* good oral resorption (85%), independent of food intake, half-life: t½ 2 days
Metabolism: hepatic degradation, glucuronidation, predominantly renal excretion of original compound (5%) and metabolites (> 80%)

Se:
- *Cardiovascular:* vasodilatation (25%), tachycardia, thromboembolic events (rare)
- *Lung:* dyspnea, cough
- *Gastrointestinal:* nausea (15%), vomiting, diarrhea, loss of appetite
- *Liver:* transient increase of transaminases, hypercholesterolemia
- *Skin:* erythema, exanthema, pruritus, perspiration
- *Nervous system:* headaches (10%), depression, anxiety disorders
- *Other:* fatigue (10%), reduced performance, flush, pain syndromes (thoracic region, back, joints, myalgia)

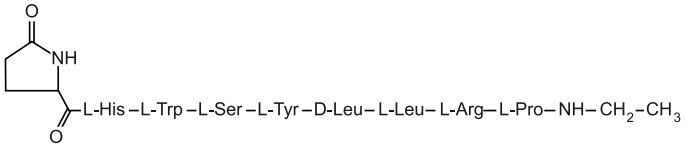
Ci:
- Premenopausal women
- Pregnancy and breast feeding
- Liver dysfunction, renal failure

Th: *Approved indications:* advanced breast cancer in postmenopausal women. Adjuvant treatment of estrogen receptor positive breast cancer

Dosage and Administration
- Oral administration, 2.5 mg (1 tablet) daily
- Dose reduction in severe liver or renal function impairment

Leuprorelin

Chem: 5-Oxo-l-prolyl- l-histidyl- l-tryptophyl- l-seryl- l-tyrosyl- d- leucyl - l-leucyl- l-arginyl- *N*-ethyl-l-prolinamide, GnRH analog



MOA: GnRH / LHRH analog with continuous stimulation of pituitary receptors → desensitization of pituitary gland → LH / FSH secretion ↓ → estrogen / testosterone synthesis ↓ ("drug-induced castration")

Pkin:
- *Kinetics:* subcutaneous injection, slow-release drug, half-life t½ 2–4 h
- *Metabolism:* hepatic degradation, biliary and renal elimination

Se:
- *Bone marrow:* anemia, leucopenia (rare)
- *Cardiovascular:* ECG changes (20%), hypertension, peripheral edema, thromboembolic events
- *Gastrointestinal:* constipation, nausea, vomiting, loss of appetite
- *Liver:* transient increase of transaminases, hypercholesterolemia
- *Kidney:* hypercalcemia (rare)
- *Skin:* erythema, exanthema, perspiration, acne, seborrhea, allergic reactions (rare)
- *Nervous system:* headaches, vertigo, sleep disturbances, somnolence, depression
- *Bone:* osteoporosis, bone pain (rare)
- *Other:* fatigue, reduced performance. In men: hot flushes (50%), gynecomastia (35%) impotence, loss of libido. In women: amenorrhea, uterine bleeding

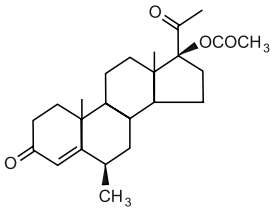
Ci:
- Pregnancy and lactation
- Not for use in children (except girls with precocious puberty vera)

Th: *Approved indications:* breast cancer, endometriosis, uterus myomatosis
Other areas of use: prostate cancer

Dosage and Administration
- 3.75 mg monthly, or 11.25 mg every 3 months i.m. (dual-chamber injection)
- ATTN: short initial stimulation of estrogen or testosterone excretion, prior to hormone blockage → simultaneous antiestrogen / antiandrogen treatment for initial 3–4 weeks recommended

Medroxyprogesterone acetate, MPA

Chem: 17-Hydroxy-6α-methyl-4-pregnene-3,20-dione, gestagen



MOA:
- Gestagen and androgenic activity
- Reduction of pituitary FSH / LH secretion
- Stimulation of estrogen and androgen degradation

Pkin:
- *Kinetics:* oral or intramuscular administration, oral bioavailability 10%, following intramuscular administration stable plasma levels for 7 days, terminal t½ 14–60 h
- *Metabolism:* hepatic degradation, biliary and renal elimination of original compound and metabolites

Se:
- *Cardiovascular:* edema, arterial hypertension, thromboembolic events
- *Gastrointestinal:* nausea, vomiting, diarrhea, constipation
- *Liver:* transient increase of transaminases, cholestasis
- *Skin:* alopecia, dermatitis, acne, hirsutism (rare)
- *Nervous system:* headaches, sleep disturbances, tremor, depression, mania
- *Other:* fatigue, reduced performance, cramps, development of diabetes mellitus, allergic reactions, anaphylaxis. In men: gynecomastia, breast pain, galactorrhea, hot flushes. In women: menstrual disorders, amenorrhea

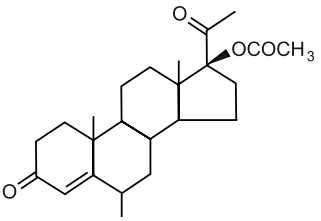
Ci:
- Pregnancy and lactation
- Previous thromboembolic events or stroke
- Severe liver or renal impairment, hypercalcemia
- Severe hypertension, diabetes mellitus

Th: *Approved indications:* metastatic breast cancer, advanced endometrial cancer
Other areas of use: advanced renal cancer

Dosage and Administration
- *Breast cancer:* 300–1,500 mg/day p.o, or 500–1,000 mg/week i.m. for 28 days, followed by maintenance dose (according to plasma level, goal > 100 ng/ml)
- *Endometrial cancer:* 300–600 mg/day p.o. or 500–1,000 mg/week i.m.

Megestrol acetate

Chem: 6-Methyl-3,20-dioxo-4,6-pregnadiene-17α-yl-acetate, gestagen



MOA:
- Gestagen and androgenic activity
- Reduction of pituitary FSH / LH secretion
- Stimulation of estrogen and androgen degradation

Pkin:
- *Kinetics:* oral administration, good oral bioavailability, terminal t½ 15–20 h
- *Metabolism:* hepatic degradation, renal elimination of original compound and metabolites

Se:
- *Cardiovascular:* edema, arterial hypertension, thromboembolic events
- *Gastrointestinal:* nausea, vomiting, diarrhea, constipation
- *Liver:* transient increase of transaminases
- *Skin:* alopecia, erythema
- *Nervous system:* headaches, carpal tunnel syndrome
- *Other:* fatigue, reduced performance. Development of diabetes mellitus, hypercalcemia. In men: gynecomastia, breast pain, galactorrhea, hot flushes. In women: menstrual disorders, amenorrhea

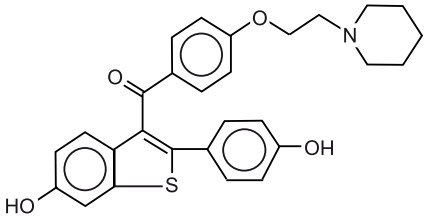
Ci:
- Pregnancy and lactation
- Previous thromboembolic events or stroke
- Severe liver or renal impairment, hypercalcemia
- Severe hypertension, diabetes mellitus

Th: *Approved indications:* metastatic breast cancer, advanced endometrial cancer
Other areas of use: cancer-induced cachexia

Dosage and Administration
- Oral administration, 160 (–320) mg/day p.o. in breast and endometrial cancer
- In cancer-induced cachexia, doses up to 400–800 mg/day have been applied

Raloxifene

Chem: 6-Hydroxy-2-(4-hydroxyphenyl)benzol[b]thiene-3-yl-4-(2-piperidinoethoxy)phenylketone, nonsteroidal antiestrogen



MOA:
- Competitive binding to cytoplasmic estrogen receptors, selective agonistic and antagonistic effects (selective estrogen receptor modulation, SERM): estradiol ↓ TGFβ ↑, TGFα ↓, EGF receptor expression ↓, IL-2 secretion ↑
- Agonist of bone and cholesterol metabolism
- No effect on pituitary gland, breast, or uterus tissue

Pkin: *Metabolism:* hepatic degradation, renal elimination

Se:
- *Cardiovascular:* vasodilatation, hypertension, venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- *Gastrointestinal:* nausea, vomiting, dyspepsia
- *Skin:* erythema, exanthema
- *Nervous system:* headaches
- *Musculoskeletal:* calf cramps
- *Other:* hot flushes, breast pain, vaginitis

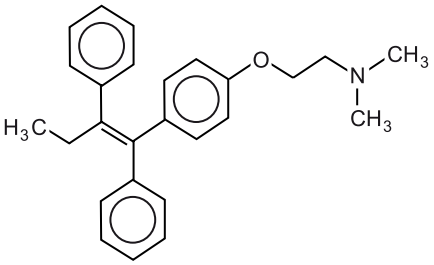
Ci:
- Use in premenopausal women
- Previous thromboembolic events
- Liver function impairment, cholestasis, renal impairment
- Endometrial cancer, uterine bleeding of unknown origin

Th: *Approved indications:* osteoporosis in postmenopausal women
Other areas of use: hormone-dependent breast cancer in postmenopausal women

Dosage and Administration
60 mg/day p.o.

Tamoxifen

Chem: (Z)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxyl]-N,N-dimethylethylamine, non-steroidal antiestrogen



MOA:
- Competitive inhibition of estrogen binding to cytoplasmic estrogen receptors, selective agonistic and antagonistic effects (selective estrogen receptor modulation, SERM), in estrogen-dependent tissues inhibition of proliferation. Estradiol ↓ TGFβ ↑, TGFα ↓, EGF receptor expression ↓, IL-2 secretion ↑
- Agonist of bone and cholesterol metabolism

Pkin:
- *Kinetics:* high bioavailability following oral administration, enterohepatic circulation, terminal t½ 7 days
- *Metabolism:* hepatic degradation, biliary elimination

Se:
- *Bone marrow:* mild thrombocytopenia, leucopenia (5%)
- *Cardiovascular:* edema, thromboembolic events (rare)
- *Gastrointestinal:* loss of appetite, nausea (5–20%), vomiting
- *Liver:* transient increase of transaminases, cholestasis, hypertriglyceridemia
- *Skin:* rash, mild alopecia, erythema multiforme
- *Nervous system:* visual disturbances (cataract, corneal changes, retinopathy), headaches
- *Musculoskeletal:* calf cramps
- *Other:* in patients with bone metastases hypercalcemia possible, hot flushes (25–30%), in premenopausal women menstrual cycle disturbances, endometrial proliferation (polyps, malignancies)

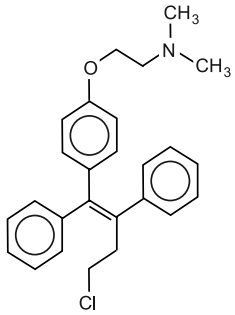
Ci:
- Known hypersensitivity, children
- Severe thrombocytopenia or leucopenia
- Hypercalcemia
- History of thromboembolic events
- Endometrial cancer, uterine bleeding of unknown origin

Th: *Approved indications:* osteoporosis in postmenopausal women
Other areas of use: breast cancer (adjuvant, advanced) hormone dependent

Dosage and Administration
20–40 mg/day p.o.

Toremifene

Chem: 2-{4-[(Z)-4 Chlor-1,2-diphenyl-1-butenyl]phenoxyl}-N,N-dimethyl-ethylamine, non-steroidal antiestrogen



MOA:
- Competitive inhibition of estrogen binding to cytoplasmic estrogen receptors, selective agonistic and antagonistic effects (selective estrogen receptor modulation, SERM), in estrogen-dependent tissues inhibition of proliferation. Estradiol ↓ TGFβ ↑, TGFα ↓, EGF receptor expression ↓, IL-2 secretion ↑
- Agonist of bone and cholesterol metabolism
- Cytostatic effect

Pkin:
- *Kinetics:* high bioavailability following oral administration, enterohepatic circulation, albumin binding (92%), terminal t½ 5–6 days
- *Metabolism:* hepatic degradation, biliary elimination

Se:
- *Bone marrow:* mild thrombocytopenia, leucopenia
- *Cardiovascular:* edema, thromboembolic events (rare)
- *Gastrointestinal:* nausea, vomiting, loss of appetite
- *Liver:* transient increase of transaminases, cholestasis
- *Skin:* pruritus, erythema
- *Nervous system:* vertigo, sleep disturbances, tiredness, headaches
- *Other:* Hot flushes (10–30%), perspiration, vaginal bleeding / fluor, bone pain, hypercalcemia, endometrial proliferation (rare)

Ci:
- Endometrial cancer, uterine bleeding of unknown origin
- History of thromboembolic events
- Severe liver impairment

Th: *Approved indications:* metastatic breast cancer, hormone dependent

Dosage and Administration

60 mg/d p.o.

3.4 Cytokines

A.K. Kaskel, H. Veelken

Def: Intercellular mediators synthesized by immune cells and mesenchymal cells (fibroblasts, endothelial cells, stroma cells) which modulate immune responses, cellular proliferation, and differentiation. Characteristics:

- Soluble proteins or glycoproteins, 15–40 kDa molecular weight
- Pleiotropic, overlapping, and/or synergistic effects

Class: **Cytokines**

Factor	Characterization
Interleukins (IL):	
IL-1	Inflammation mediator
IL-2	T-cell expansion and activation, IL-2 receptor expression ↑
IL-3	Proliferation of pluripotent stem cells
IL-4	B-/T-cell proliferation / differentiation, TH2 cells ↑, dendritic cells ↑
IL-5	Activation and differentiation of eosinophils
IL-6	Acute-phase reaction, thrombopoiesis stimulation
IL-7	Lymphopoiesis induction, T-cell proliferation / differentiation
IL-8	Activation / chemotaxis of neutrophils
IL-9	B-cell activation, antibody production
IL-10	Suppression of macrophage function, TH2 induction
IL-11	Inflammation mediator, thrombopoiesis stimulation
IL-12	T-cell activation / differentiation, TH1 induction
IL-13	B-cell activation / differentiation, dendritic cells ↑
IL-14	B-cell proliferation / differentiation
IL-15	T-/NK cell activation/differentiation
IL-16	CD4 ligand, inflammation mediator
IL-17	Cytokine secretion by mesenchymal cells ↑
IL-18	"IFNγ-inducing factor," inflammation mediator
IL-19	Secretion of IL-6 and TNFα in monocytes ↑, proapoptotic
IL-20	Proliferation of keratinocytes ↑, mediator of inflammation
IL-21	B-cell apoptosis, production of IFNγ ↑ in T- and NK cells
IL-22	"T-cell-derived inducible factor," inflammation mediator
IL-23	Associated with TH1 response, IL-12 secretion ↑
IL-24	Growth-inhibiting, proapoptotic in tumor cell lines
IL-25	Associated with TH2 response, IL-4, IL-5, IL-13 ↑, eosinophils
IL-26	T- and NK cells
IL-27	Proliferation of naive CD4 cells, TH1 differentiation
IL-28	Antiviral activity
IL-29	Antiviral activity

Hematopoietic growth factors ► Chap. 4.3

Class: **Cytokines *(continued)***

Factor	Characterization
Interferons (IFN) and other:	
IFNα	Antiproliferative, antiviral
IFNβ	Antiproliferative, antiviral
IFNγ	Antiproliferative, antiviral, monocyte stimulation
TNFα	Tumor necrosis factor α (cachectin), inflammation mediator
TNFβ	Tumor necrosis factor β (= lymphotoxin α, LTα), inflammation mediator

Hematopoietic growth factors ► Chap. 4.3

Interferon α (IFNα)

Chem: Type 1 interferon, "leukocyte interferon"; glycoprotein, > 20 variants, 156–172 amino acids, 19–26 kDa. Peginterferon is a polyethylene-glycol conjugated form with an increased half-life.

Phys:
- *Gene locus:* chromosome 9p22, variable expression of IFNα variants
- *Expression:* leukocytes, monocytes / macrophages, B-lymphocytes, fibroblasts

MOA: All IFNα types display antiviral, antiparasitic, and antiproliferative activity:
- *T-cells:* T-suppressor activity, activation of cytotoxic T-cells, TH1 induction
- Modulation of B- and NK cell function, monocyte activation / macrophages
- Antigen expression ↑, oncogene expression ↓, inhibition of angiogenesis

Pkin:
- *Kinetics:* half-life: terminal t½ $IFN\alpha_{2a}$: 4–8 h, $IFN\alpha_{2b}$: 2–3 h, peg-IFN: 40–80 h
- *Metabolism:* proteolysis, renal elimination

Se:
- *Bone marrow:* moderate anemia, granulocytopenia, thrombocytopenia
- *Thyroid gland:* hyper/hypothyroidism (partly irreversible), thyroiditis
- *Cardiovascular:* arrhythmia, myocardial infarction, cardiomyopathy, cardiac failure, hypotension, hypertension, hemorrhages, cerebrovascular disorders
- *Pulmonary:* cough, dyspnea, pulmonary edema, pneumonia
- *Gastrointestinal tract:* moderate nausea, diarrhea, loss of appetite
- *Liver / pancreas:* reversible increase of transaminases, hyperglycemia
- *Kidney:* fluid retention, edema, hypocalcemia
- *Skin:* erythema, pruritus, dry skin, scaling, alopecia
- *Nervous system:* central nervous disorders, depression (increased risk of suicide), dizziness, insomnia, somnolence, peripheral neuropathy, paresthesia, optic neuritis
- *Other:* flu-like symptoms (fever, sweating, chills, fatigue), myalgia, arthralgia, headaches, arthritis

Ci:
- Human protein allergy, autoimmune diseases, immunosuppression
- Severe cardiopulmonary or vascular disease
- Severe hepatic or renal dysfunction
- Diseases of the central nervous system
- Untreated hyper/hypothyroidism (TSH / T3 / T4 evaluation before treatment)
- Severe bone marrow damage
- Lactation, pregnancy (effective contraception during treatment)

Th: *Indications:* chronic active hepatitis B/C, CML, NHL, multiple myeloma, melanoma, Kaposi's sarcoma, renal cell carcinoma
Clinical trial use: solid tumors, myeloproliferative syndromes

Dosage: application s.c., i.v., or i.m., e.g.:
- IFNα 2–9 × 10^6 IU/day, 3–7 × per week, slowly increasing dose
- High-dose IFNα up to 20 × 10^6 IU/m^2/day
- PEGylated IFNα 40–150 µg once a week with hepatitis C

ATTN: Patients on high-dose IFNα treatment need to be closely monitored. Chest x-ray if cough or dyspnea develop. Laboratory tests including full blood count, liver and renal function, blood glucose. Development of antibodies possible.

Interferon β (IFNβ)

Chem: Type 1 interferon, "fibroblast interferon"; glycoprotein, 166 amino acids, 20 kDa

Phys:
- *Gene locus:* chromosome 9p22, close to interferon α gene group
- *Expression:* fibroblasts

MOA: Antiviral, antiparasitic, antiproliferative, and immune-modulating properties like interferon α, T-suppressor-cell activation

Pkin:
- *Kinetics:* terminal half-life $IFN\beta_{1a}$ 8–10 h, $IFN\beta_{1b}$ 1–4 h
- *Metabolism:* proteolysis, renal excretion

Se:
- *Bone marrow:* granulocytopenia, lymphopenia, thrombocytopenia (rare), anemia
- *Cardiovascular:* arrhythmia, tachycardia, hypotension, hypertension
- *Gastrointestinal:* nausea, vomiting, loss of appetite, stomatitis
- *Liver:* transient increase of transaminases
- *Kidney:* urea ↑, creatinine ↑
- *Skin:* exanthema, pruritus, alopecia, dry skin, injection site reactions, re-activation of herpes virus infections
- *Nervous system:* central nervous disorders, paresthesia, neuropsychiatric changes (depression, somnolence, confusion, risk of suicide) possible
- *Other:* flu-like symptoms: fever, sweating, chills, fatigue, myalgia, arthralgia, headaches (may be treated with paracetamol)

ATTN: Close monitoring of patients when using high dose. Possible antibody formation against recombinant IFNβ. Single cases of rapidly progressing glomerulonephritis after combined treatment with IFNβ and interleukin 2.

Ci:
- Human protein allergy
- Pre-existing cardiac disease
- Severe hepatic dysfunction, renal insufficiency

Th: *Indications:* multiple sclerosis, severe viral disease (e.g., encephalitis, generalized *Herpes zoster*)
Clinical trial use: nasopharyngeal carcinoma, other solid tumors, cutaneous T-cell lymphomas

Dosage: s.c. or i.v. application, e.g.:
- $0.5–5 \times 10^6$ IU/day i.v., 3–6 × per week, maximum 25×10^6 IU/day
- With multiple sclerosis: 44 μg $IFN\beta_{1a}$ i.m. 3 × per week

Interferon γ (IFNγ)

Chem: Type 2 interferon, "T-lymphocyte interferon"; protein dimer, subunits of 146 amino acids, 6 variants, 20–25 kDa

Phys:
- *Gene locus:* chromosome 12q24.1
- *Expression:* T-cells, NK cells

MOA: Antiviral, antiparasitic, and proliferation-modulating properties:
- *T-cells:* stimulation of proliferation, modulation of T-cell differentiation, activation of cytotoxic T-cells, and induction of IL-2 receptors
- *B-cells:* induction of immunoglobulin synthesis
- *Monocytes / macrophages, NK cells:* activation
- Stimulation of MHC class I *and* class II antigen expression, modulation (increase) of tumor antigen expression
- Modulation of hematopoiesis and lipid metabolism

Pkin:
- *Kinetics:* half-life: s.c. application: 6 h, i.m.: 3 h, i.v.: 38 min
- *Metabolism:* proteolysis, renal excretion

Se:
- *Bone marrow:* moderate leukopenia, anemia (rare)
- *Cardiovascular:* arrhythmias, tachycardia, hypotension, hypertension, thromboembolic events (rare), myocardial infarction
- *Gastrointestinal:* nausea, vomiting, diarrhea, loss of appetite
- *Liver:* transient increase of transaminases
- *Kidney:* urea ↑, creatinine ↑
- *Skin:* exanthema, pruritus, injection site reactions
- *Nervous system:* central nervous system disorders, hallucinations, depression, confusion, tremor, impaired vision, paresthesias
- *Other:* flu-like symptoms: fever, sweating, chills, fatigue, myalgia, arthralgia, headaches (may be treated with paracetamol)

Ci:
- Human protein allergy
- Severe cardiovascular disease
- CNS disorders, epilepsy
- Severe hepatic dysfunction, renal insufficiency

Th: *Indications:* progressive septic granulomatosis (chronic granulomatous disease, CGD)
Clinical trial use: invasive aspergillosis, infection with mycobacteria, solid tumors (renal cell carcinoma, pleural mesothelioma)

Dosage: application s.c., i.m., or i.v., usually
- Progressive septic granulomatosis (CGD): 50 μg/m²/day s.c. 3 × per week
- Renal cell carcinoma: 50–100 μg s.c. once a week

Interleukin 2 (IL-2), Aldesleukin

Chem: Glycoprotein, 133 amino acids, 15 kDa

Phys:
- *Gene locus:* chromosome 4q26-28
- *Expression:* T-cells (CD4+)

MOA:
- *T-cells:* proliferation, clonal expansion, chemotaxis, activation, induction of non-MHC restricted cytotoxic T-cells, binding to IL-2 receptor
- *B- and NK cells:* proliferation, differentiation, activation
- Induction / release of several other cytokines (interferon γ)
- Stimulation of cytotoxic tumor infiltrating monocytes / macrophages

Pkin:
- *Kinetics:* rapid distribution after parenteral administration, terminal half-life t½ 30–90 min
- *Metabolism:* proteolysis, renal elimination

Se:
- *With high-dose treatment:* capillary leak syndrome (dose-limiting), neurological / renal / gastrointestinal / cardiovascular symptoms
- *Bone marrow:* anemia, thrombocytopenia, leukopenia, eosinophilia
- *Cardiovascular:* hypotension, edema, endocarditis, cardiac arrhythmias, angina pectoris, cardiac arrest, thromboembolic events
- *Pulmonary:* dyspnea, pulmonary edema, cough, hemoptysis, ARDS, bronchospasm
- *Gastrointestinal:* nausea, vomiting, diarrhea, mucositis, gastritis, gastrointestinal hemorrhage, constipation, meteorism, loss of appetite
- *Kidney:* oligo- / anuria, interstitial nephritis, acute renal failure, hypocalcemia
- *Liver / pancreas:* transient increase of transaminases, hyperglycemia
- *Skin:* pruritus, dermatitis, alopecia, conjunctivitis
- *Nervous system (central and peripheral neuropathy):* depression, confusion, agitation, hallucination, neuralgia, paresthesia, sensory and motor dysfunction, seizures, somnolence, coma
- *Cerebrovascular disorders:* TIA, cerebral hemorrhage, cerebral infarction
- *Other:* flu-like symptoms: fever, sweating, chills, fatigue, myalgia, arthralgia, headaches

ATTN: Nephrotoxic, cardiotoxic, and myelotoxic drugs and hypertensives can enhance the side effects. Glucocorticoids decrease the effects of IL-2.
High-dose IL-2 treatment only under strict monitoring: cardiovascular system, neurostatus, renal function, liver function, full blood count, thyroid function.

Ci:
- Performance status ECOG > 2, cerebral metastasis
- Human protein allergy, severe infections
- Severe cardiovascular or pulmonary disorders (pO_2 < 60 mmHg)
- Lactation, pregnancy (strict contraception is mandatory)

Th: *Indications:* metastatic renal cell carcinoma
Clinical trial use: malignant melanoma, NHL, solid tumors, donor lymphocyte infusion after allogeneic transplantation, AIDS-associated malignancies

Dosage and administration: i.v. or s.c., e.g.:
- Continuous infusion: 3–24 × 10^6 IU/m^2/day (18 × 10^6IU = 1 mg) c.i.v. for 2–5 days
- S.c.: 1–5 × 10^6 IU/m^2/day s.c. once or several times a week

Interleukin 11 (IL-11)

Chem: Protein, 178 amino acids, 19 kDa

Phys:
- *Gene locus:* chromosome 19q13.3-q13.4
- *Expression:* bone marrow fibroblasts, various mesenchymal and epithelial cell types (e.g., bronchial / alveolar and gastrointestinal epithelial cells, osteoblasts, CNS)

MOA:
- *Inflammation mediator* (mainly in lung)
- *Hematopoiesis:* synergistically with other cytokines, stimulation of megakaryopoiesis, erythropoiesis, myelopoiesis, lymphopoiesis, and (in vitro) bone marrow stroma cells, increase of thrombocytes usually 5–9 days after application
- *Gastrointestinal:* in vitro inhibition of the proliferation of intact crypt stem cells, in vivo stimulation of proliferation / apoptosis inhibition in damaged crypt cells
- *Other:* adipogenesis inhibitor, modulator of the metabolism of extracellular matrix (fibrosis-enhancing)

Pkin:
- *Kinetics:* rapid distribution after s.c. application, terminal half-life: t½ 7 h
- *Metabolism:* proteolysis, renal excretion

Se: Usually, only mild and transient side effects:
- *Cardiovascular:* supraventricular arrhythmias, tachycardia
- *Pulmonary:* dyspnea, pulmonary edema, cough, pleural effusion
- *Gastrointestinal:* nausea / vomiting, diarrhea
- *Kidney:* fluid retention → dilution anemia, electrolyte imbalance, effusions, edema, papillary edema (visual disturbances)
- *Skin:* erythema
- *Nervous system:* amentia, insomnia, headache
- *Other:* flu-like symptoms, increase of acute phase proteins, anaphylaxis

Ci:
- Cardiac insufficiency, absolute arrhythmia
- Electrolyte / fluid imbalance

Th: *Indications:* prevention of severe thrombocytopenia and reduction of the need for platelet transfusions following myelosuppressive chemotherapy (USA)

Dosage: 50 µg/kg body weight/day s.c., application 6–24 h after chemotherapy, daily application until thrombocytes > 50,000/µl, maximum 21 days

Tumor Necrosis Factor α (TNFα)

Chem: 157 amino acids, 17.3 kDa

Phys:
- *Gene locus:* chromosome 6 (within MHC complex)
- *Expression:* activated monocytes, macrophages

MOA:
- *Inflammation mediator:* induction of cytokines and low molecular weight mediators (prostaglandin, PaF) ↑, leukocyte migration ↑
- *B- and T-cells:* proliferation and activation, phagocytosis / cytotoxicity ↑
- *Vascular effect:* endothelial cell proliferation ↓, vessel wall damage, modulation of adhesion molecule and cytokine expression → local procoagulant effects → microthrombosis

Pkin:
- *Kinetics:* half-life dose-dependent, i.v. application of 150 μg/m²: 15–30 min

Se:
- *Bone marrow:* leukopenia, anemia, thrombocytopenia
- *Cardiovascular:* hypotension and tachycardia, arrhythmia, shock
- *Kidney:* acute renal failure
- *Nervous system:* central nervous system disorders, peripheral neuropathy
- *Other:* flu-like symptoms (fever, chills, sweating, fatigue, nausea), thromboembolic events, DIC (disseminated intravascular coagulation) in isolated cases

Ci:
- Severe cardiovascular or pulmonary diseases, simultaneous treatment with cardiotoxic drugs
- Peptic ulcer, severe ascites, limited bone marrow function
- Renal or hepatic dysfunction, hypercalcemia

Th: *Indications:* isolated limb perfusion in combination with melphalan and hyperthermia in non-resectable soft tissue sarcoma

ATTN: Isolated limb perfusion must be carried out in specialized centers under intensive surveillance and permanent monitoring of systemic drug concentrations (objective: leakage of drugs into the systemic circulation < 10%).

Dosage: i.v. application for isolated limb perfusion in combination with chemotherapy (e.g., melphalan), 3–4 mg TNFα per liter of perfused volume (maximum 150 mg)

Ref:

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Web:

1.	http://www.weizmann.ac.il/cytokine	International Cytokine Society
2.	http://www.sciencedirect.com/science/journal/10434666	Cytokines Journal
3.	http://www.elsevier.com/wps/product/cws_home/868	Cytokine Growth Factor Reviews
4.	http://cytokine.medic.kumamoto-u.ac.jp	Cytokine Family Database

3.5 Monoclonal Antibodies

K. Potthoff, H. Veelken

Def: Monoclonal immunoglobulin preparations with specific effects directed against defined target structures (antigens). Monoclonal antibody production is usually based on "recombinant" DNA technology.

Antibody Nomenclature

Notations for monoclonal antibodies consist of several components and follow internationally valid systematics. In general, they are formed by one prefix and three suffixes (according to the following pattern: "prefix – suffix 1 – suffix 2 – suffix 3"):

- Suffix 1: indicating the target structure: colon ("col"), mammary ("ma"), testis ("got"), prostate ("pr" / "pro"), cardiovascular ("cir"), viral ("vir"), immune system ("lim" / "li"), infect associated ("les"), mixed / diverse tumors ("tum" / "tu")
- Suffix 2: indicating the species of origin: human ("u"), mouse ("o"), rat ("a"), hamster ("e"), primate ("i"), chimeric ("xi"), humanized ("zu")
- Suffix 3: "mab" indicating a monoclonal antibody or antibody fragment

Example: *Alem-tu-zu-mab:* humanized antibody against an antigen that is expressed by different malignant tumors.

Th:

Potential Mechanism of Action of Monoclonal Antibodies

- Competitive receptor blockade → blockage of receptor-mediated effects (e.g., inhibition of cytokines or growth factors)
- Receptor activation → induction of receptor-mediated effects (e.g., apoptosis induction)
- Complement activation and complement-mediated cytotoxicity (CDC)
- Antibody-mediated cellular cytotoxicity (ADCC)
- Conjugation of antibodies and radioactive ("radioimmunoconjugates") or cytotoxic components ("immunotoxins")

Use of Monoclonal Antibodies

Since 1998, several different monoclonal antibodies have been licensed for treatment of solid tumors and hematological neoplasias. Application as monotherapy or in combination, e.g., with chemotherapy.

Species Specificity

Antibodies are usually specific for each species. Application of murine antibodies in humans might lead to loss of effect due to generation of antibodies as well as to incompatibility reactions. Several different types of antibodies with human parts are clinically used:

- "Chimeric" antibodies: constant region of human origin, variable region (including antigen-binding site) of primary species of origin
- "Humanized" antibodies: antigen-binding region of primary species of origin, remainder of human origin (95%)
- "human" antibodies: 100% human sequence

New monoclonal antibodies in clinical trials (selection)

Compound	Target structure (cell type)	Indication
Apolizumab (Hu1D10)	HLA-DR-β-chain (B-cells, macrophages, dendritic cells)	B-NHL, CLL
Basiliximab	Interleukin-2 receptor (activated T-cells)	GVHD prophylaxis
Daclizumab	Interleukin-2 receptor α (T-cells)	T-NHL, T-cell leukemia

New monoclonal antibodies in clinical trials (selection) ***(continued)***

Compound	Target structure (cell type)	Indication
Epratuzumab	CD22 (B-cells)	B-NHL, autoimmune diseases
HuM291	CD3 (mature T-cells)	T-NHL
Infliximab	TNFα (monocytes, macrophages, lymphocytes)	GVHD treatment
^{131}I-Lym-1	HLA-DR10	B-NHL
Pertuzumab (rhuMAb-2C4)	HER dimerization (HER1/EGFR, HER1/HER4)	Solid tumors

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2. http://www.cancer.org/ — American Cancer Society
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4. http://www.fda.gov/cber/ — FDA, Center for Biologics Evaluation and Research
5. http://www.gallartinternet.com/mai — Monoclonal Antibody Index
6. http://www.cancerbackup.org.uk/treatments/biologicaltherapies/monoclonalantibodies — Cancer Backup UK
7. http://en.wikipedia.org/wiki/monoclonal_antibodies — Wikipedia, Monoclonal Antibodies

Alemtuzumab

Chem: Humanized, recombinant, monoclonal IgG1-κ antibody (rat / human), specifically binding to the CD52 antigen

MOA:
- Binding to CD52 (on B- / T- / NK cells, monocytes, macrophages)
  → complement-mediated cytotoxicity (CDC), antibody-mediated cytotoxicity (ADCC), apoptosis induction, depletion particularly of CD52-positive lymphocytes
  → peripheral T-cell depletion for 3–6 months. Recovery of CD4+ T-cells to 75% of baseline within 6–12 months after treatment
- Strong CD52 expression on T-cells → effective in T-CLL

Pkin: *Kinetics:* half-life: median t½ 12 days

Se:
- *Bone marrow:* prolonged myelosuppression (neutropenia, lymphocytopenia, thrombocytopenia, 50–70%) → infections (in 10–15% of cases, dose-limiting), esp. HSV, CMV, Candida, aspergillosis, *Pneumocystis carinii* pneumonia (PcP), mycobacterioses
- *Cardiovascular:* hypotension, hypertension, tachycardia, arrhythmia, vascular spasms
- *Pulmonary:* pneumonia, bronchitis, pulmonary edema, bronchospasms, dyspnea
- *Gastrointestinal:* nausea (50%), vomiting, diarrhea, constipation, abdominal pain, gastrointestinal hemorrhage, loss of appetite
- *Liver:* transient increase of transaminases, hyperglycemia
- *Nervous system:* headache, dysgeusia, tremor, rigor, paresthesia, dizziness, confusion, anxiety, depression, insomnia
- *Infusion-induced reactions:* fever (85%), chills, hot flushes, sweating, erythema, urticaria, pruritus, rhinitis, conjunctivitis, sore throat, angioedema
- *Other:* night sweat, fatigue, reduced performance status, peripheral edemas, arthralgia, myalgia, bone pain, LDH ↑, coagulation disorders

Ci:
- Hypersensitivity to murine proteins
- Severely impaired cardiac, renal, or hepatic function
- Florid systemic infections, immune deficiency, HIV infection
- Pregnancy, lactation

Th: *Indications:* CLL, second line treatment
Clinical trial use: first-line and consolidation therapy for CLL, T-cell NHL, T-cell depletion in GVHD prophylaxis, ITP, immunocytopenia

Dosage: i.v. application (infusion over 2 h), with dose escalation:
- Week 1: 3 mg i.v. day 1, 10 mg i.v. day 2, 30 mg i.v. day 3; weeks 2–12: 30 mg i.v. 3 × per week, over 4–12 weeks
- ATTN: risk of severe infusion-induced reactions including fever, chills, thrombocytopenia, decrease of blood pressure, tumor lysis syndrome. Premedication with paracetamol and antihistamines (e.g., clemastine). No dose escalation in case of severe infusion-associated side effects. Close monitoring of vital parameters
- Infection prophylaxis with cotrimoxazole and virustatics from day 8 until CD4 cell count is ≥ 200/µl

Bevacizumab

Chem: Chimeric, recombinant, monoclonal IgG1 antibody (mouse / human), specifically binding to VEGF (vascular endothelial growth factor)

MOA:
- VEGF binds to VEGF receptors (VEGF-R1, -R2, -R3) on endothelial cells → endothelial cell proliferation → development of blood vessels (angiogenesis)
- Bevacizumab binds to VEGF → inhibiting VEGF-VEGF receptor binding (esp. VEGF-R1 = Flt-1 and VEGF2 = KDR) → inhibiting tumor neoangiogenesis → inhibiting tumor growth and metastasis

Pkin: *Kinetics:* median half-life t½ 20 days (11–50 days)

Se:
- *Bone marrow:* leukopenia and anemia (rare)
- *Cardiovascular:* hypotension, hypertension, cardiac insufficiency (esp. in combination with anthracyclines), myocardial infarction, thromboembolic events
- *Pulmonary:* cough, bronchitis, pneumonia, hemoptysis (esp. in patients with squamous cell carcinoma), dyspnea
- *Gastrointestinal tract:* nausea, vomiting, diarrhea, constipation, mucositis, gastrointestinal perforation (2–4%), abdominal pain, loss of appetite
- *Liver:* transient increase of transaminases, cholestasis
- *Kidney:* proteinuria (15–30%), nephrotic syndrome, hypocalcemia, hyponatremia
- *Nervous system:* headache, tumor pain, dizziness, syncopes
- *Infusion-induced reactions ("cytokine release syndrome"):* fever, chills, hot flushes, rigor, urticaria, pruritus, rhinitis, sore throat, dyspnea, bronchospasm, stridor
- *Other:* hemorrhages (epistaxis, hemoptysis, gastrointestinal bleeding), fatigue, reduced performance status, infections, myalgia, arthralgia, peripheral edema

Ci:
- Hypersensitivity to mouse proteins, severe cardiac disease
- Increased risk for bleeding or previous hemorrhages
- Uncontrolled hypertension
- Pregnancy, lactation

Th: *Indications:* metastatic colorectal carcinoma, non-small cell lung cancer
Clinical trial use: breast cancer, ovarian cancer, glioblastoma, pancreatic carcinoma, renal cell carcinoma

Dosage: i.v. application over 90 min
- 5 mg/kg i.v. every 2 weeks, initial intravenous infusion over 90 min, consecutive infusions over 30–60 min
- ATTN: application at the earliest 28 days following surgery (impaired wound healing)

Cetuximab

Chem: Recombinant, monoclonal, chimeric IgG1 antibody (mouse / human), high affinity binding to the extracellular domain of human epidermal growth factor receptor 1 (EGF-R1, HER1)

MOA: Binding to EGF-R1 (on solid tumor cells):
- Inhibition of endogenous ligands (EGF, TGFα), competitive inhibition of EGF-R1-tyrosine kinase, signal transduction ↓
- Receptor internalization and downregulation
- Antibody-mediated cytotoxicity, apoptosis induction, tumor neoangiogenesis ↓
- Inhibition of tumor growth and metastasis

Pkin: *Kinetics:* median half life t½: 60–100 h with standard dose

Se:
- *Bone marrow:* moderate myelosuppression
- *Cardiovascular:* hypertension, hypotension, tachycardia
- *Pulmonary:* dyspnea, bronchospasm, stridor
- *Gastrointestinal:* nausea / vomiting, diarrhea (esp. in combination with irinotecan), constipation, abdominal pain, loss of appetite
- *Liver:* transient increase of transaminases
- *Nervous system:* headache, insomnia
- *Skin:* acne-like eczema, nail changes (up to 80%, reversible), skin dryness, pruritus, alopecia (rare)
- *Infusion-induced reactions:* severe hypersensitivity reactions (5%) during or 1 h after first infusion, with pulmonary obstruction (bronchospasm, stridor, hoarseness), hypotension, fever, chills, urticaria, exanthema
- *Other:* fatigue, reduced performance status, infections, headache, peripheral edema

Ci:
- Hypersensitivity to cetuximab
- Pregnancy, lactation

Th: *Indications:* metastasized colorectal carcinoma, head and neck cancer
Clinical trial use: breast cancer, non-small cell lung cancer

Dosage: i.v. application:
- Initially 400 mg/m² i.v. over 2 h
- Consecutive infusions: 250 mg/m² i.v. over 1 h
- EGFR expression analysis in tumor tissue recommended prior to treatment (e.g., immunohistochemistry)
- ATTN: risk of infusion-induced reaction with fever, chills, thrombocytopenia, hypotension, tumor lysis syndrome. Premedication with paracetamol 500–1,000 mg p.o. and antihistamines (e.g., clemastine 2 mg i.v.) recommended

Eculizumab

Chem: Recombinant humanized monoclonal $IgG_{2/4}\kappa$ antibody specifically binding to the complement protein C5, molecular weight 148 kDa.

MOA:
- Binding to complement protein C5
  → Inhibition of cleavage of C5 to C5a and C5b
  → Prevention of formation of terminal complement complex C5b-9
- Inhibition of terminal complement mediated intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) (► Chap. 6.4.3)

Pkin:
- *Kinetics:* elimination half-life t½ 272 ± 82 h
- *Metabolism:* proteolysis

Se:
- *Bone marrow:* anemia (2%)
- *Pulmonary:* cough, nasopharyngitis, respiratory tract infection, sinusitis
- *Gastrointestinal:* nausea (16%), vomiting, constipation
- *Nervous system:* headache (44%)
- *Infusion-induced reactions ("cytokine-release syndrome"):* fever, chills, rigor, rhinitis, conjunctivitis, sore throat, bronchospasm, angioedema
- *Other:* serious hemolysis after discontinuation (LDH ↑), systemic infections, serious meningococcal infections, viral infections (including herpes simplex), backache, arthralgia, myalgia, limb pain, fatigue, influenza-like symptoms

Ci:
- Patients who are not vaccinated against *Neisseria meningitidis*
- Unresolved *Neisseria meningitidis* infection

Th: *Approved indications:* paroxysmal nocturnal hemoglobinuria (PNH)

Dosage and application:
- 600 mg i.v. infusion weekly for 4 weeks, then 900 mg every 14 days
- ATTN: increased risk of meningococcal infections → patients must receive a meningococcal vaccine at least 2 weeks prior to initiation of eculizumab therapy
- Monitor for signs and symptoms of infusion reactions
- Monitor for signs of hemolysis, serum LDH levels

Gemtuzumab Ozogamicin

Chem: Immunotoxin conjugate, humanized, recombinant, monoclonal IgG4-κ antibody specifically binding to the antigen CD33, conjugated with the cytostatic antibiotic calicheamicin

MOA:
- Binding to CD33 on leukemic myeloblasts and myeloid cells (myelomonocytic progenitors, neutrophils, erythrocytes, thrombocytes, monocytes / macrophages). In AML, over 80% of cells are CD33 positive. CD34-positive hematopoietic stem cells are CD33 negative.
- Internalization of CD33 with gemtuzumab ozogamicin → release of calicheamicin derivatives in lysosomes → DNA strand breaks → cytotoxic effect.
- Simultaneously, antibody-mediated cytotoxicity (ADCC), apoptosis induction.

Pkin:
- *Kinetics:* median serum half-life t½ of gemtuzumab ozogamicin 45–60 h, t½ of unconjugated calicheamicin 100 h
- *Metabolism:* internalization and hydrolysis, hepatic and renal elimination

Se:
- *Bone marrow:* severe myelosuppression (neutropenia, thrombocytopenia, anemia), bone marrow recovery after approximately 40 days. Infections due to neutropenia (50%), hemorrhages (15% of cases, cerebral, gastrointestinal, epistaxis, hematuria, in rare cases disseminated intravascular coagulation)
- *Cardiovascular:* hypotension, hypertension, tachycardia
- *Pulmonary:* cough, dyspnea, pharyngitis, bronchitis, pneumonia, pulmonary edema, ARDS
- *Gastrointestinal:* nausea / vomiting (70%), diarrhea (40%), constipation, abdominal pain, loss of appetite
- *Liver:* transient increase of transaminases, cholestasis (25%), hyperglycemia
- *Skin:* local reactions, erythema, pruritus, petechiae
- *Infusion-induced reactions ("cytokine release syndrome"):* fever (85%), chills (75%), hot flushes, sweat, erythema, urticaria, hypo- or hypertension, dyspnea
- *Other:* tumor lysis syndrome (rare, risk of acute renal failure), arthralgia, myalgia, hypercalcemia

Ci:
- Hypersensitivity to gemtuzumab ozogamicin
- Pregnancy, lactation
- Severely impaired liver function (bilirubin > 2 g/dl)

Th: *Indication (USA):* relapse of CD33-positive AML in patients ≥ 60 years
Clinical trial use: AML patients < 60 years

Dosage: i.v. application (infusion over 2 h)
- 9 mg/m²/day i.v. on days 1, 15
- ATTN: risk of infusion-induced reactions including fever, chills, thrombocytopenia, hypotension, tumor lysis syndrome. Premedication with paracetamol 500–1000 mg p.o. and antihistamines (e.g., clemastine 2 mg i.v.)

Rituximab

Chem: Recombinant, monoclonal, chimeric IgG1-antibody (mouse / human) specifically binding to the transmembrane antigen CD20

MOA:
- Binding to CD20 (on normal pre-B- / B-cells and 95% of malignant B-NHL) → complement-mediated cytotoxicity (CDC) and antibody-mediated cellular cytotoxicity (ADCC), apoptosis induction, depletion of CD20-positive lymphocytes → B-cell depletion, serum immunoglobulins ↓, commencing regeneration after 2 weeks, complete reconstitution after 9–12 months
- Direct antiproliferative effect against malignant B-cell lines shown in vitro
- Sensitization against cytotoxic compounds (combination therapy)

Pkin:
- *Kinetics:* median half-life t½ after first infusion: 68–76 h, after fourth infusion t½ 190–200 h. Pronounced intra- and interindividual variability of serum concentration, detection of rituximab in serum 3–6 months after treatment possible
- *Metabolism:* proteolysis

Se:
- *Bone marrow:* lymphopenia (50%), marginal myelosuppression
- *Cardiovascular:* hypotension, hypertension, arrhythmia, rare cuses of angina pectoris, cardiac insufficiency, myocardial infarction, mainly with pre-existing heart disease
- *Pulmonary:* cough, dyspnea, sinusitis, bronchitis, bronchiolitis obliterans, pulmonary infiltrates, ARDS ("acute respiratory distress syndrome")
- *Gastrointestinal:* nausea / vomiting, diarrhea, abdominal pain
- *Liver:* transient increase of transaminases, hyperglycemia
- *Nervous system:* central neuropathy, headache, paresthesia, dizziness, anxiety, insomnia, somnolence, nervousness
- *Skin:* erythema, pruritus, urticaria
- *Infusion-induced reactions ("cytokine-release syndrome"):* fever (50%), chills, rigor, rhinitis, conjunctivitis, sore throat, bronchospasm, angioedema
- *Other:* infections, night sweat, fatigue, reduced performance status, edema, arthralgia, myalgia, skeletal pain, hypercalcemia, LDH ↑, lymphadenopathy, coagulation disorders, dysgeusia, tumor lysis syndrome

Ci:
- Hypersensitivity to murine proteins, severe pre-existing cardiac disease

Th: *Approved indications for use:* refractory / relapsed B-cell lymphoma
Clinical trial use: multiple myoma, ITP, rheumatoid arthritis, autoimmune disease

Dosage and application:
- 375 mg/m²/day i.v. weekly with monotherapy, in combination with CHOP on day 1 of each cycle
- ATTN: infusion-induced reaction prophylaxis: premedication with paracetamol 500–1,000 mg p.o. and clemastine 2 mg i.v., slow increase of infusion rate (initially 50 mg/h, gradually increasing up to maximum 400 mg/h). Close monitoring. Discontinue antihypertensive medication 12 h before treatment
- ATTN: in case of high tumor load (lymphomas > 10 cm, lymphocytosis > 50,000/µl, leukocytosis > 50,000/µl): acute tumor lysis syndrome possible (→ Chap. 9.6)

Panitumumab

Chem: Recombinant, monoclonal, fully human IgG2 antibody, with selective high affinity binding to the human epidermal growth factor receptor (EGF-R, HER1), inhibiting ligand binding.

MOA: Binding to EGF-R (on solid tumor cells):
- Inhibiting the effect of endogenous EGF-R ligands (EGF, TGFα), competitive inhibition of EGF-R tyrosine kinase, signal transduction ↓
- Receptor internalization and downregulation
- Antibody-mediated cytotoxicity, apoptosis induction, tumor neoangiogenesis ↓
- Inhibiting tumor growth and metastasis

Efficacy of panitumumab monotherapy in metastatic colorectal carcinoma is increased with expression of the wild-type KRAS gene. Tumors with expression of mutated KRAS show reduced response rates. KRAS status should be considered in selecting patients with metastatic colorectal carcinoma as candidates for panitumumab therapy.

Pkin: *Kinetics:* elimination half life (t½): 7.5 days (3.6 – 10.9 d)

Se:
- *Pulmonary*: dyspnea, cough, pulmonary fibrosis (rare)
- *Gastrointestinal*: nausea / vomiting, diarrhea (esp. in combination with irinotecan), constipation, abdominal pain, mucositis
- *Skin:* acneiform skin rash, pruritus, erythema, exfoliation, nail disorders, dry skin
- *Other*: fatigue, reduced performance status, infections, peripheral edema, hypomagnesemia, infusion reactions (rare), allergic reactions (rare)

Ci: Pregnancy, lactation

Th: *Indications for use*: metastasized colorectal carcinoma
Clinical trial use: breast cancer, non-small cell lung cancer

Dosage:
- 6 mg/kg i.v. every 14 days, 1 h-infusion
- Examination of EGFR and KRAS status in tumor tissue recommended prior to treatment (e.g., immunohistochemistry)
- ATTN: reduced risk of infusion-reduced reactions as compared to other EGFR inhibitors, due to fully human nature of the antibody.

Trastuzumab

Chem: Humanized, recombinant, monoclonal IgG1-κ antibody (mouse / human), selectively binding with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 (EGF-R2, HER2)

MOA:
- HER2 protooncogene encodes the transmembrane receptor protein p185 (185 kD, HER2/neu) with intrinsic tyrosine kinase activity. HER2 overexpression in 25–30% of primary breast cancer and in other epithelial neoplasias, e.g., non-small cell lung cancer, bladder / gastric / ovarian / prostate cancer
- Specific binding of trastuzumab to extracellular domain of p185 → complement-mediated cytotoxicity (CDC) and antibody-mediated cytotoxicity (ADCC), apoptosis induction, inhibition of signal transduction, receptor downregulation, cell cycle arrest

Pkin: *Kinetics:* median half-life t½: 28 days (1–32 days), elimination period up to 24 weeks

Se:
- *Bone marrow:* mild myelosuppression
- *Cardiovascular:* acute cardiotoxicity (dose-limiting): hypotension, syncope, tachycardia, cough, dyspnea, edema, 3rd heart sound, reduced cardiac ejection fraction, decompensated cardiac insufficiency (monotherapy: 5%, combination treatment with anthracyclines: 19%); ischemia, pericardial effusion, arrhythmia, cardiomyopathy, cardiac arrest. Vascular thrombosis
- *Pulmonary:* cough, dyspnea, rhinitis, sinusitis, pharyngitis, pleural effusion, pulmonary infiltrates, ARDS
- *Gastrointestinal:* nausea (30%), vomiting, abdominal pain, diarrhea, loss of appetite
- *Nervous system:* headache, dizziness, insomnia, paresthesias, neuropathy, tremor, anxiety, depression
- *Infusion-induced reactions ("cytokine release syndrome," 40%):* fever, chills, cough, erythema, urticaria, pruritus, angioedema, anaphylaxis
- *Other:* infections (mainly rhinitis, bronchopulmonary infections, catheter infections, mastitis), flu-like symptoms, arthralgia, myalgia, pruritus, back pains, transient tumor pain, fatigue, reduced performance status, antibody formation

Ci:
- Hypersensitivity to mouse proteins
- Pre-existing cardiac disease, dyspnea at rest
- Combination treatment trastuzumab + anthracyclines is not recommended due to increased cardiotoxicity

Th: *Indications:* breast cancer

Dosage and application:
- Initially 4 mg/kg over 90 min i.v., then 2 mg/kg once a week over 30 min i.v., no premedication necessary
- ATTN: cardiotoxicity, esp. in combination with anthracyclines and with pre-existing cardiac disease (e.g., cardiac diseases, thoracic radiotherapy)
- BEFORE TREATMENT: ECG, echocardiography (LVEF determination), diagnosis of HER2 overexpression (immunohistochemistry and/or fluorescence in situ hybridization (FISH) in tumor tissue)

3.6 Specific Protein Kinase Inhibitors ("Targeted Therapies")

K. Potthoff, R. Waesch, J. Scheele, U. Martens

In addition to therapeutically used antibodies (► Chap. 3.5), low molecular weight antineoplastic compounds specifically binding to biologically relevant target structures are also classified as "targeted therapies."

The identification of classic cytostatic drugs was based on a multitude of empirical studies ("screening") in tumor model systems (e.g., murine tumors). In contrast, the development of "targeted therapies" is based on the knowledge of pathogenesis and pathophysiology of malignant diseases ("rational drug design").
Main approaches:

- *Modification of gene function:* gene therapy, antisense oligonucleotides, ribozymes
- *Modification of protein function:* monoclonal antibodies, receptor antagonists, binding proteins, angiogenesis inhibitors
- *Specific toxic effect:* combination of specific "cognition" molecules (e.g., receptor ligands, monoclonal antibodies) and toxins (synthetic or natural toxins), so-called "drug targeting", e.g., with immunotoxins

Signal transduction inhibitors inhibit specific protein kinases, other enzymes or effector molecules of intracellular signal transduction.

Ma:

Mode of Action and Target Structures

The effects of specific inhibitors depend on the cellular target structures. Molecules targeting different structures are used in preclinical and clinical trials.

Point of attack	Target structure (selection)
Regulation of angiogenesis	VEGF, angiopoietin, tie, HIF
Regulation of apoptosis	TRAIL-R1, bcl-2, p53, NFκ-B, PI3-kinase, ubiquitin
Oncogenes	ras, raf, jun, fos, kinases
Regulation of proliferation	Growth factors, e.g., EGF, IGF
Signal transduction	Tyrosine kinases (EGF-R, VEGF-R, PDGF-R), serine-threonine kinases (TOR)
Cell cycle regulation	Cyclins, cyclin-dependant kinases (CDK), mitotic kinases

VEGF vascular endothelial growth factor, *HIF* hypoxia-inducible factor, *TRAIL* tumor necrosis factor-related apoptosis-inducing ligand, *NFκ-B* nuclear factor kappa B, *PI3* phosphatidylinositol-3, *EGF* epidermal growth factor, *IGF* insulin-like growth factor, *PDGF* platelet-derived growth factor, *TOR* target of rapamycin

Tyrosine Kinases

Kinases are enzymes which phosphorylate specific substrates (e.g., tyrosine residues). Tyrosine kinases play an important role in signal transduction. Differentiation between:

- Receptor tyrosine kinases
- Intracellular tyrosine kinases

Tyrosine kinase inhibitors are the most important clinically used "targeted therapies."

Ref:

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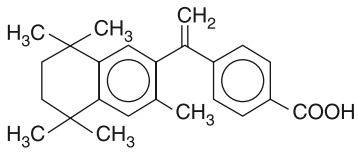
2. http://www.nature.com/nrc/focus/targetedtherapies Nature Reviews Cancer
3. http://www.oncolink.com/treatment/treatment.cfm?c=12 Oncolink "Targeted Therapies"
4. http://www.fda.gov/cder/drug/infopage/gleevec FDA, Glivec Information

Bexarotene

Chem: Retinoid receptor X activator, 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8,-pentamethyl-2-naphthalenyl)-ethenyl]benzoic acid



MOA

- Selective activation of retinoid X receptors (RXR) α, β, and γ
  → Activated receptors function as transcription factors
  → Impact on apoptosis, cellular proliferation and differentiation
- Growth inhibition of specific malignant cells lines in vitro and vivo

Pkin:

- *Kinetics:* moderate oral absorption, peak plasma levels reached after 2 h, plasma protein binding > 99%, terminal half-life t½ 7 h
- *Metabolism:* hepatic degradation via cytochrome P450 system (CYP3A4) and glucuronidation, hepatobiliary elimination

Se:

- *Bone marrow:* leukopenia, neutropenia, anemia
- *Cardiovascular:* peripheral edema
- *Pulmonary:* dyspnea, cough, pneumonia
- *Gastrointestinal:* nausea, vomiting, diarrhea, abdominal pain
- *Liver / pancreas:* transient elevation of transaminases, cholestasis, lipid abnormalities (triglycerides ↑, cholesterol ↑, LDL ↑, HDL ↓), acute pancreatitis
- *Nervous system:* headaches, confusion
- *Skin:* rash, dry skin, pruritus, exfoliative dermatitis
- *Other:* fatigue, asthenia, infections, muscle cramps, hypothyroidism (TSH ↓, thyroxin ↓), posterior subcapsular cataracts

DDI:

- Cytochrome P450 (CYP3A4) inhibiting substances (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin) are expected to increase bexarotene plasma concentrations
- CYP3A4-inducing substances (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) are expected to decrease bexarotene plasma concentrations
- Effects of insulin may be enhanced → risk of hypoglycemia

Ci:

- Hypersensitivity to retinoids, pregnancy, lactation
- Relative CI: patients with risk factors for pancreatitis

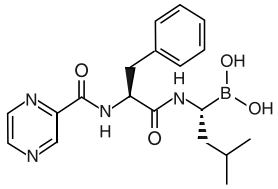
Th: *Approved indications:* cutaneous manifestations of cutaneous T-cell lymphoma (CTCL)
Clinical trial use: head and neck cancer, NSCLC, renal cell carcinoma, Kaposi's sarcoma

Dosage: oral application (300 mg/m²/day p.o.) or topical application

- *ATTN:* bexarotene may cause fetal harm when administered to pregnant women. Appropriate precautions should be taken to avoid pregnancy and fathering
- *BEFORE TREATMENT:* full blood count, hepatic and renal function tests, thyroid function, blood lipids

Bortezomib (PS-341)

Chem: Proteasome inhibitor, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]-propyl]amino]butyl]boric acid



MOA:
- Reversible inhibitor of 26S-proteasome → inhibiting degradation of ubiquitinated proteins → apoptosis induction in cells with bcl-2 overexpression, angiogenesis inhibition, IL-6 mediated effects ↓, adhesion molecules ↓
- Proteasome inhibition reversible after 72 h

Pkin:
- *Kinetics:* median half-life t½ 9–15 h
- *Metabolism:* hepatic degradation via several cytochrome P450 enzymes

Se:
- *Bone marrow:* neutropenia, anemia, thrombocytopenia (15–40%)
- *Cardiovascular:* orthostatic hypotension, syncope, hypertension, arrhythmia, cardiac failure, myocardial infarction
- *Gastrointestinal tract:* diarrhea (dose-limiting, 51%), nausea (65%), vomiting, abdominal cramps, loss of appetite
- *Kidney:* renal function disorders, electrolyte disorders (rare)
- *Nervous system:* peripheral neuropathy (dose-limiting), headaches, drowsiness
- *Other:* fever, fatigue, reduced performance status (65%), arthralgia, myalgia, conjunctivitis, hyperbilirubinemia, tumor lysis syndrome, allergic reactions (rare)

DDI:
- Cytochrome P450 (CYP3A4) inhibiting substances (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin) → bortezomib concentration ↑
- CYP3A4 induction (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) → effect of bortezomib ↓
- *ATTN:* no simultaneous administration of phenprocoumon (metabolization via CYP2C9) → patients with anticoagulation therapy should switch to low molecular weight heparin

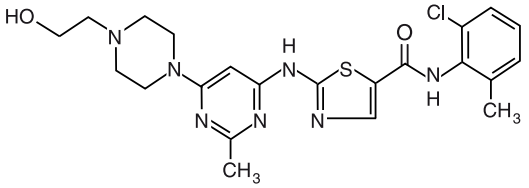
Ci:
- Hypersensitivity to bortezomib, boric compounds, or mannitol
- Pregnancy, lactation
- Cardiac or neuropathic disorders

Th: *Indication:* multiple myeloma, cutaneous T-cell lymphoma
Clinical trial use: solid tumors

Dosage: 1.3 mg/m²/day i.v. on days 1, 4, 8, 11, repetition on day 22

Dasatinib

Chem: Tyrosine kinase inhibitor, N-(2-chloro-6-methylphenyl)-2-[6-[4-(2-hydroxyethyl)-1-piperazinyl]-amino]-5-thiazolcarboxamide



MOA:
- Inhibiting tyrosine kinases BCR-ABL, c-kit, EPHA2, PDGFRβ as well as kinases that belong to SRC family (SRC, LCK, YES, FYN)
- Inhibiting proliferation / apoptosis induction in Philadelphia-positive CML and ALL by inhibiting BCR-ABL fusion protein and in gastrointestinal stromal tumors (GIST) by inhibiting c-kit-protein (CD117, stem cell factor receptor)

Pkin:
- *Kinetics:* oral bioavailability, plasma protein binding 93–96%, median half-life t½ 3–5 h
- *Metabolism:* hepatic inactivation (cytochrome P450 3A4) and elimination (glucuronidation)

Se:
- *Bone marrow:* neutropenia, thrombocytopenia (48–83%), impaired thrombocyte function, anemia
- *Cardiovascular:* QT elongation
- *Gastrointestinal:* nausea, vomiting, abdominal pain, diarrhea, loss of appetite, gastrointestinal bleeding (7–14%)
- *Liver:* transient increase of transaminases, cholestasis
- *Nervous system:* headaches, somnolence, insomnia
- *Skin:* dermatitis, exanthema, pruritus, alopecia
- *Other:* fluid retention (50%, with effusions, peripheral edema, pulmonary edema), dyspnea, fever, fatigue, reduced performance status, weight loss, hemorrhages

DDi:
- Cytochrome P450 (CYP3A4) inhibiting substances (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin) → dasatinib concentration ↑
- CYP3A4 induction (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) → effect of dasatinib ↓
- Antacids reduce the oral bioavailability of dasatinib

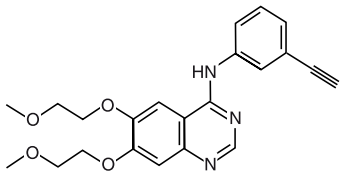
Ci: Use cautiously in patients with QT elongation, hypokalemia, hypomagnesemia, therapy with antiarrhythmics

Th: *Indications:* CML, Ph+ ALL, if refractory to primary treatment

Dosage:
- 140 mg/day p.o. (70 mg tablets in the morning and evening)
- Dose increase up to 200 mg/day possible

Erlotinib

Chem: Tyrosine kinase inhibitor, N-(3-ethynylphenyl-)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine



MOA:
- EGFR (epidermal growth factor receptor) expression on solid tumors, especially with non-small cell lung cancer, esophageal carcinoma, head and neck tumors, renal cell carcinoma, gastrointestinal carcinoma, breast cancer
- Inhibiting epidermal growth factor receptor type 1 (HER1/EGFR1) tyrosine kinase → inhibiting EGFR activation / signal transduction → inhibiting proliferation and angiogenesis, apoptosis induction

Pkin:
- *Kinetics:* oral bioavailability 60–80%, median half-life t½ 36 h
- *Metabolism:* hepatic degradation (cytochrome P450 3A1/1A2) and renal excretion

Se:
- *Pulmonary:* dyspnea, cough, interstitial pneumonia, pneumonitis, bronchiolitis obliterans, pulmonary fibrosis
- *Gastrointestinal:* nausea, vomiting, abdominal pain, diarrhea, loss of appetite, gastrointestinal hemorrhages
- *Liver:* transient increase of transaminases, cholestasis, impaired coagulation
- *Nervous system:* headaches
- *Eyes:* conjunctivitis, keratitis, visual disturbances, lacrimation ↑
- *Skin:* erythema (70%), dermatitis, exanthema, pruritus
- *Other:* fatigue, reduced performance status

DDi:
- Cytochrome P450 (CYP3A4) inhibiting substances (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin) → erlotinib concentration ↑
- CYP3A4 induction (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) → effect of erlotinib ↓
- *ATTN:* do not use phenprocoumon with erlotinib due to metabolization by CYP2C9. Anticoagulated patients should receive low molecular weight heparin.

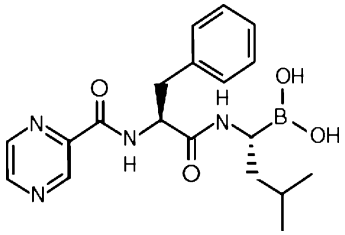
Ci: Hypersensitivity, pregnancy, lactation, impaired liver function

Th: *Approved indications (USA):* non-small cell lung cancer, pancreatic cancer
Clinical trial use: solid tumors

Dosage: oral application, 1 h before or 2 h after meals
150 mg/day p.o.

Imatinib Mesylate

Chem: Tyrosine kinase inhibitor, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate



MOA:
- Inhibition of the Bcr-Abl fusion protein (tyrosine kinase) in Philadelphia chromosome positive CML and ALL cells → proliferation inhibition and apoptosis induction
- Inhibition of the c-kit protein (CD117, stem cell factor receptor SCF-R, tyrosine kinase) in gastrointestinal stromal tumors (GIST)
- Inhibition of the activated PDGF receptor (platelet-derived growth factor receptor)

Pkin:
- *Kinetics:* oral bioavailability 98%, plasma protein binding 95%, median half-life t½ 18 h (imatinib) to 40 h (active metabolite N-demethyl-imatinib)
- *Metabolism:* renal and hepatic elimination via cytochrome P450 (CYP3A4)

Se:
- *Bone marrow:* neutropenia, thrombocytopenia, anemia
- *Gastrointestinal tract:* nausea, vomiting, abdominal pain
- *Liver:* reversible increase of transaminases, cholestasis
- *Nervous system:* headaches, drowsiness, dysgeusia, fatigue, paresthesia, dizziness, insomnia, conjunctivitis, visual disturbances, lacrimation ↑
- *Skin:* dermatitis, exanthema, pruritus, alopecia, allergic reactions
- *Other:* fluid retention (60%, effusions, peripheral edema, pulmonary edema), dyspnea, fatigue, reduced performance status, muscle cramps, arthralgia, myalgia, gastrointestinal and intratumoral hemorrhages (GIST)

DDi:
- Cytochrome P450 (CYP3A4) inhibiting substances (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin) → imatinib plasma concentration ↑
- CYP3A4-inducing substances (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) → effect of imatinib ↓
- *ATTN:* do not use phenprocoumon with imatinib mesylate due to metabolization by CYP2C9. Anticoagulated patients should receive low molecular weight heparin.

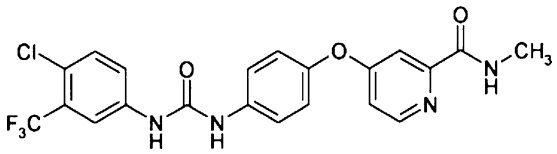
Ci: Hypersensitivity, pregnancy, lactation, impaired liver function

Th: *Indications:* Philadelphia chromosome positive (Ph+) CML, Ph+ ALL, c-kit-positive gastrointestinal stromal tumors (GIST)
Clinical trial use: mastocytosis, hypereosinophilic syndrome, solid tumors

Dosage: oral application with meals
- GIST: 400–800 mg/day p.o.
- CML: 400 mg/day p.o. (chronic phase), 600 mg/day p.o. (accelerated phase / blast crisis), 800 mg/day (in case of progression after at least 3 months of treatment)

Sorafenib Tosylate

Chem: Multikinase inhibitor, 4-(4-[3-[4-chloro-3-(trifluoromethyl)phenyl]ureido]phenoxy-N-methyl-pyridine-2-carboxamide



MOA:
- Inhibiting multiple intracellular kinases (CRAF, BRAF) and receptor tyrosine kinases (c-kit, FLT-3, VEGFR-2, VEGFR-3, PDGFR-β)
- Inhibiting signal transduction of VEGF (vascular endothelial growth factor) → angiogenesis inhibition → inhibiting growth of angiogenesis-dependent solid tumors

Pkin:
- *Kinetics:* oral bioavailability 38–49%, plasma protein binding > 99%, median half-life t½ 25–48 h
- *Metabolism:* hepatic degradation (cytochrome P450 3A4, glucuronidation via UGT1A9), fecal and renal elimination

Se:
- *Bone marrow:* neutropenia, lymphopenia, thrombocytopenia
- *Cardiovascular:* hypertension, myocardial ischemia (rare)
- *Gastrointestinal:* nausea, vomiting, diarrhea, loss of appetite, amylase ↑, lipase ↑, mucositis, dysphagia, gastrointestinal hemorrhage (rare)
- *Liver:* transient increase of transaminases, cholestasis
- *Nervous system:* headaches, sensory neuropathy
- *Skin:* erythema, dermatitis, skin edema, dysesthesia, paresthesia, hand-foot syndrome, in rare cases with desquamation and ulceration
- *Other:* fatigue, reduced performance status, fever, weight loss, arthralgia, myalgia, hemorrhages, hypophosphatemia

DDi:
- CYP3A4-inducing substances (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) → effect of sorafenib ↓

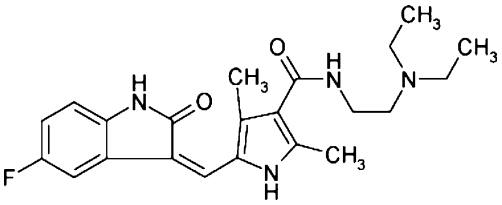
Ci:
- Hypersensitivity, pregnancy, lactation

Th: *Approved indications:* advanced renal cell carcinoma
Clinical trial use: solid tumors

Dosage: oral application, 1 h before or 2 h after meals
800 mg/day p.o. (400 mg in the morning and evening)

Sunitinib Malate

Chem: Multikinase inhibitor, N-[2-(diethylamino) ethyl]-5-[(z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidin)methyl]-2,4-dimethyl-1H-pyrrol-3-carboxamide



MOA:
- Inhibition of > 80 tyrosine kinases, including PDGF receptors α and β, VEGF receptor 1-3, SCF receptor (kit), FLT-3, CSF-1 receptor, and GCDNF receptor (RET)
- Inhibiting signal transduction of VEGF (vascular endothelial growth factor) → angiogenesis inhibition → inhibiting growth of angiogenesis-dependent solid tumors

Pkin:
- *Kinetics:* plasma protein binding 90–95%, terminal half-life t½ 40–60 h, t½ of active metabolite 80–110 h
- *Metabolism:* hepatic activation and degradation via cytochrome P450 system (CYP3A4), fecal (61%) and renal (16%) elimination

Se:
- *Bone marrow:* neutropenia, lymphopenia, anemia, thrombocytopenia
- *Cardiovascular:* hypertension, LVEF ↓, peripheral edema, myocardial ischemia, thromboembolic events (rare)
- *Pulmonary:* dyspnea, cough
- *Gastrointestinal:* nausea, vomiting, diarrhea, constipation, loss of appetite, amylase ↑, lipase ↑, mucositis, dysphagia, abdominal pain
- *Liver:* transient increase of transaminases, cholestasis
- *Kidney:* creatinine ↑, hyperuricemia, hypokalemia, hypernatremia
- *Nervous system:* headaches, dysgeusia, amentia
- *Skin:* dermatitis, erythema, skin edema, hand-foot syndrome, pigmentation, change of hair color, alopecia
- *Other:* fatigue, reduced performance status, fever, weight loss, arthralgia, myalgia, hemorrhage, hypophosphatemia

DDi:
- Cytochrome P450 (CYP3A4) inhibiting substances (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin) → sunitinib plasma concentration ↑, consider dose reduction to 37.5 mg/day
- CYP3A4-inducing substances (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) → effect of sunitinib ↓, consider dose increase to 87.5 mg

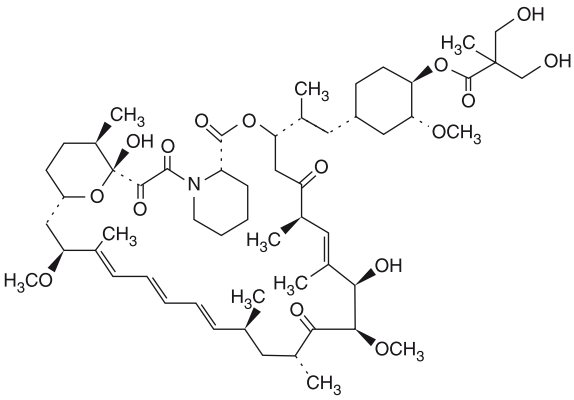
Ci:
- Hypersensitivity, pregnancy, lactation
- Relative CI: pre-existing cardiac disorders, left ventricular insufficiency

Th: *Approved indications:* gastrointestinal stromal tumors (GIST), advanced renal cell carcinoma
Clinical trial use: solid tumors

Dosage: oral application, 50 mg/day p.o.

Temsirolimus

Chem: mTOR ("mammalian target of rapamycin") inhibitor



MOA:
- Intracellular binding to protein FKBP-12
  → Protein–drug complex inhibits activity of mTOR
  → Blocking of PI3/AKT pathway through decreased phosphorylation of p70S6k and S6 ribosomal proteins
  → Inhibition of cell division, cell cycle phase G1 growth arrest

Pkin:
- *Kinetics:* hepatic formation of metabolites via cytochrome P450 system (CYP3A4), active metabolite sirolimus, terminal half-life t½ 17 h (t½ of sirolimus 55 h)
- *Metabolism:* hepatobiliary elimination

Se:
- *Bone marrow:* leukopenia, neutropenia, lymphopenia, anemia, thrombocytopenia
- *Cardiovascular:* peripheral edema
- *Pulmonary:* dyspnea, cough, pneumonia, interstitial lung disease (ILD)
- *Gastrointestinal:* nausea, vomiting, mucositis, anorexia, abdominal pain, bowel perforation
- *Liver / pancreas:* transient increase of transaminases, lipid abnormalities, hyperglycemia
- *Kidney:* creatinine ↑, hyperphosphatemia, renal failure
- *Skin:* rash, dry skin, pruritus
- *Other:* hypersensitivity reactions, fatigue, asthenia, infections, delayed wound healing, arthralgia, myalgia

DDi:
- Cytochrome P450 (CYP3A4) inhibitors (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin) → sirolimus plasma concentration ↑, consider dose reduction of temsirolimus to 12.5 mg/day
- CYP3A4 inducers (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, St. John's wort) → effect of temsirolimus ↓, consider dose increase to 37.5–50 mg

Ci: Hypersensitivity, pregnancy, lactation

Th: *Approved indication:* advanced renal cell carcinoma

Dosage: 25 mg/day i.v. once weekly
- *ATTN:* temsirolimus may cause fetal harm when administered to pregnant women. Appropriate precautions should be taken to avoid pregnancy and fathering. Antihistamine pretreatment is recommended
- *BEFORE TREATMENT:* full blood count, hepatic and renal function tests, blood lipids. Monitor blood lipids and blood glucose

3.7 Drug Development and Clinical Studies

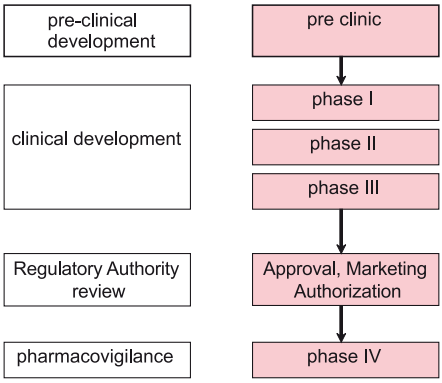
C. Schmoor, S. Stoelben, H. Maier-Lenz, D. Berger, H. Henß

Def: Clinical development of a drug takes place after completion of preclinical development and involves a series of clinical trials and defined test phases. It should be conducted in accordance with:

- Ethical principles (Declaration of Helsinki, local ethics commission)
- Legal regulations (e.g., pharmaceutical law, administrative regulations)
- "Good clinical practice," GCP (international GCP guidelines of the "International Conference on Harmonization," ICH-GCP)
- "Good manufacturing practice," GMP
- "Good laboratory practice," GLP

Adequate statistical methods and scientifically accurate analysis of results are essential for the design and evaluation of clinical studies of all phases.

Meth: **Phases of drug testing**



Preclinical Phase

- Chemical / biochemical / biotechnological development
- Pharmacological evaluation, stability
- Toxicology: acute toxicity, long-term toxicity, carcinogenic / mutagenic / teratogenic effects in animal models
- Preclinical in vitro and in vivo efficacy testing

Phase I

- "First in human" testing after successful preclinical development.
- In the majority of clinical settings, phase I trials are conducted with healthy volunteers at specific clinical research organizations (CROs). However, due to the potential for side effects (e.g., cytostatic toxicity), classic oncological phase I trials are frequently conducted in hospital units, providing experimental treatment to inpatients. Test group: usually 15–20 patients per trial.
- Primary questions: acute tolerance, dosage ("maximum tolerable dose," MTD), initial dose for phase II trials.
- Other questions: acute toxicity, pharmacokinetics, pharmacodynamics, development of formulations.

Phase II

- After successful phase I trial
- Evaluation of experimental drugs in patients with specific target indications, e.g., selected tumor types
- Test group: usually < 100 patients; trial design open or blinded, randomized, placebo-controlled
- Primary questions: efficacy, dose-response-relationship, safety

Phase III

- After successful phase II trial
- Comparison of treatment group (experimental treatment) versus control group (standard treatment), generally conducted as prospective randomized, double-blind trials; test group: usually > 100 patients
- Primary objective: efficacy in specific target indications compared with standard treatment, long-term safety
- Other objectives: drug safety, side effects, drug interactions

Regulatory Authority Approval

- After successful preclinical and clinical (phase I to III) testing, the drug development data can be submitted to Regulatory Authorities for review and approval.
- European approval:
  - Centralized procedure: submission of data to the European Medicines Agency (EMEA) in London.
  - Decentralized procedure: submission of data to a national licensing authority.
- US approval: FDA, Food and Drug Administration
- After successful evaluation by the regulatory authorities, a product license (Marketing Authorization) is issued.

Phase IV

- Clinical studies *after* drug has been licensed
- Primary objective: efficacy in particular situations, rare side effects and interactions, rare contraindications
- Pharmacovigilance: continuous monitoring of drug-related adverse reactions at national and international Regulatory Authority level as well as by the manufacturer

Good Clinical Practice (GCP)

"Good clinical practice" (GCP) refers to international ethical and scientific standards that must be complied with when planning, executing, and documenting clinical studies with human beings. Objectives are:

- Protection of the study participants' rights
- Protection of safety and wellbeing of the study participants
- Correct documentation and presentation of the study results

GCP guidelines were originally developed for clinical trials with registrational intent. However, there is agreement among the scientific community that GCP principles are relevant for all clinical research, including investigator-initiated studies and cooperative group trials.

ICH-GCP

The current GCP guidelines were developed by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1st May 1996) and are referred to as ICH-GCP. The following recommendations were incorporated:

- Ethical principles for medical research involving human subjects (Declaration of Helsinki)
- GCP guidelines by the WHO (World Health Organization), the European Union, USA, Japan, Australia, Canada, and Scandinavia

Principles of Good Clinical Practice (ICH-GCP) (excerpts)

Clinical trial requirements

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)
- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks
- The rights, safety, and wellbeing of the trial subjects are the most important considerations and should prevail over interests of science and society
- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial
- Clinical trials should be scientifically sound, and described in a clear, detailed protocol
- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) / independent ethics committee (IEC) approval / favorable opinion
- Freely given informed consent should be obtained from every subject prior to clinical trial participation
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)
- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol
- Systems with procedures that assure the quality of every aspect of the trial should be implemented

Requirements for Investigators

- The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)

Ref:

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5. World Medical Association. Helsinki Declaration, 1975. In: Beauchamp TL, Walters LW (eds) Contemporary Issues in Bioethics, 2nd edn. Wadsworth, Belmont, CA, 1982

Web:

1.	http://eudract.emea.europa.eu/	European Clinical Trials Database
2.	http://www.clinicaltrials.gov	US Clinical Trials Database
3.	http://www.controlled-trials.com/	Study Register
4.	http://www.centerwatch.com	Clinical Trials Listing Service
5.	http://www.emea.europa.eu/	EMEA, European Agency for Evaluation of Medicinal Products
6.	http://www.fda.gov/	FDA, Food and Drug Administration, USA
7.	http://www.ich.org	ICH, International Conf. Harmonization

3.8 Pharmacogenetics and Pharmacogenomics

J.S. Scheele , A. Müller , U. Martens

Def: *Pharmacogenetics:* study of genetic factors determing efficacy and safety of drugs
Pharmacogenomics: study of the entire spectrum of genes which can influence pharmacodynamics and pharmacokinetics of specific drugs

Meth: *Pharmacogenetic Methods*

- Genotyping of "single nucleotide polymorphisms" (SNPs): selective genetic polymorphisms impact the activity of key proteins essential for drug response and drug metabolism. With some cytostatics, SNPs allow rational predictions about response and toxicity.
- Gene expression analysis (► Chap. 2.3): global gene expression analysis using DNA arrays → genetic determinants of efficacy and toxicity of chemotherapeutics can be empirically identified. The term pharmacogenomics encompasses not only the influence of gene expression on a drug, but also the effect drugs have on the gene expression pattern.
- Drug development: identification of potential targets for new drugs.

Phys: Identification of genetic determinants of efficacy and toxicity of chemotherapeutics is useful if the following conditions are met:

- Wide interindividual differences in pharmacokinetic parameters (e.g., oral bioavailability, half-life, etc.)
- Bimodal AUC distribution ("area under the curve") for the concentration-time curve of active metabolites
- Occurrence of severe toxicities, with lack of dose-response relationship

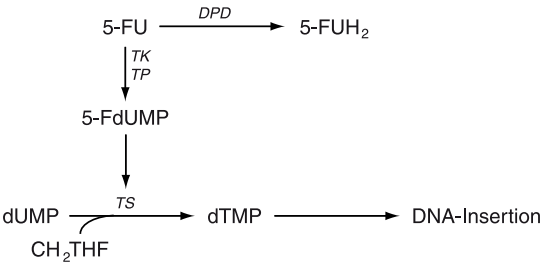
Examples of Pharmacogenetic determinants of chemotherapy-induced toxicity

Substance	Enzyme	Mutation	Mode of action
6-Mercaptopurine (6-MP)	Thiopurine methyltransferase (TPMT)	SNPs: TPMT*2 TPMT*3A TPMT*3C	6-MP catabolism ↓
5-fluorouracil (5-FU)	Dihydropyrimidine dehydrogenase (DPD)	SNPs: DPYD*2A DPYD*9A	5-FU catabolism ↓
Irinotecan (CPT11)	UDP- glucuronosyltransferase 1A1 (UGT1A1; Gilbert's syndrome)	Insertion in promoter and SNPs	Catabolism of the active metabolite SN-38 ↓
Methotrexate + 5-fluorouracil (e.g., CMF protocol)	Methylenetetrahydrofolate reductase (MTHFR)	C677T	MTHFR ↓ → CH_2-THF ↑

Examples of Pharmacogenetic determinants of chemotherapy response

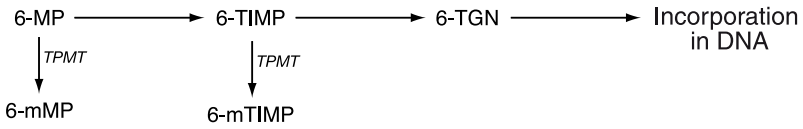
Substance	Enzyme	Mutation	Mode of action
Cytosine arabinoside	Human equilibrative nucleoside transporter 1 (hENT1)	MLL-gene rearrangement	hENT1 expression ↑ → response ↑
Doxorubicin	Glutathione-S-transferase (GST)	GSTP1 gene	GSTP1 expression ↑ → response ↓
5-Fluorouracil	Thymidylate synthase (TS)	Promoter polymorphism	TS induction, amplification → response ↓
Prednisone	Glutathione-S-transferase	GSTP1 gene	SNPs with amino acid changes → response ↑

Pharmacogenetics of 5-fluorouracil (5-FU)



- Formation of inactive 5-fluoro-5,6-dihydrouracil (5-FUH_2) by dihydropyrimidine dehydrogenase (DPD) is the rate-limiting step in the catabolism of 5-FU.
- The antineoplastic effect of 5-FU in the tumor cell is mediated by the active metabolite 5-fluorodeoxyuridine monophosphate (5-FdUMP). FdUMP is formed in two steps, involving thymidine phosphorylase (TP) and thymidine kinase (TK). Inhibition of thymidylate synthase (TS) by 5FdUMP represents the critical step of 5-FU cytotoxicity. TS catalyses the transformation of dUMP into deoxythymidine 5' monophosphate (dTMP), which is the rate-limiting step of DNA synthesis. TS inhibition depends on the cofactor 5,10-methylenetetrahydrofolate (CH_2THF) which forms a ternary complex with 5-FdUMP and TS.
- A defect in the catabolic enzyme DPD, which occurs in its complete form in 0.1% of patients and in its partial form in 3–5% of patients, triggers a life-threatening toxic syndrome encompassing severe myelotoxicity, neurotoxicity, and gastrointestinal toxicity.
- The DPD genotype has an autosomal recessive pattern of inheritance. An allelic inactivation leading to 50% reduction of normal DPD activity is sufficient for the development of 5-FU toxicity. At least 20 mutations have been found in the DPD coding region and promoter. Two mutations with proven clinical relevance are DPYD*2A and DPYD*9A. DPYD*2A is a splice site mutation resulting in the production of shortened mRNA. DPYD*9A is a common missense T85C mutation in exon 2, leading to a C29R amino acid exchange. Correlation between the two mutations and the clinical phenotype together with other SNPs in enzymes of the 5-FU metabolism should yield improved prediction of 5-FU-associated toxicity.

Pharmacogenetics of 6-mercaptopurine (6-MP)



- At the cellular level, 6-mercaptopurine (6-MP) is converted into 6-thioinosine monophosphate (6-TIMP) and 6-thioguanine triphosphate nucleotide (TGN). The incorporation of 6-TGN into DNA mediates the antileukemic activity of 6-MP.
- At the same time, steps of deactivation take place. How much 6-MP can be activated in the bone marrow depends on the extent of deactivating methylation by thiopurine methyltransferase (TPMT).
- Patients with genetic deficiency in TPMT accumulate 6-TGN to toxic concentrations, leading to severe and prolonged myelosuppression. Due to the long latency period of this toxicity, pharmacogenetic prediction of TPMT activity is clinically relevant.
- Ten TPMT variants with diminished enzyme activity have been described. TPMT*2, TPMT*3A, and TPMT*3C are responsible for 80–95% of the phenotype in TPMT deficiencies. Patients with the wildtype genotype show high TPMT activity. Patients who are heterozygous or homozygous for variant alleles display medium or low enzyme activity.
- The TPMT*3A allele contains two SNPs in exon 7 (G460A) and exon 10 (A719G). With a frequency of 3–6%, it is the most prevalent variant amongst the Caucasian population. TPMT*3A was found in 55% of patients with a phenotype for this enzyme deficiency. Patients with this deficiency should only receive 5–10% of the planned 6-MP dose.

Ref:

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2.	http://www.ncbi.nlm.nih.gov/About/primer/pharm.html	Pharmacogenomics Primer
3.	http://www.pharmgkb.org	Pharmacogenetics Database
4.	http://www.nigms.nih.gov/Initiatives/PGRN	Pharmacogenetics Research Network
5.	http://snp.cshl.org	SNP Consortium