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THIRD-LINE CHEMOTHERAPY IN METASTASIZED BREAST CANCER

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Patients who have been treated successfully for metastases from breast cancer invariably suffer from further metastases. Due to this less than satisfactory result 2 none cross-reactive chemotherapies were introduced in 1976 namely Adriamycin and Vincristine in addition to Cyclophosphamide, Methotrexate and Fluorouracil as part of the so called Second-line therapy. The remission rate has been subsequently reported to be between 20 an 50 %. A paucity of information exists for drugs used in Third-line therapies. We have treated 40 pts. undergoing the Third-line treatment, 15 experienced a new remission, 13 of which were partial remissions and 2 were complete remissions. Tumorreduction was observed in 8 pts, although this reduction was less than 50 %. The average remission rate was 6.5 months - however remissions up to 19 months were observed.
In spite of the massive Second-line therapy which normally included 2 cytostatic agents, hormone and radiation therapy, general toleration was good. The most prominent side-effect were bone marrow toxicity and erythropoesis. Blood transfusions were therefore indicated for those patients in remission who undergo long-term chemotherapy.
Third-line therapy in metastasizing breast cancer with Mitomycin, Vincristine and Prednison resulted in a 37 % remission rate with a good subjective tolerance to the side-effects of the drugs.

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MONOTHERAPY WITH IDARUBICIN (4-DEMETHOXY-DAUNORUBICN) IN ADVANCED BREAST CANCER (ABC)

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Background and aims: Oral 4-demethoxydaunorubicin (4-dm-DNR), a new analogue of daunorubicin, has been found to be effective in ABC. A phase II trial showed the therapeutic effect of 4-dm-DNR for the first time in pts with ABC who had received no prior chemotherapy. Patients and methods: 31 pts were recruited. Characteristics: mean age: 58 (36-78); metastatic sites: osseous 8, soft tissue 8, hepatic 1, pulmonal 2, two sites 10, >two sites 2; regimen: idarubicin 30 mg orally days 1-3 (total 90 mg) every 3 weeks. Results: 156 cycles were given. 25 pts were evaluable (more than 2 cycles):

	N	%	duration of remission in months	cycles
CR	1	4	+ 9	12
PR	6	24	+ 7.5 (4-10)	8 (5-12)
NC	13	52	+ 4.0 (3-7)	5 (3-10)
PD	5	20		4 (3-6)

Main side-effects in 31 pts were nausea/vomiting (23) (WHO I (14), II (7), III (2)), alopecia (16) (WHO I (11), II (4), III (1)), transient exhaustion (13), mild infections (8), loss in weight >3 kg (7) (3.5-9 kg), diarrhoea (5), stomatitis (3) (WHO I (2), III (1)), blood transfusions (4). A delayed application was given 14x and a dose reduction 4x due to haematological toxicity (leucopenia). WBC nadir of cycle I: WHO 0 (9), I (11), II (8), III (3), IV (0); cycle II: WHO 0 (4), I (15), II (8), III (1), IV (0). No systemic variations have been noted in the cardiac radionuclide ejection fractions so far. Conclusions: Oral idarubicin is effective in ABC. Objective remissions are not to be gained with less than 4-6 cycles.

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LEUCOCYTE NADIR ADAPTED CHEMOTHERAPY (LNAC) IN PATIENTS (PTS) WITH ADVANCED BREAST CANCER (ABC) (VAC/MPA VERSUS VEC/MPA)

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Aims: To gain first experiences with LNAC in pts with ABC. Patients and methods: Pts of poor prognosis with ABC were given (v)indesine 3 mg/m² i.v. on days 1 and 12 when the leucocyte nadir was expected, (a)driamycin or (e)pirubicin 40 mg/m² i.v. on days 1 and 12 and (c)yclophosphamide 200 mg/m² per os on days 3 to 6 and 14 to 17 with medroxyprogesterone acetate (MPA) 1500 mg per os daily during induction and 1000 mg thereafter until relapse. These double cycles were repeated twice at 3 weekly intervals for a total induction period of 15 weeks. Results:

	VAC/MPA N	%	duration of remission	VEC/MPA N	%	duration of remission
CR	8	29.6	+ 25 (5-36)	9	52.9	+ 9.5 (6-14)
PR	13	48.2	8.4 (4-13.5)	2	11.8	+ 8.0 (5-11)
NC	6	22.2	6.2 (2-13)	6	35.3	+ 5.0 (4-7)
PD	0	0		0	0	

The induction treatment was mostly well tolerated. Discontinuation of therapy was not necessary. The most serious complications, e.g. stomatitis, infectious episodes, anaemia and thrombosis, were overcome by appropriate supportive therapy. Myelotoxicity was distinctly inferior in the regimen with epirubicin. No dose-limiting cardiac toxicity was observed in pts regularly controlled by LVEF, ECG, CK and CKMB. Conclusions: It is possible to obtain a high number of remissions with LNAC, which seem to need no therapy to be maintained longer than responders to chemotherapy of more usual regimens. These data justify prospective randomized trials of LNAC as a new form of induction therapy.

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MITOXANTRON AND CYCLOPHOSPHAMID AS SECOND LINE CHEMOTHERAPY IN DISSEMINATED BREAST CANCER

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Mitoxantron (N), an anthracenedione, has proved to be effective in chemotherapy of breast cancer. Early trials suggested comparable effectiveness with lower toxicity rate (cardiotoxicity, alopecia, gastrointestinal) with regard to Adriamycin.
N 12 mg/sqm and Cyclophosphamid (C) 600 mg/sqm d 1 q 3-4 w were assessed as second line therapy. 50 pts entered this phase II trial, 20 pre- 30 postmenopausal, median age 57 ys (range 27-73), all pretreated usually with CMF.
Of 43 evaluable pts none achieved complete remission (CR), 8 partial (PR) and 19 stable disease (SD) according to WHO criteria. Response rate (CR+PR) 19%. Median duration of PR 5.5 months and of SD 4. Among responders there was no predominating site of metastasis. PR, SD and progressive (PD) pts did not show differences in prognostic criteria e.g. time of disease since diagnosis.
The most important side effect was considerable myelosuppression. 56% of documented leucocyte nadir below 2000/cmm. Thrombopenia below 50000/cmm in only one pt. No infectious complications were seen. Alopecia and gastrointestinal side effects were mild. Cardiotoxicity was surveyed by serial echocardiograms, ECG and at higher cumulative doses radionucleidventriculograms. On the average echocardiographic shortening fractions (SF) did not deteriorate. Individually 2 pts showed significant decline in SF: one pt pretreated with ADM 580 mg/sqm develloped congestive heart failure after additional N 36 mg/sqm. The other pt irradiated at left side chest dropped with SF after N 12 mg/sqm without clinical symptoms.
We conclude: 1) N+C is an effective and tolerable combination 2) Low toxicity recommends N especially for palliative treatment, 3) cardiotoxicity must be expected even after low dose of N in pts pretreated with ADM or irradiation.

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