Liv 06

AUTOMATIC ANTICANCER CHRONOTHERAPY USING IMPLANTED PROGRAMMABLE PUMPS: AN ATTEMPT TO IMPROVE THERAPEUTIC INDEX.
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Toxicity and efficacy of at least a dozen most commonly used cytotoxic drugs vary predictably depending upon the time of day when they are given (W. Hrushesky, Science 228,73-75,1985). In a series of murine experiments involving more than 700 CD_2F_1 mice and F344 rats, we have repeatedly shown that the safest time for FUDR administration is the mid- to late-activity span.
An implantable, programmable drug administration device (Medtronic, Inc.), allowing automatic dose modifications of continuous longterm infusion, was implanted in 19 patients (pt), while 26 pt received an Infusaid pump for continuous flat infusion. 31 pt with metastatic adenocarcinomas confined to the liver received intra-arterial hepatic (IA) FUDR infusions. Toxicity of the same daily dose of flat vs time-modified infusion patterns (6-hourly portions of 68% (3-9 p.m.),15%,2%,15%) was compared.

IA-FUDR Infusion (monthly 0.2-0.3mg/kg/dx14)

		flat	timed	X^2	p
No. of patients		22	8		
Hepatitis/cholangitis	(%)	46	25	2.8	<.05
Gastrointestinal tox.	(%)	67	0	9.9	<.01
Dose reductions	(%)	20	0		

14 patients with widely spread cancer received central venous (IV) FUDR either as flat or time modified continous infusion as above.

IV-FUDR Infusion (monthly 0.15 mg/kg/day x14)

	flat	timed	X^2	p
No. of courses	13	7		
Severe diarrhea	8	0	10.1	<.03
Hospital admissions	5	0		
Dose reductions	4	0		

This time qualified infusion-chemotherapy is less toxic.

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Liv 07

ARTERIAL CHEMOTHERAPY OF LIVER METASTASES USING IMPLANTABLE INFUSION SYSTEMS
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In a multicenter trial regional chemotherapy of liver metastases was performed in 17 patients, in whom the following primary tumors were diagnosed: 15 colorectal cancer, 1 neurofibrosarcoma, 1 primary hepatocellular cancer. A subcutaneous catheter system (Port-A-Cath^R) was implanted into the common hepatic artery via the gastroduodenal artery. The chemotherapy was given as follows. Day 1: 20 mg 4-Epirubicin as bolus. Day 3 - 4 : 40 mg 4-Epirubicin as infusion over 48 hours. Day 22-25 : 20 mg 4-Epirubicin as daily bolus combined with 450 mg microspheres (Spherex^R). The therapy was repeated after 18 days up to a maximum of 7 courses. In 2 of 7 patients a decrease of CEA occured, the other 5 patients had constant CEA values. Complications such as thrombosis, infection, and liver failure occured in 7 patients and caused interruption of therapy in 5 patients. Abdominal pain and nausea has been observed as side effect after microsphere injection. The evaluation showed alopecia when a thrombosis of the hepatic artery led to systemic delivery of the cytostatic drug by retrograde flow into the aorta or a.v. shunting of big necrotic metastases.. In 12 out of 13 patients with more than 2 therapeutic courses no further tumor growth could be observed. In 3 patients an extrahepatic recurrence was seen during therapy. 8 of these 13 patients are still alive, with a median survival time of 5+ months, 7 patients are still under therapy. The venous blood concentration of 4-Epirubicin was not found to be different when 4-Epirubicin was injected with or without microspheres.
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Liv 08

CONTINOUS INTRAARTERIAL CHEMOTHERAPY FOR LIVER METASTASES - A JUSTIFIABLE THERAPY PROTOCOL?
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The continous intraarterial chemotherapy via an implantable pump was propagated by some authors to be the therapy of choice for liver metastases having response rates of about 80%. Recent controlled studies, however, show realistic response rates of 50-60% according to the WHO guide lines. Now it also appears, that the complication rate is not quite significant.
Patients: In the last 3 years we implanted 48 pumps on patients having gastrointestinal tumors (colon carcinoma n=40, gastric carcinoma n=4, hepatocellulary carcinoma n=4).
Results: Complete remission n=2, partial remission n=26, stable disease n=9, progression n=11
Complications: So called chemical hepatitis n=12, biliary sclerosis n=4, ulcus ventriculi n=3.
Catheter complications: vessel thrombosis n=4, catheter perforation n=1, infection n=1.
Summary: The response of the continous intraarterial chemotherapy being 58% is clearly higher than that of conventional systemic therapy protocols. The complication rate, however, being nearly 40% is also extremely high, the usual side effects of cytotoxic drugs not even being considered.
Conclusion: The complication rate of the continous intraarterial chemotherapy must be lowered by changing therapy protocols in order to achieve a reasonable advantage/disadvantage relation.

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Liv 09

DRUG TESTING IN REGIONAL CHEMOTHERAPY (RC).
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In vitro chemosensitivity testing with the 'Human Tumor Colony-forming Assay' (HTCA) was performed in 70 pts with liver tumors of various primary origin, to be treated by 'High Dose Intraartrial Chemotherapy' (HDIAC). The biopsies were taken at surgery for Implantofix-catheter insertion and tested with the drugs to be used for HDIAC. The chosen test concentrations in vitro corresponded to the achievable drug levels in vivo. If possible, additional drugs at various doses were tested to identify alternative drugs and to confirm dose response behaviour.
The overall sensitivity (= inhibition of the colony forming efficiency in vitro by ≥50%) at the drug levels relevant for HDIAC was 36%.
In 30 pts with liver metastases (24 colorectal, 4 melanoma, 1 breast, 1 carcinoid) the HTCA results were correlated to the clinical response (R) of HDIAC in a prospective correlative trial. In these cases, sensitivity in vitro was associated with R in vivo in 100%, for resistance in vitro this value was 73%. Overall, the in vitro results in the HTCA correlated correctly with the R in HDIAC in 90%.
Our results indicate the clear dose response of solid tumors to various drugs in vitro and the reliability of drug testing in vitro for RC.
- A prospective decision-aiding study to identify active drugs for clinical application in HDIAC has been activated.

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