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Short communication

Combined haemoperfusion, haemofiltration and haemodialysis for systemic detoxification in locoregional 5-fluorouracil therapy

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Summary. Combined haemoperfusion, haemofiltration and haemodialysis (HPFD) was examined for its systemic effect on 5-fluorouracil (5-FU) kinetics after locoregional application to one female patient with liver metastases of a colon carcinoma. During each HPFD treatment, which lasted 4 h, 5-FU was given via a port-a-cath system into the hepatic artery on 4 separate days. The HPFD extraction rate was 99%. Extracorporal 5-FU clearance (89 ml/min) was 9% of total body clearance (1094 ml/min). The fraction eliminated within 4 h was only 6% of the applied dose (3500–4000 mg 5-FU). Sufficient extracorporal detoxification during combined HPFD can thus not be guaranteed in locoregional chemotherapy with a high dose of 5-FU.

Introduction

Locoregional application of cytostatics may increase the response rate of tumours and decrease the therapeutic risk [10]. The locoregional cytostasis can be dosed even more effectively without increasing the rate of side-effects, if the fraction of the cytostatic reaching the systemic circulation can be immediately eliminated [1, 7, 11].

Extracorporal detoxification with combined haemoperfusion, haemofiltration and haemodialysis (HPFD) was examined for its effect on 5-fluorouracil (5-FU) kinetics in a female patient with liver metastases of a colon carcinoma.

Patients and methods

Patient. The 59-year-old woman was hemicolectomized in February 1988 because of an adenocarcinoma of the descending colon. In November, the radiological examination raised suspicion of one pulmonary metastasis and sonography that of two hepatic metastases (1 and 2 cm in diameter). During laparotomy in February 1989, three metastases were detected in the right and one in the left liver lobe so that resection was not carried out. Instead, a port-a-cath system was inserted in the hepatic artery for locoregional chemotherapy (12×1 g 5-FU for 90 min) and percutaneous irradiation was performed (12×2 Gy for 1–2 h). This treatment lasted 3 weeks and was repeated every 2 months.

Owing to a progression of the liver metastases in the presence of an otherwise good general condition (76 kg body weight, 170 cm height) and unchanged lung findings, the decision was made to carry out a high-dose locoregional cytostasis during concomitant extracorporal detoxification in order to prepare the patient for possible resection of the right liver lobe. Except for an increased alkaline phosphatase (243 U/l), the patient had normal laboratory values (leucocytes 9.1/nl, haematocrit 41 1/1, haemoglobin 14 g/dl, thrombocytes 127/nl, serum aspartate aminotransferase 9 U/l, serum alanine aminotransferase 12 U/l, creatinine 95 μmol/l).

Haemoperfusion, haemofiltration and haemodialysis. To perform combined haemoperfusion, haemofiltration and haemodialysis (HPFD), a double-lumen Shaldon catheter was placed into the right internal jugular vein. Haemodialysis was done with controlled ultrafiltration and an additional biofiltration programme (Monitral Hospal). A high-flux dialyser with a polysulphone membrane was used (F60, Fresenius). A resin-coated charcoal haemoperfusion cartridge (Hemosorba CH-350, Ashai) was interposed into the dialysis system prior to the dialyser. Haemofiltration of 4000 ml filtration solution (HF/41 4500 ml, Fresenius) was done in addition to haemodialysis and haemoperfusion. HPFD with a blood flow of 200 ml/min, a dialysate flow of 500 ml/l and heparinisation of 2000 U/h was carried out for 4 h each.

Cytostasis. A dose of 200 mg/m^2 folic acid was given intravenously as a bolus (400 mg) 10 min before dialysis was started. The dose of 3500–4000 mg 5-fluorouracil was administered by continuous infusion. The 5-FU infusion was applied in the hepatic artery via the locoregional port-a-cath system for 2.5–3.5 h (150–210 min) during the 4-h HPFD treatment.

5-Fluorouracil measurement and calculations. During dialysis, between three and five blood samples were taken at different time intervals, each of them simultaneously from the arterial and the venous line of the dialysis system (Fig. 1). The samples were taken in heparinized 5-ml syringes, sealed air-tight, centrifuged (15000 rpm) and deep-frozen at −20° C. The concentration of 5-fluorouracil was determined by high-pressure liquid chromatography (HPLC) in a specialized laboratory (Prof. Gundert-Remy, Federal Health Agency, Berlin). HPLC was carried out with an ODS-hypersil-coated chromatography column at a wave length of 254 nm [3].

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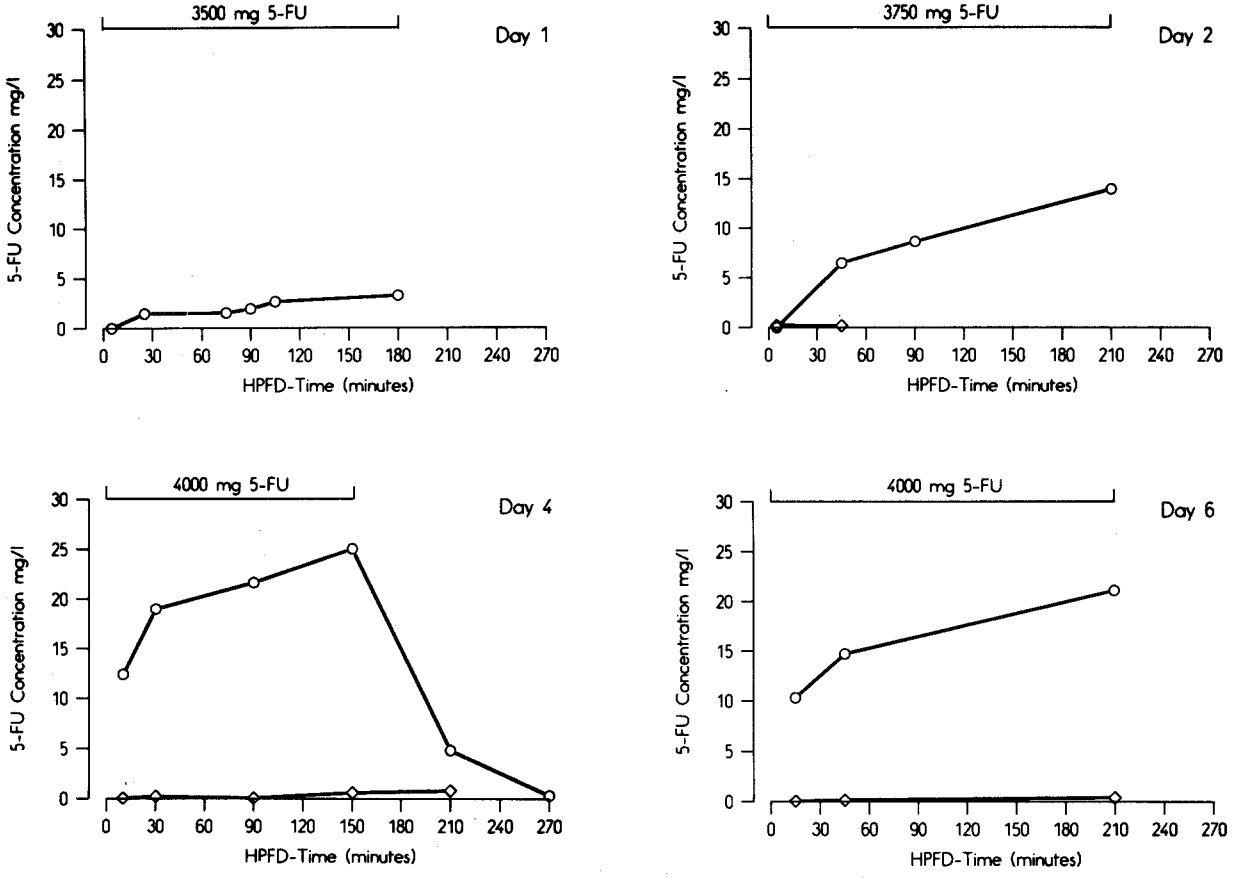

Fig. 1. Course of the 5-fluorouracil concentration (*5-FU*) in combined haemoperfusion, haemofiltration and haemodialysis (*HPFD*). Each HPFD was performed for 4 h and 5-FU was given as a continuous infusion in the hepatic artery via the port-a-cath. The concentrations were measured in the arterial (○) and the venous line (◇) of the HPFD system. On days 4 and 6, the arterial concentrations were in the toxic range (>3.0 mg/l)

Total body clearance (C_{tot}) was calculated from the plasma concentration (c_{ss}) at the end of continuous infusion and from the infusion rate (D/t) of 5-FU ($C_{tot} = [D/t]/c_{ss}$), where D is the applied dose. The extraction rate (E) was calculated from the difference of the concentration in the arterial (c_{art}) and the venous (c_{ven}) line [$E = (c_{art} - c_{ven})/c_{art}$]. The extracorporal clearance (C_{HPFD}) was calculated from the extraction rate, the blood flow (Q) and the haematocrit (H_k) value ($C_{HPFD} = Q\,H_k\,E$). The total eliminated amount (R_{AUC}) was calculated from the area under the concentration/time curve (AUC_t) and the clearance (C_{HPFD}) of the system ($R_{AUC} = C_{HPFD}\ AUC_t$). AUC_t was determined according to the trapezoidal rule.

On day 4, the 5-FU dose was infused within 2.5 h and three successive concentrations were measured to calculate the elimination rate constant (k_e) by ln-linear regression from the drop in blood levels after the end of infusion. The elimination half-life ($t_{1/2}$) was calculated from the elimination rate constant ($t_{1/2} = 0.693/k_e$). The distribution volume (V_d) was calculated from the total body clearance and the elimination rate constant ($V_d = C_{tot}/k_e$). At the third HPFD, venous blood was withdrawn after the haemoperfusion cartridge and before the dialyser yielding the exclusive extraction rate of the haemoperfusion cartridge.

In addition, several dialysate samples were obtained. The dialysed amount (R_{dial}) was calculated from the concentration in dialysate (c_{dial}) measured at several time intervals (Δt_i) during the duration of the dialysis (t) and the flow (Q_{dial}) of the dialysate [$R_{dial} = \Sigma(c_{dial}\ Q_{dial}\ \Delta t_i)$], whereby $\Sigma(\Delta t_i) = t$. The difference of the total eliminated amount and the amount eliminated in the dialysate corresponds with the amount absorbed (R_{abs}) on the charcoal cartridge ($R_{abs} = R_{AUC} - R_{dial}$).

The total eliminated amount (R_{AUC}) was related to the applied dosage (D) to determine the eliminated fraction (f_R) as the measure of effectivity ($f_R = R_{AUC}/D$).

Results

A total of four locoregional 5-FU applications were done during concomitant HPFD on day 1, day 2, day 4 and day 6 (Fig. 1). The total body clearance (C_{tot}) was 1094 ml/min, the half-life ($t_{1/2}$) was 19 min, the distribution volume (V_d) was 21 l, the extracorporal clearance (C_{HPFD}) was 89 ml/min and the eliminated fraction (f_R) was 6% (Table 1).

The patient had a pancytopenia (leucocytes 1.1 /nl, erythrocytes 2.6/pl, haemoglobin 9.8 g/dl, thrombocytes 14 /nl) and mucositis 1 week after the last application, from which she recovered only 3 weeks later. Computerized tomography revealed a decrease in the size of the metastases in the right liver lobe. The single metastasis in the left liver lobe was no longer detectable. However, a resection of the right liver lobe could not be carried out because of the poor general condition of the patient. The patient was discharged 8 weeks after treatment. She died 10 months later from a progression of the malignant disease.

Discussion

The antimetabolite 5-fluorouracil (5-FU) affects tumour cells by influencing different RNA functions [8]. Fluoro-

Table 1. Pharmacokinetic parameters of 5-fluorouracil (5-FU) after continuous locoregional intrahepatic application and combined haemoperfusion, haemofiltration and haemodialysis (HPFD) for 4 h

Parameter	Day 1	Day 2	Day 4	Day 6	Median
Dose D (mg)	3500	3750	4000	4000	3875
c_{ss} (mg/l)	3.2	13.9	25.1	21.1	17.5
Total body clearance C_{tot} (ml/min)	5208	1285	759	903	1094
$t_{1/2}$ (min)			19.1		19.1
V_d (l)			20.9		20.9
Extraction rate E	0.98±0.04	0.99	0.99±0.05	0.99±0.01	0.99
Extracorporal clearance C_{HPFD} (ml/min)	89 ±3.5	89	88 ±2.5	89 ±1	89
AUC (min mg/l)	370	1824	3894	3409	2617
R_{AUC} (mg)	33	163	346	305	234
R_{dial} (mg)	0	21	18	39	21
R_{AUC}/D (f_R)	0.01	0.044	0.087	0.076	0.06

uracil (1 mg = 7.53 μM) is quickly metabolized by the liver after intravenous application. Total body clearance is normally 1000 ml/min, the half-life 18 min and the distribution volume 18 l [5]. Protein binding is 0% and dialysability was given as 37% [6]. Non-toxic plasma concentrations were between 0.5 mg/l and 3.0 mg/l [3]. There is a linear correlation between the myelotoxic sideeffects of 5-FU and the area under the concentration curve (AUC) in the systemic circulation [5]. 5-FU cardiotoxicity, which is not dose-dependent, is an additional risk [4].

It was unknown whether extracorporal 5-FU elimination would be most efficient by haemoperfusion, haemofiltration or haemodialysis. Therefore combined HPFD detoxication was applied to obtain the maximal efficacy. It has been shown for methotrexate detoxification that the efficacy of combined haemodialysis and haemoperfusion is superior to that of either method alone [9]. Combined HPFD had only a limited effect on 5-FU elimination. HPFD could not reduce the systemic toxicity of 5-FU in a locoregional cytostasis. Extracorporal clearance was only 9% of the total body clearance. Despite an HPFD extraction rate of 99% for 5-FU, only 6% of the the applied dose is actually eliminated, the most important fraction (9/10) being eliminated via the charcoal haemoperfusion cartridge.

An additional problem was that just a 1.25-fold increase of the dose led to a 10-fold increase of the area under the curve, resulting in an overdose with considerable systemic side-effects. Unfortunately, no 5-FU concentrations were measured on days 4 and 6 before the start of 5-FU infusion. But after cessation of 5-FU infusion (day 4) the blood concentration rapidly decreased (0.3 mg/l). No 5-FU was given on day 3 and day 5. Therefore, the high 5-FU concentrations (days 4 and 6 at 10 min and 15 min respectively), must be explained by saturation kinetics, not accumulation kinetics. Such saturation kinetics of hepatic 5-FU elimination occurs at concentrations of more than 3.0 mg/l and a dose of more than 4000 mg/24 h [2, 13].

Further efforts must be directed towards adjusting the 5-FU dose to the extracorporal detoxification and defining the maximum tolerated dosages. The prerequisite for such a therapy, however, is a therapeutic drug monitoring and rapid availability of the cytostatic blood level within 24 h.

References

1. Aigner KR, Helling HJ, Link KH, Walther H, Bill G (1985) Zytostatikafiltration unter regionaler Chemotherapie. Beitr Onkol 21: 229–245
2. Boublil JL, Milana G, Khater R, Bourry J, Thyss A, Bruneton JN, Renee N, Philip C, Namer M (1985) Continuous 5-day regional chemotherapy by 5-fluorouracil in colon carcinoma: pharmacokinetic evaluation. Br J Cancer 52: 15–20
3. Calabro-Jones PM, Byfield JE, Ward JF, Sharp TR (1982) Time-dose relationships for 5-FU cytotoxicity against human epithelial cancer cells in vitro. Cancer Res 42: 4413–4420
4. Freeman NJ, Kostanza ME (1988) 5-Fluorouracil-associated cardiotoxicity. Cancer 61: 36–40
5. Goldberg JA, Kerr DJ, Willmott N, McKillop JH, McArdle CS (1988) Pharmacokinetics and pharmacodynamics of locoregional 5-fluorouracil (5 FU) in advanced colorectal liver metastases. Br J Cancer 57: 186–189
6. Keller F, Schwarz A (1987) Pharmakokinetik bei Niereninsuffizienz. Fischer, Stuttgart, p 176
7. Kihara T, Nakazawa H, Agishi T, Honda H, Ota K (1988) Superiority of selective bolus infusion and simultaneous rapid removal of anticancer agents by charcoal haemoperfusion in cancer treatment. ASAIO Trans 34: 581–584
8. Parker WB, Cheng YC (1990) Metabolism and mechanism of action of 5-fluorouracil. Pharmacol Ther 48: 381–395
9. Relling MV, Stapleton FB, Ochs J, Jones DP, Meyer W, Wainer IW, Crom WR, McKay CP, Evans WE (1988) Removal of methotrexate, leucovorin, and their metabolites by combined haemodialysis and haemoperfusion. Cancer 62: 884–888
10. Safi F, Roscher R, Bitter R, Schumacher KA, Gaus W, Berger HG (1989) Regionale Chemotherapie von Lebermetastasen kolorektaler Karzinome. Dtsch Med Wochenschr 114: 1478–1483
11. Sauer H, Füger K (1989) Haemodialysis of cytostatic drugs in vitro and in vivo (abstract). Blut 59: 276
12. Schalhorn A, Kühl M (1988) Pharmakokinetik von 5-Fluorouracil und Lekovorin. In: Nagel GA, Sauer R, Schreiber HW (eds) Aktuelle Onkologie, vol 40. Karger, Basel, pp 20–37
13. Wagner JG, Gyves JW, Stetson PL, Walker-Andrews SC, Wollner IS, Cochran MK, Ensminger WP (1986) Steady-state nonlinear pharmakokinetics of 5-fluorouracil during hepatic arterial and intravenous infusions in cancer patients. Cancer Res 46: 1499–1506