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ORIGINAL ARTICLE

Pharmacokinetics of oxaliplatin in patients with severe hepatic dysfunction

Martina Baur · Anne Drescher · Margit Gneist · Christian Dittrich · Ulrich Jaehde

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Abstract
Purpose Data are lacking on the pharmacokinetics of oxaliplatin in patients with severe hepatic dysfunction. The aim of this study was to determine the pharmacokinetic parameters of platinum after administration of oxaliplatin in cancer patients with severe hepatic impairment due to extended metastases into the liver.
Patients and methods Two female breast cancer patients and one male colon cancer patient were treated with oxaliplatin monotherapy at 130 mg/m^2 given as a 3-h intravenous infusion. The patients exhibited bilirubin concentrations of 9.6, 22.5 and 41.1 mg/dl indicating severe hepatic dysfunction. Serial blood samples were collected immediately before treatment, and at fixed intervals up to 27 h after start of therapy. Platinum concentrations in plasma, ultrafilterable plasma, and whole blood were determined using a validated flameless atomic absorption spectrometry (FAAS) method. Pharmacokinetic data analysis was performed assuming a two-compartment model. Individual pharmacokinetic parameters were compared with a reference population with normal hepatic function.
Results The area under the curve (AUC from 0 to infinity) as well as the elimination half-life of platinum in ultrafilterable plasma were substantially increased and clearance accordingly decreased in the three patients with severe hepatic dysfunction. In plasma and whole blood, the deviations from the reference population were less pronounced. However, partial AUC from 0 up to 2 h after end of infusion reflecting better the exposure with cytotoxic platinum species was not different or only slightly altered. Moreover, no acute oxaliplatin-associated neurotoxicity was observed.
Conclusions The comparable platinum exposure early after administration in conjunction with the lack of acute toxicity do not support a dose reduction of oxaliplatin in patients with markedly elevated bilirubin concentrations. However, a larger number of patients must be examined before valid dose recommendations can be derived.

Keywords Oxaliplatin · Pharmacokinetics · Hepatic dysfunction · Liver dysfunction · Dose adaptation

M. Baur · M. Gneist · C. Dittrich
Applied Cancer Research-Institution for Translational Research Vienna (ACR-ITR VIEnna), Vienna, Austria

M. Baur · M. Gneist · C. Dittrich
Ludwig Boltzmann-Institute for Applied Cancer Research (LBI-ACR VIEnna), Vienna, Austria

M. Baur · C. Dittrich
3rd Medical Department Centre for Oncology and Hematology, Kaiser Franz Josef-Spital, Vienna, Austria

A. Drescher · U. Jaehde (✉)
Institute of Pharmacy, Department of Clinical Pharmacy, Rheinische Friedrich-Wilhelms-Universität Bonn, An der Immenburg 4, 53121 Bonn, Germany
e-mail: u.jaehde@uni-bonn.de

Introduction

Approximately 50–60% of colorectal cancer patients will develop hepatic metastases during the course of their disease [1]. Preoperative treatment of liver metastases with a curative intention or palliative treatment with oxaliplatin (Eloxatin®) result in high response rates and prolongation of survival [2, 3]. Oxaliplatin is also very effective in upper gastrointestinal cancer patients frequently exhibiting liver metastases [4]. In addition, efficacy has also been shown in pretreated patients with metastatic breast cancer [5].

The pharmacokinetic disposition of oxaliplatin has been described mainly by measuring platinum concentrations determined by flameless atomic absorption spectrometry (FAAS) or inductively coupled plasma mass spectrometry (ICP-MS). The alpha half-life of ultrafilterable plasma platinum ranges from 10 to 30 min and its beta half-life from 15 to 30 h. Using the more sensitive ICP-MS method, a gamma half-life of about 270 h was described representing a third elimination phase [6, 7]. Binding to plasma proteins (mainly albumin and gamma-globulins) occurs rapidly and is irreversible [8]. Oxaliplatin rapidly crosses cellular membranes due to its lipophilicity. Approximately 40% of blood platinum is found in erythrocytes at the end of a 2-h infusion. Elimination half-life of platinum in erythrocytes is 12–50 days reflecting erythrocyte turnover [6]. Thirty to 50% of the administered platinum are recovered in the urine within 2–5 days, the predominant route of elimination [6]. Renal clearance of platinum is correlated with glomerular filtration rate [9].

Hepatic metastases occur frequently and often lead to hepatic dysfunction as indicated by liver function test abnormalities. Since many anticancer agents are eliminated by the liver, it is of upmost interest for the clinician to know whether the dose has to be adapted in those patients in order to prevent nontolerable toxic adverse effects [10]. Although, the liver is not the major elimination organ for oxaliplatin, it seems prudent to know whether the pharmacokinetic disposition is altered in patients with severe hepatic dysfunction. So far, only a working group of the NCI investigated the platinum pharmacokinetics in patients with mild, moderate or severe hepatic dysfunction after administration of oxaliplatin [11]. The authors did not find major alterations in platinum concentration-time profiles, even in patients with severe hepatic dysfunction indicated by serum bilirubin concentrations higher than 3 mg/dl [11]. Since the exact range of bilirubin concentrations is not reported in that publication it is still unclear whether patients with extremely high bilirubin concentrations should receive normal or reduced doses [10].

We treated three patients with metastatic cancer and extensive liver involvement with oxaliplatin monotherapy using the dose of oxaliplatin of 130 mg/m^2 every 3 weeks which represents the recommended dose from phase I trials. The recommended infusion duration is 2 h [6, 12]. The infusion time was prolonged to 3 h bearing in mind that in case of severe hepatic dysfunction the predominant toxicity of oxaliplatin, i.e. neurotoxicity, might be increased. Prolongation of infusion time is recommended in the case of acute neurologic sensations [13]. Before initiation of treatments, the three patients exhibited extremely high bilirubin concentrations. We report here the pharmacokinetic disposition of platinum in plasma, ultrafilterable plasma and whole blood for this special group of patients.

Methods

All patients were instructed in detail about the experimental nature of their therapy and signed a written informed consent. Blood samples of 5 ml were collected immediately before treatment, at 0.5, 3.5, 5.3 and 27 h after start of therapy in the first patient, and immediately before treatment, at 0.5, 2, 3, 3.5, 6, 8 and 27 h after start of therapy in the second and third patient. For analysis of platinum in the whole blood, two 200 µl samples were stored at –20°C. The residual blood was centrifuged at 3,200 g and 4°C for 5 min, and two 200 µl plasma samples were stored at –20°C. For ultrafiltration, 1 ml of plasma was transferred to a Centrisart™ ultrafiltration system (Sartorius AG, Göttingen, Germany; cut off 10,000) and centrifuged for 20 min at 2,000 g and 4°C.

Platinum concentrations in plasma, ultrafilterable plasma and whole blood were determined by a flameless atomic absorption spectrometry method [14] using an atomic absorption spectrometer (SpectrAA™ Zeeman 220; Varian, Darmstadt, Germany) equipped with a graphite tube atomisator (GTA 100), a programmable sample dispenser (PSD 100) and a platinum hollow cathode lamp (UltrAA™ lamp). The temperature program was optimised for each matrix and concentration range. After a matrix-based calibration, samples were measured after a single dilution step with Triton™ solution 1% (Triton™ X-100, Sigma-Aldrich Chemie, Steinheim, Germany) or nitric acid 6.5% (dilution of nitric acid ''Suprapur'', 65% (V/V), Merck, Darmstadt, Germany). Blood cells in whole blood samples were lysed with nitric acid 65% (V/V) at 60°C before analysis. The method was validated and met the international requirements on bioanalytical methods [15]. The intra-erythrocyte concentrations (C_e) were calculated from whole blood concentration (C_b), plasma concentration (C_p) and hematocrit (Hct) according to $C_e = [C_b - C_p \cdot (1–Hct)]/Hct$.

Individual pharmacokinetic parameters in ultrafilterable plasma, plasma and whole blood were estimated using a compartmental approach. Data analysis was performed by means of the validated software WinNonlin™ 4.0 (Pharsight Corporation, California). The following secondary parameters were calculated assuming a two-compartment model: area under the concentration-time curve from 0 to infinity ($AUC_{0–\infty}$), total clearance (CL), volume of distribution at steady-state (V_{ss}), and beta elimination half-life ($t_{1/2\beta}$). Since parent oxaliplatin is eliminated rapidly from plasma with a half-life of 0.3 h [16] to metabolites with presumably less or no cytotoxic activity [16, 17] we also estimated the partial platinum AUC from 0 to 2 h after the end of infusion ($AUC_{0–2h}$). It was assumed that $AUC_{0–2h}$ might better reflect exposure with active platinum than $AUC_{0–\infty}$. Intra-erythrocyte AUC was calculated using the trapezoidal rule.

The pharmacokinetic parameters of the three patients were compared with a cohort of 33 patients with normal hepatic function exhibiting bilirubin values between 0.21 and 1.17 mg/dl. Platinum concentrations of these patients in ultrafilterable plasma, plasma and whole blood were determined in a different study where patients were also treated with 130 mg/m^2 oxaliplatin but in combination with the multiple kinase inhibitor sorafenib [18, 19]. The infusion time of oxaliplatin was 2 h. For a valid comparison, only concentrations under oxaliplatin monotherapy, i.e. before the start of sorafenib treatment, were used for pharmacokinetic data analysis. In addition, only concentrations until 24 h were considered as only samples up to this time-point were available from the three patients with severe hepatic dysfunction.

Case reports

Case report 1

A 75-year-old woman was admitted with breast cancer metastatic to the liver, lungs and bones. The patient had been pretreated with palliative chemotherapy consisting of epirubicin monotherapy in first-line, gemcitabine monotherapy in second-line and the combination of capecitabine and vinorelbine in third-line. The last treatment cycle of capecitabine and vinorelbine was administered in September 2003. Because of disease progression in November 2003 when the patient exhibited multiple nodules in all liver segments, oxaliplatin monotherapy was started as fourth-line therapy.

Oxaliplatin 130 mg/m^2 on day 1 was given in a 3-h intravenous infusion. The patient's demographic and laboratory data before start of treatment are summarised in Table 1. The cutaneous colorit was icteric, the liver was enlarged, three fingerbreadths. There were spider-naevi on the trunk and scratch marks on the skin due to itching. Physical examination of the caput, collum, heart, the lungs and mammae were normal as well as the blood pressure and the heart rate. Computed tomography excluded signs of extrahepatic bile duct occlusion and revealed multiple lung metastases measuring 9 mm in dimension at maximum, a small right-sided pleural effusion and multiple osteosclerotic bone metastases.

The patient tolerated the infusion of oxaliplatin very well. There were no signs of acute toxicity, in particular no acute emesis, no diarrhea, no laryngospasms and no muscle cramps. The patient was dismissed 2 days later at her request exhibiting the same performance status as that at admission. Thereafter, no laboratory monitoring or clinical visit could be done because of the deteriorating performance status of the patient. The patient died at home 17 days after start of treatment. No autopsy was performed.

Table 1 Demographic and laboratory data of the three patients with severe hepatic dysfunction before start of oxaliplatin administration

	Normal range	Case 1	Case 2	Case 3
Age (years)	NA	75	66	54
Weight (kg)	NA	86	85	77
Height (cm)	NA	168	68	178
BSA (m^2)	NA	1.96	1.95	1.96
Karnofsky index (%)	NA	40	50	60
Bilirubin (mg/dl)	0.1–1.0	9.6	41.1	22.5
AP (U/l)	35–105	405	813	420
AST (U/l)	0–35	406	217	326
ALT (U/l)	0–35	208	111	184
GGT (U/l)	0–39	900	1,371	ND
LDH (U/l)	135–235	1,227	580	1,740
Total protein (g/l)	60–80	72.0	49.0	ND
-Albumin fraction (%)	55–70	42.3	34.4	ND
-γ-Globulin fraction (%)	10–20	32.7	ND	ND
Albumin (g/l)	35–52	ND	28.3	29.7
PT (%)	70–130	95	48	ND
Creatinine (mg/dl)	0.5–1.0	1.23	1.23	2.58
GFR (ml/min)	≥60	63	47	36
Hemoglobin (g/dl)	13–17	12.3	14.3	9.4
WBC (10^9/l)	4–10	13.9	10.7	12.8
Platelet count (10^9/l)	150–350	212	241	455

NA not applicable, *ND* not determined, *ALT* alanine transaminase, *AST* aspartate transaminase, *AP* alkaline phosphatase, *BSA* body surface area, *GFR* glomerular filtration rate, *GGT* γ-glutamyl transferase, *LDH* lactate dehydrogenase, *PT* prothrombine time, *WBC* white blood cells

Case report 2

A 66-year-old woman was admitted with breast cancer metastatic to the liver, the pleura and the bones. The patient had been operated by a lumpectomy of the left breast because of breast cancer, in January 2003. The tumor stage at diagnosis of breast cancer was pT3 L1 V0 pN2 (15/15) G3. Postoperatively, the patient underwent four cycles of adjuvant anthracycline-containing chemotherapy which was stopped because of side effects. Subsequently, locoregional irradiation of the left breast was performed. Since August 2003, an adjuvant hormone therapy with an aromatase inhibitor was prescribed. Since March 2004, mixed osseous metastases were known and were irradiated several times until January 2005 for palliation. Since April 2005, diffuse hepatic metastases occurred.

Because of a deteriorating performance status (50% according to Karnofsky), loss in weight of 16 kg, dyspnea, icterus and pain on the vertebral column and on the left hip,

the patient was hospitalised on 15 April 2005. Physical examination registered an icteric cutaneous coloration and a hand-breadth damping of the right lung because of a pleural effusion. Physical examination of the head, the collum, the breasts, the heart, as well as the blood pressure and the heart rate were normal. The computed tomography exhibited multiple disseminated intrahepatic nodules without signs of extrahepatic bile duct occlusion, an extensive right-sided pleural effusion and mixed osteoblastic–osteolytic metastastes of the bones. For alleviation of painful osseous metastases, irradiation of the left hip was performed. A porth-a-cath system was implanted on the right subclavian vein.

Oxaliplatin was started as first-line systemic palliative therapy on 28 April 2005. The patients demographic and laboratory data before start of treatment are summarised in Table 1. Oxaliplatin 130 mg/m^2 on day 1 was given in a 3-h intravenous infusion. One day after oxaliplatin infusion, the patient vomited three times and reported a loss of appetite. There were no signs of diarrhea, laryngospasms or muscle cramps. Laboratory values on 29 April 2005 exhibited a further increase of bilirubin to 43.4 mg/dl, of alkaline phosphatase to 911 U/l and of creatinine to 1.41 mg/dl. The patients situation deteriorated from the next day after start of treatment. Three days later, the patient was completely bedridden and needed support by two nurses for her personal hygiene. Since 2 May 2005, respiratory breaks and fever of 38°C occurred. Intravenous diuretics and diazepam and subcutaneous opioids were administered. The patient died on 3 May 2005. No autopsy was performed.

Case report 3

A 54-year-old man was admitted with colon cancer metastatic to the liver, to retroperitoneal lymph nodes and to the peritoneum. The patient had been operated by a sigmoideostomy because of a stenotic rectosigmoid cancer in April 2005. This was followed by concomitant radiochemotherapy consisting of irradiation with 50.4 Gy to the field of the primary tumor and of three cycles of chemotherapy consisting of fluorouracil 319 mg/m^2 (equals a dose reduction of 25%) and calcium folinate (leucovorin) 20 mg/m^2, both administered as a bolus intravenously on days 1–5 repeated every 21 days. In July 2005, anterior resection and a protective colostomy were performed. Histology evolved invasive adenocarcinoma of the rectum ypT3d G3 ypV0 ypL1 ypN2 (5/24), R1 resection (circumferential margin). A second resection was completed as R0 resection. Intraoperatively, the patient was irradiated with ten Gy on the field of the primary. From October to December 2005, adjuvant chemotherapy consisting of peroral capecitabine 2500 mg/m^2 daily for 14 days, every 21 days was performed. The patient tolerated the chemotherapy very well. A right hydronephrosis due to stenosis by lymph nodes had to be drained by a pig-tail catheter.

Because of intraabdominal pain and occurrence of an icterus the patient was admitted in the ward on 3 January 2006. Physical examination registered an icteric cutaneous coloration. Physical examination of the head, the lungs, the heart, the abdomen, the blood pressure and the heart rate were normal. Intrahepatic metastases with tumor nodules of 4 cm in diameter and a dilatation of the left ductus hepaticus caused by intrahepatic metastases were diagnosed; an extern–intern drainage had to be positioned on 9 January 2006. Cholangiography of 25 January 2006 showed a correctly positioned drainage catheter of the left bile duct with a narrow left bile duct but a highly strictured central intrahepatic duct. Hyperbilirubinemia deteriorated exhibiting bilirubin concentrations of 22.54 mg/dl on 26 January 2006. A porth-a-cath system was implanted on the right subclavian vein.

Oxaliplatin treatment with palliative intent was started on 26 January 2006 administering 130 mg/m^2 on day 1 in a 3-h intravenous infusion. The patient's demographic and laboratory data before start of treatment are summarised in Table 1. Already at start of treatment an impaired renal function indicated by an elevated creatinine concentration was present. Fluids, 3 l per day, were administered. There were no signs of diarrhea, vomitation, laryngospasms or muscle cramps due to administration of oxaliplatin. Bilirubin continued to be increased exhibiting a concentration of 20.8 mg/dl on 2 February 2006. Due to the deteriorating performance status parenteral nutrition was started. 3 days after infusion the patient had fever of 38.3°C, singultus, loss of appetite and obstipation. Renal function continuously deteriorated, exhibiting a creatinine concentration of 5.41 mg/dl on 3 February 2006. C-reactive protein (CRP) (normal values: 0.8–5 mg/l) increased to 272 mg/l. *Enterococcus faecium* sensitive to teicoplanin was cultured from three blood cultures requiring start of antibacterial therapy consisting of piperacillin-tazobactam and teicoplanin. Itroconazol was administered perorally due to a candidiasis of the mouth. Though fever declined and CRP decreased to 162 mg/l the performance status deteriorated obviously. The patient died on 4 February 2006 presumably due to the infection and consecutive renal failure. No autopsy was performed.

Results

In order to visualise and quantify potential alterations in pharmacokinetic disposition in patients with severe hepatic dysfunction a typical platinum concentration-time profile of the reference population (33 patients with normal

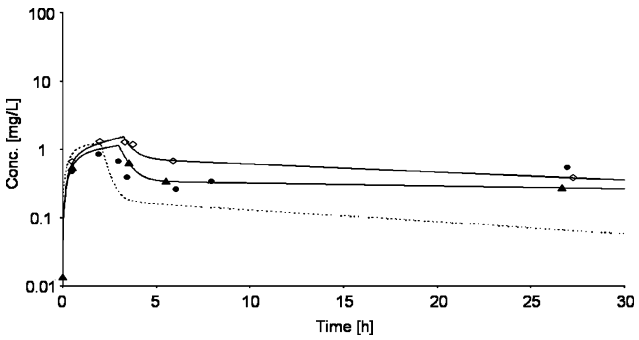

Fig. 1 Platinum concentration-time profiles in ultrafilterable plasma in patients with severe hepatic dysfunction after administration of 130 mg/m^2 oxaliplatin infused over 3 h, patient 1 ▲ *with line*, patient 2 ◇ *with line* and patient 3 ● (no curve fitting could be performed, see text) compared to patients with normal hepatic function (- -) (n = 33)

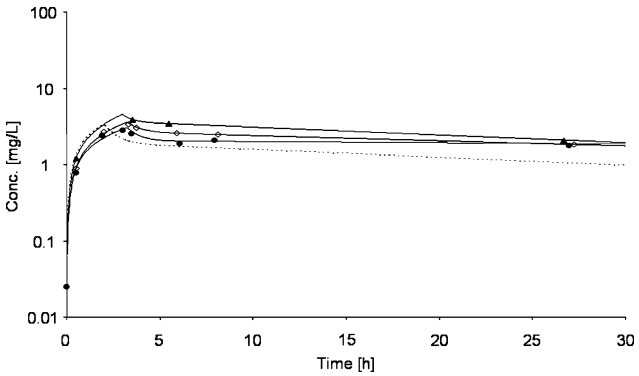

Fig. 2 Platinum concentration-time profiles in plasma in patients with severe hepatic dysfunction after administration of 130 mg/m^2 oxaliplatin infused over 3 h patient 1 ▲ *with line*, patient 2 ◇ *with line* and patient 3 ● *with line*, compared to patients with normal hepatic function (- -) (n = 33)

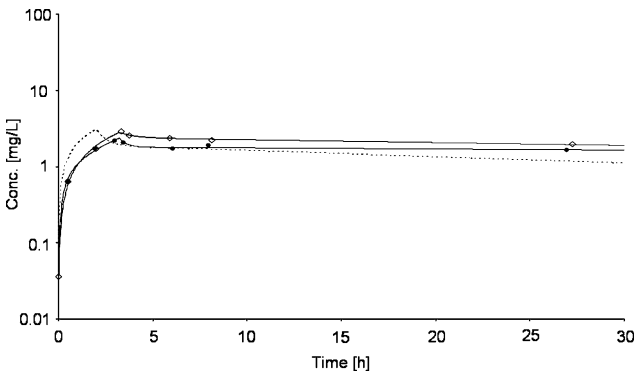

Fig. 3 Platinum concentration-time profiles in whole blood in patients with severe hepatic dysfunction after administration of 130 mg/m^2 oxaliplatin infused over 3 h, patient 2 ◇ *with line* and patient 3 ● *with line* compared to patients with normal hepatic function (- -) (n = 33)

hepatic function) was generated by fitting a two-compartment model to all concentrations simultaneously that were measured in the same body fluid. The respective curves and the individual concentration-time profiles of the three patients with severe hepatic dysfunction are shown in Figs. 1, 2, 3. The curves show higher platinum concentrations of the three patients in ultrafilterable plasma, plasma and whole blood.

The pharmacokinetic parameters of platinum in ultrafilterable plasma, plasma, and whole blood of the three patients with severe hepatic dysfunction are summarised in Tables 2, 3, 4. In addition, means and standard deviations as well as parameter values estimated by simultaneous curve fitting of all concentrations of the reference population are listed for comparison.

In ultrafilterable plasma, $AUC_{0-\infty}$ was six to seven times higher in patients 1 and 2 compared to the reference population. For patient 3, no curve fitting could be performed due to the re-increasing concentrations at late time-points. This is probably due to enterohepatic recirculation which has been described for oxaliplatin [20]. However, concentrations of this patient were similar to the other two patients (Fig. 1). Consequently, CL was lower and $t_{1/2\beta}$ was considerably prolonged in patients with severe hepatic dysfunction. V_{ss} was not different. However, partial AUC from 0 to 2 h after end of infusion (AUC_{0-2h}) which was supposed to reflect better the exposure to active platinum species was only less than twofold higher in patients with severe hepatic dysfunction.

Pharmacokinetic parameters derived from plasma were generally altered to a minor extent compared to ultrafiltrate. Only patient 3 exhibited considerably different $AUC_{0-\infty}$ and CL which was a consequence of the extremely long $t_{1/2ß}$. The values for partial AUC up to 2 h after the end of infusion were in the range of the reference population except for patient 1 who exhibited a partial AUC which was about twice higher.

Whole blood concentrations were only determined in patients 2 and 3. Again the patients with hepatic dysfunction differed from the reference population only when the total AUC was considered. Partial platinum AUC in whole blood was in the same range in both populations. In addition, intra-erythrocyte concentrations were calculated and the AUC was calculated from 0 to 24 h using the trapezoidal rule: the values were 80.2 and 69.1 µg·h/ml for patients 2 and 3, respectively. This was in the upper range of the reference population (58.8 ± 27.0 µg·h/ml).

No signs of oxaliplatin-associated acute toxicity were observed in the three patients. None of them complained of cold-induced or perioral paraesthesias. There were no signs of cramps, stiffness of the jaw, change of voice, ptosis or visual changes. No acute organ toxicity was registered either. The observed fever and gastrointestinal symptoms

Table 2 Pharmacokinetic parameters of platinum in ultrafilterable plasma after administration of 130 mg/m^2 oxaliplatin in three patients with severe hepatic dysfunction and patients with normal hepatic function (n = 33)

	Patients with severe hepatic dysfunction			Patients with normal hepatic function	
	Patient 1	Patient 2	Patient 3	Mean ± SD	Simultaneous fit
$AUC_{0-\infty}$ (μg·h/ml)	38.7	46.1	NE	8.32 ± 2.68	6.57
AUC_{0-2h} (μg·h/ml)	3.56	4.91	NE	3.20 ± 0.83	2.58
$t_{1/2\beta}$ (h)	73.3	59.7	NE	18.0 ± 7.54	17.3
Cl (l/h)	3.23	2.70	NE	15.4 ± 4.56	17.8
V_{ss} (l)	320	216	NE	281 ± 80.6	307

NE not evaluated as a two-compartment model could not be fitted to the data

Table 3 Pharmacokinetic parameters of platinum in plasma after administration of 130 mg/m^2 oxaliplatin in three patients with severe hepatic dysfunction and patients with normal hepatic function (n = 33)

	Patients with severe hepatic dysfunction			Patients with normal hepatic function	
	Patient 1	Patient 2	Patient 3	Mean ± SD	Simultaneous fit
$AUC_{0-\infty}$ (μg·h/ml)	163	174	402	90.0 ± 24.5	82.9
AUC_{0-2h} (μg·h/ml)	15.4	12.0	10.0	11.0 ± 3.3	8.68
$t_{1/2\beta}$ (h)	29.7	43.3	138	26.5 ± 8.0	28.9
CL (l/h)	0.77	0.72	0.31	1.41 ± 0.43	1.41
V_{ss} (l)	32.3	44.0	61.6	48.7 ± 13.0	56.8

Table 4 Pharmacokinetic parameters of platinum in whole blood after administration of 130 mg/m^2 oxaliplatin in three patients with severe hepatic dysfunction and patients with normal hepatic function (n = 33)

	Patients with severe hepatic dysfunction			Patients with normal hepatic function	
	Patient 1	Patient 2	Patient 3	Mean ± SD	Simultaneous fit
$AUC_{0-\infty}$ (μg·h/ml)	ND	282	520	119 ± 55	102
AUC_{0-2h} (μg·h/ml)	ND	9.42	7.88	8.7 ± 2.4	7.97
$t_{1/2\beta}$ (h)	ND	80.2	197	40.8 ± 20.6	36.7
Cl (l/h)	ND	0.44	0.24	1.14 ± 0.41	1.14
V_{ss} (l)	ND	50.9	68.1	57.6 ± 14.6	59.1

ND not determined since no whole blood samples were collected

in patients 2 and 3 and the candidiasis in patient 3 were most likely due to other reasons than the oxaliplatin infusion, e.g. the progredient extensive liver metastases or the low performance status.

Discussion

In this study we investigated the pharmacokinetic disposition of oxaliplatin in patients with extremely high bilirubin values (9.6, 22.5, and 41.1 mg/dl). The individual pharmacokinetic parameters of these patients were compared to values estimated in patients with normal hepatic function. Such comparisons of pharmacokinetic parameters are often limited by differences in the methodology used. Therefore, we have attempted to estimate the parameters under comparable conditions: (1) the same dose of oxaliplatin was administered as monotherapy, (2) the same analytical method was used and drug analysis was performed in the same laboratory, (3) the same pharmacokinetic model was applied using the same software package, and (4) only concentrations up to 24 h after the end of infusion were considered for data analysis which is highly relevant for the estimation of beta half-life. However, one limitation was the difference in infusion time. The patients in our study received oxaliplatin for over 3 h in order to minimise the risk of acute neurotoxicity, the other patients over 2 h. Never-

theless, a comparison of the pharmacokinetic parameters seems to be valid.

The pharmacokinetic data of the patient group with normal hepatic function were summarised in two ways. First, mean values and standard deviations of individual parameters were calculated. Second, we fitted a two-compartment model to all concentrations of the same body fluid simultaneously in order to obtain pharmacokinetic parameter values that can be regarded as typical for a patient with normal liver function. Using this approach, we found a considerably higher AUC and beta half-life and a lower clearance of platinum in the ultrafilterable plasma of patients with severe hepatic impairment. In general, a higher AUC and beta half-life and a lower clearance were observed in plasma and whole blood as well but the difference was less pronounced. The larger deviation of the unbound (ultrafilterable) concentrations is probably due to the lower plasma protein concentrations observed in two of the three patients. However, volume of distribution reflecting binding to macromolecules and tissue distribution was not altered. This apparent discrepancy can be explained by the fact that protein binding of oxaliplatin is mainly irreversible and hence affects clearance rather than volume of distribution, a phenomenon which is well known for oxaliplatin and other platinum complexes [8].

In the case of patient 3, it has to be considered that he also exhibited high creatinine values reflecting impaired kidney function. The relationship between creatinine clearance and platinum clearance is well described [9]. Thus, the reduction in clearance is probably also due to a reduced renal elimination. However, patients 1 and 2 also exhibited lower clearance values although their creatinine values were normal indicating that there is an effect of hepatic dysfunction as well.

From these observations one may conclude that the dose of oxaliplatin should be reduced in patients with severe hepatic dysfunction. However, when interpreting ultrafilterable platinum concentrations, one must consider that the measured platinum consists of cytotoxic as well as inert platinum species. Decay of oxaliplatin in the plasma ultrafiltrate is rapid with a half-life of less than half-an-hour [16, 21]. After 3 h, the concentration of oxaliplatin in ultrafiltrate falls below the detection limit. Most of the platinum measured at late time-points reflects low molecular weight adducts of oxaliplatin with glutathione, L-methionine and L-cysteine [22, 23]. These adducts are most likely inactive as they are not able to react with the DNA. For example, Strickmann et al. showed that L-methionine when coordinated to oxaliplatin cannot be replaced anymore by 5′-GMP which represents the major target within the DNA [17]. Therefore, it has been suggested that the pharmacokinetics of oxaliplatin and its $Pt(dach)Cl_2$ metabolite are more likely to correlate with efficacy and toxicity [16, 24]. However, the exact measurement of intact oxaliplatin and $Pt(dach)Cl_2$ in clinical routine is difficult since oxaliplatin quickly degrades in whole blood ex vivo without stabilisation [20].

In an attempt to approximate the patients exposure to active platinum species, we calculated the partial AUC from start of infusion up to 2 h after the end of infusion using the individual pharmacokinetic model. Most of the partial AUC values were found to be within the mean value and the respective lower and upper standard deviation, except patient 2 in ultrafiltrate and patient 1 in plasma who presented slightly higher values. This suggests that exposure to active platinum species, especially parent oxaliplatin, is, if at all, only slightly elevated in patients with severe hepatic dysfunction. This may explain why we did not observe any symptoms of acute oxaliplatin-induced toxicity in any patient. However, as oxaliplatin was only administered once in each patient and all patients finally succumbed to death from progression of their disease within 5, 9, and 17 days, respectively, we do not know whether this is also true for chronic toxicity, e.g. delayed neuropathy.

Both findings, i.e. an only slightly higher exposure to active platinum species and no acute toxicity with the standard dose, do not support a dose reduction of oxaliplatin in patients with severe hepatic dysfunction. This recommendation corresponds to that of Doroshow et al. [11] although they argue in a different way. In their study, severe hepatic dysfunction was defined by increased bilirubin values of higher than 3 mg/dl. Unfortunately, they do not report the actual bilirubin values of the three patients included. Doroshow et al. conclude that there is no apparent alteration in oxaliplatin clearance in patients with severe hepatic impairment. However, the graph of their patients with severe hepatic dysfunction showing the concentration-time profile in ultrafilterable plasma clearly suggests an increase of AUC which means a decrease of clearance in those patients. This corresponds to our observations. However, these alterations are probably of no clinical relevance as outlined above.

In conclusion, we report here an altered pharmacokinetic disposition of platinum after administration of oxaliplatin to patients with severe hepatic dysfunction. However, the alterations were mainly observed in the late part of the concentration-time curve where the measured platinum mainly reflects inactive platinum species. Early pharmacokinetics was only altered to a minor extent. Together with the fact that no acute oxaliplatin-associated toxicity was observed after administration of a standard dose, our data confirm the recommendation that the dose of oxaliplatin should not be reduced in patients with severe hepatic dysfunction. However, a larger number of patients exhibiting extremely high bilirubin values should be studied in order to further verify this conclusion.

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