Cancer Chemother Pharmacol (1995) 36: 345–351

ORIGINAL ARTICLE

Joel E. Wright · Anthony Elias · Olga Tretyakov
Sylvia Holden · Janet Andersen · Catherine Wheeler
Gary Schwartz · Karen Antman · Andre Rosowsky
Emil Frei III · Lois J. Ayash

High-dose ifosfamide, carboplatin, and etoposide pharmacokinetics: correlation of plasma drug levels with renal toxicity

Received: 10 June 1994/accepted: 15 October 1994

Abstract An autologous bone marrow transplant regimen of ifosfamide, carboplatin, and etoposide (ICE) has been developed as treatment for certain malignancies. At maximum tolerated doses renal insufficiency precludes dose escalation. The objective was to examine whether measurement of plasma drug levels early during treatment would provide warning of renal failure. Nine patients received a 96-h continuous infusion of ifosfamide 16000 mg/m^2, carboplatin 1600 mg/m^2, and etoposide 1200 mg/m^2. Pharmacokinetics, including drug levels and plasma concentration-time curves, of ifosfamide, ultrafiltrable platinum (uPt) and etoposide were analyzed and correlated with renal function. One of the nine patients developed anuric renal failure requiring hemodialysis. By 17 h from the start of infusion, this patient showed substantially higher drug levels of ifosfamide (200 vs mean 217 μM) and uPt (19 vs mean 10μM) than those patients with preserved renal function. The 95% confidence intervals suggested that a 16–22 h ifosfamide level > 153 μM and an uPt level $> \mu M$ predict the development of significant renal dysfunction. Although drug levels were substantially higher at 56 h, the serum creatinine did not yet reflect kidney injury. This study suggests that high plasma ifosfamide and uPt levels, analyzed early in the course of a 96-h infusion of high-dose ICE, provide warning of severe and potentially fatal renal injury. Since ICE has substantial activity in a number of malignancies, but significant renal morbidity, real-time pharmacokinetic-guided dosing may reduce treatment-related toxicity.

Key words Pharmacokinetics · Chemotherapy · Bone marrow transplantation

A. Elias · S. Holden · K. Antman E. Frei III · L.J. Ayash (✉)
Department of Medicine, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA

J.E. Wright · O. Tretyakov · A. Rosowsky
Department of Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute, Boston, MA, USA

J. Andersen
Department of Biostatistics, Dana-Farber Institute, Boston, MA, USA

C. Wheeler · G. Schwartz
The Beth Israel Hospital, Harvard Medical Schol, Boston, MA, USA

Supported in part by US. Public Health Service Grants PO1-CA-38493 and CA-06516 and a grant from the Mathers Foundation. Drs. Ayash and Schwartz are recipients of a Career Development Award from the American Cancer Society

Introduction

Many chemotherapeutic agents have steep dose-response curves and narrow therapeutic windows. These properties assume particular importance in the high-dose autologous bone marrow transplant (ABMT) setting in which a 5–20-fold increase over standard doses is administered possibly resulting in cure of previously resistant or relapsed tumors. While such high chemotherapeutic doses can achieve substantial tumor cell kill, this intensive treatment also presents the potential for injury to normal organs. Most clinical trials employing high-dose chemotherapy in ABMT show a range of toxicities, with some exhibiting relatively few non-myelosuppressive side effects and others resulting in a 10–20% regimen-related mortality.

A high-dose ABMT regimen combining ifosfamide, carboplatin, and etoposide (ICE) has been developed as an intensification for certain solid tumors (testis, lung and ovarian carcinomas, and sarcomas) and relapsed lymphomas [3, 4]. The chemotherapeutic agents are administered by 96-h continuous infusion and pharmacokinetic analyses, which include measurements of plasma drug levels and total exposure (as determined by the area-under-the-curve, AUC), have been performed. At the maximum tolerated doses of ifosfamide 16000 mg/m^2, carboplatin (1800 mg/m^2), and etoposide

(1200 mg/m)^2, renal insufficiency (most common in patients with prior cisplatin exposure) precludes further dose escalation.

Both ifosfamide and, to a much lesser extent, carboplatin cause renal insufficiency as a major dose-limiting toxicity when myelosuppression is ameliorated by reinfusion of marrow [2, 15]. Combining these two agents theoretically could lead to a significant reduction of their single-agent maximum tolerated doses due to overlapping end-organ toxicities. Renal damage from prior antitumor therapy (e.g. cisplatin) has been shown to be responsible for greater organ sensitivity during subsequent treatment [3, 4]. Prior treatment can influence the pharmacokinetics of drugs given in later courses, further enhancing toxicity through increased drug exposure [1, 14]. In the most adverse circumstances, synergistic toxicities in a previously treated patient could lead to irreversible organ failure. Since the patient population to be given the potentially curative ICE most likely has had significant prior exposure to nephrotoxic chemotherapeutic agents, it is important to identify those at risk for severe or irreversible renal damage.

The objective of this study was to examine whether measurements of plasma drug levels early in the treatment course might provide a timely warning of impending renal failure. Nine patients received a 96-h continuous infusion of ifosfamide 16000 mg/m^2, carboplatin 1600 mg/m^2, and etoposide 1200 mg/m^2 with ABMT. One of the nine developed anuric renal failure requiring hemodialysis. An early and rapid rise in plasma ifosfamide and ultrafiltrable platinum (uPt) levels, prior to the completion of chemotherapy, foretold a severe renal injury before elevations in serum creatinine became clinically apparent.

Materials and Methods

Patient selection

Adults with histologically documented malignancy, incurable with conventional chemotherapy, were eligible for inclusion in the study. In addition, patients with relapsed germ cell carcinomas or soft tissue sarcomas were eligible if responding to chemotherapy. No significant impairment of hepatic (SGOT, bilirubin $\geq 1.5 \times$ normal), renal (creatinine clearance < 60 ml/min) or performance score (ECOG > 1) was allowed. Patients with marrow or central nervous system (CNS) metastases were excluded. All gave informed consent.

Treatment regimen

Ifosfamide (16000 mg/m^2), carboplatin (1600 mg/m^2), and etoposide (1200 mg/m^2) were administered by 96-h continuous infusion (days –7 to –3). For uroprotection, mesna was given during ifosfamide infusion and for an additional 24 h after its completion. Hydration with D_5W/sodium bicarbonate (44–132 mEq/l) at 200 ml/h was maintained to prevent ifosfamide-associated metabolic acidosis. Barbiturates, steroids, and other agents known to affect cytochrome P450 oxidase metabolism were prohibited during chemotherapy. Autologous marrow with or without peripheral blood progenitor cells was reinfused on day 0.

Pharmacology

Clinical samples

Blood samples were collected prior to infusion, every 2 h $\times$ 4 after the start, and then every 12 h until its completion. Three Post-infusion samples were drawn every 2 h, and then approximately every 12 h for three additional samples (t = 98, 100, 102, 112, 130 and 140 h). Samples were also obtained from a single patient (patient X) at intervals prior to and following hemodialysis (t = 143, 148, 160, 165, 183, 191, 201, 207, 225 and 250 h).

Samples were collected in heparinized tubes placed on ice, spun for recovery of plasma (a portion of which was ultrafiltered; Amicon Centrifree), and both plasma and ultrafiltrates were stored at – 80° C prior to assay. Upon thawing, a 100-µl aliquot was assayed for ifosfamide, uPt, and etoposide. Drug assays were repeated three times for patient X (for verification of results) and once for controls.

Ifosfamide assay and p-nitrobenzylpyridine (NBP) assay

To assay for ifosfamide, plasma containing cyclophosphamide (added as internal standard) was extracted with ethyl acetate, evaporated, and derivatized with trifluoroacetic anhydride. After reevaporation, the residue was dissolved in ethyl acetate and analyzed by gas chromatography [7].

Ifosfamide metabolite-alkylating activity was detected by treating plasma with NBP, boiling for 5 min, extracting with ethyl acetate and developing the bright blue benzyl carbanion with alkali [17]. This qualitative assay (performed after dialysis at t = 183, 191, 201, 207, and 225 h) nonspecifically detects nitrogen mustards, but not carboplatin, etoposide or their metabolites [19]. Positive results therefore indicate the presence of activated ifosfamide metabolites.

Ultrafiltrable platinum and platinum species assay

Plasma samples were analyzed for platinum by flameless atomic absorption spectrophotometry (AAS) at 266 nm. Standards were prepared by dilution into ultrafiltrates from pretreatment plasma. Samples were quantitated by least squares analysis of the standard curve [6].

Some ultrafiltered platinum samples (t = 85–201 h) were further characterized by high-performance liquid chromatography (HPLC) on a silica gel column eluted with acetonitrilewater 9:1 [6]. Fractions of 0.5 ml were collected and the platinum content determined by AAs as described above.

Etoposide assay

Plasma samples and etoposide standards dissolved in pretreatment plasma were 50% saturated with ammonium sulfate, extracted with ethyl acetate, evaporated and reconstituted with methanol containing teniposide as internal standard. Samples and standards were analyzed by HPLC on a phenyl column eluted with wateracetonitrileacetic acid (66:32:2) and detected by electrochemical oxidation [16].

Table 1 Renal function and prior nephrotoxic chemotherapy

Patient	Creatinine clearance (ml/min)	Serum creatinine (mg/dl) Pre-ABMT	Peak during ABMT	at discharge	Prior nephrotoxic chemotherapy Drug	Total dose (mg/m^2)
X (242)	117	1.3	9.2	Died	Cisplatin	500
					Ifosfamide	11800
237	114	0.8	0.9	0.5	Cisplatin	1114
238	132	0.9	1.4	1.2	Cisplatin	125
					Carboplatin	1200
					Ifosfamide	7500
239	76	0.6	0.9	0.7	Ifosfamide	36500
240	142	0.8	1.4	1.0	Ifosfamide	22500
241	161	0.7	1.3	0.7	Cisplatin	420
					Carboplatin	1575
					Ifosfamide	48648
243	139	0.8	1.4	0.8	Ifosfamide	48600
244	68	0.8	1.4	0.7	Carboplatin	1578
245	173	0.9	1.7	1.3	Cisplatin	819
					Ifosfamide	23404

Bone marrow toxicity

Pretreatment plasma (negative controls), plasma spiked with carboplatin (positive controls), and pre- and postdialysis plasma samples were ultrafiltered, lyophylized, diluted, and then dissolved in liquid agar. Cryopreserved marrow was thawed and plated into wells containing the treated agar. After 2 weeks in culture, colonies were counted and IC_{50} (drug concentration in microorgans per liter which results in 50% inhibition of marrow colony formation) values determined by comparison with negative controls [18].

Pharmacokinetics

Drug levels (C) were plotted as a function of time, from $t = 0$ until C returned to 0. AUCs for ifosfamide, uPt, and etoposide were calculated by the trapezoidal method [5]. The final time for the last trapezoid was estimated by extrapolating a plot of time versus log concentration to the time point at which the drug level reached $\leq 0.1\%$ of that at the end of infusion. Total body clearance was calculated by dividing the total dose of drug (expressed in millimoles) by the AUC (expressed in molar-minute units).

Statistical methods

Plasma drug levels from the sixth blood collection ($t = 18.5 \pm 3.5$ h) from eight patients who did not develop renal failure were compared with three replicates from patient X ($t = 17$ h), using nonparametric analyses. Two-sided P-values ≤ 0.05 were considered to be statistically significant.

Results

Patient characteristics

From July 1988 through March 1992, 64 adults were entered onto a dose-escalation study of ICE with ABMT [4]. Complete pharmacokinetic data on nine patients, treated on dose level 10 from January through June 1991, comprise this report. The median age was 35 years (range 26–49 years); 55% were male. Malignancies included sarcomas (3), and testis (3) and ovarian carcinomas (3).

Patients had received a median of five cycles (range 3–10) of prior chemotherapy. Baseline renal function and any observed changes in serum creatinine during and at hospital discharge following ABMT, as well as total prior nephrotoxic chemotherapy doses (mg/m^2), are shown in Table 1. Previous episodes of clinically significant renal insufficiency or renal tubular acidosis were not observed.

Patient X

A 27–year–old male, diagnosed with extragonadal germ cell tumor, presented with superior vena cava (SVC) syndrome from massive anterior mediastinal adenopathy. Biopsy revealed an endodermal sinus tumor, and tumor markers showed an elevation of alpha fetoprotein (AFP) to 1280 ng/ml. He received chest radiotherapy, followed by three cycles of bleomycin, etoposide, and cisplatin. Although the symptoms of the SVC syndrome had resolved, restaging revealed a residual mediastinal mass and an AFP of 33 ng/ml, which quickly rose to 150 ng/ml. Chemotherapy was changed to ifosfamide, velban, and cisplatin. After two cycles, the AFP rose further to 260 ng/ml. The decision was made to proceed directly to ABMT in the hope of achieving disease control of this chemotherapy-refractory tumor.

He was hospitalized and received high-dose ICE. Pretreatment 24-hr creatinine clearance was 117 ml/min. Serial serum creatinine levels (mg/dl) were 1.3 at 0 h, 1.2 at 56 h, 1.8 at 80 h and 2.0 at 92 h,

Table 2 Pharmacokinetics of continuous infusion chemotherapy

	AUC (μ*M* h)		Clearance (ml/min)				
Patient	Ifosfamide	UPt	Etoposide	Ifosfamide	UPt	Etoposide	Peak creatinine
X (242)	21215	3536	1929	96	41	35	9.2
237	6505	892	1559	261	134	36	0.9
238	11093	869	1976	171	154	32	1.4
239	9889	719	1300	161	156	41	0.9
240	9770	1236	1327	202	112	49	1.4
241	9229	1037	1590	206	129	40	1.3
243	13520	1062	1872	140	125	34	1.4
244	10106	1124	1791	174	110	33	1.4
245	8434	1306	1692	228	127	38	1.7

respectively, from the start of chemotherapy. The patient developed acute renal failure (creatinine 6.3 mg/dl) 48 h after completion of chemotherapy with anuria and CNS dysfunction (asterixis, hallucinations, and somnolence).

Hemodialysis (5–10 h treatment sessions) was begun 156 h from the start of chemotherapy and repeated daily for eight days. Upt levels and ifosfamide metabolite alkylating activity tests were performed to monitor the success of dialysis in removing drug and to guide the timing timing of marrow reinfusion. Despite aggressive supportive care, the patient developed pneumonia with acute respiratory distress requiring intubation. He died 4 days later.

Pharmacokinetics

The pharmacokinetics of the continuous infusion chemotherapy in each patient are shown in Table 2.

Patient X

For patient X, who required dialysis for acute renal failure, the AUCs of the chemotherapeutic agents were as follows: ifosfamide, 21225 μ*M* h; carboplatin, 3483 μ*M* h; and etoposide, 1927 μ*M* h. The total body clearances of ifosfamide, carboplatin, and etoposide were 96, 41, and 35 ml/min, respectively.

Predialysis chemotherapy assays Ifosfamide levels increased continuously during administration, peaking at 280 μ*M* at $t = 54$ h (Fig. 1). Levels fell to 170 μ*M* at 72 h, and to 144 μ*M* at 96 h. A rapid postinfusion decline was seen over the next 18 h, reaching a level of 55 μ*M*. By 132 h, ifosfamide levels had fallen to 5 μ*M* and were unmeasurable by 183 h.

UPt rose rapidly to a plateau of 19 μ*M*, *persisted there for* 60 *h, and then climbed further to* 27 μ*M* (Fig. 2). This new plateau was sustained for 24 h ($t = 96$ h). After completion of chemotherapy, uPt fell to 18 μ*M* ($t = 124$ h). During the next 24 h, uPt levels stayed at 13–15 μ*M* and then fell to 4–8 μ*M* 12 h later, persisting at that plateau until dialysis was begun.

Etoposide levels were not significantly elevated by the renal failure. A steady-state (15–19 μ*M*) was reached within 18 h from the start of infusion, and remained there until discontinuation. Rapid postinfusion elimination brought levels below detection by 144 h.

Hemodialysis chemotherapy assays Although ifosfamide had disappeared by 183 h, the NBP assay indicated that alkylating activity was still present through 207 h (after four hemodialysis sessions), but absent by 225 h.

Unlike ifosfamide and its metabolites, uPt could not be removed by dialysis, with levels revealing a pattern of redistribution and rebound after dialysis. UPt assays were performed just prior to each of five daily sessions of dialysis and after the first three (Fig. 2). The first session decreased uPt from a level of 8.3 μ*M* predialysis to 3.6 μ*M* postdialysis. Prior to session two, however, uPt rebounded to 5.4 μ*M*. Dialysis reduced the level to 3.1 μ*M*, but by the next morning ultrafiltrates contained 4.4 μ*M* uPt. This level fell to 1.3 μ*M* after the third dialysis, but rebounded again to 3.9 and 3.7 μ*M* prior to dialysis sessions four and five, respectively.

In the hope of identifying the platinum species still present after dialysis, plasma ultrafiltrates were fractionated by HPLC and reanalyzed by AAS. HPLC-AAS analysis of uPt rebound peaks at $t = 122$, 201 and 225 h indicated 65%, 20% and 0% carboplatin, respectively. The possible conversion, in a high-chloride environment, of carboplatin to cisplatin has been reported [13]. However, cisplatin was not detected in these ultrafiltrates.

Although characterization of the platinum species persisting after dialysis was elusive, the ultrafiltrates in the plasma postdialysis were more cytotoxic to cryopreserved (patient X) marrow than would be expected from carboplatin alone. The IC_{50} of the ultrafiltrate collected at 122 h was not significantly different from that of carboplatin (19 vs 22 μ*M*, respectively). In contrast, the ultrafiltrate contained in the rebound peak at 183 h had an IC_{50} of 3.4 μ*M* against marrow. It seems likely that ifosfamide metabolites, still present as

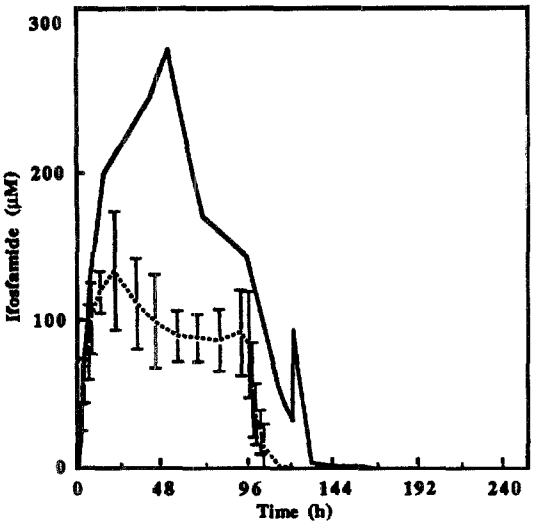

Fig. 1 Time versus plasma ifosfamide concentrations for patient X with acute renal failure (*solid line*) and eight similarly treated patients without renal failure (*dashed line*). *Bars* show patient-to-patient standard deviation

detected by the NBP assay, were also contributing to the marrow toxicity observed.

Etoposide was eliminated well before dialysis began. It was unlikely that any cytotoxic metabolites remained after 122 h, and none was detected.

Pharmacokinetic comparison with controls

The median AUCs for eight patients (controls) without renal failure were as follows: ifosfamide, 9836 μ*M* h (range 6531–13 691); carboplatin, 1059 μ*M* h (range 723–1312); and etoposide, 1634 μ*M* h (range 1339–1973). The median total body clearances of ifosfamide, carboplatin, and etoposide were 194 (138–260), 126 (103–157), and 37 (32–48) ml/min, respectively.

Differences in drug levels between patient X and controls became evident within 16–22 h of the start of chemotherapy. Ifosfamide levels had moderately increased by 8 h (128 vs mean 103 μ*M* for controls), but then substantially increased by 17 h (200 vs mean 127 μ*M*). Halfway through the 96-h infusion, ifosfamide levels were 2 1/2 times greater (250 vs mean 101 μ*M* at $t = 43$ h), and persisted at twice the control level until the end of the infusion. The differences in uPt levels were noticeable even earlier. By 4 h, increases in uPt became evident (13 vs mean 8 μ*M*). By 6–8 hours, a large difference in drug levels was seen (17 vs mean 10 μ*M*; $p = 0.11$), which persisted throughout the infusion, and continued to increase after completion of chemotherapy (22 vs mean 0 μ*M* at $t = 122$ h). The 95% confidence intervals suggest that a 16–22 h ifosfamide level > 153 μ*M* and a uPt level > 14 μ*M* might be associated with the development of severe renal

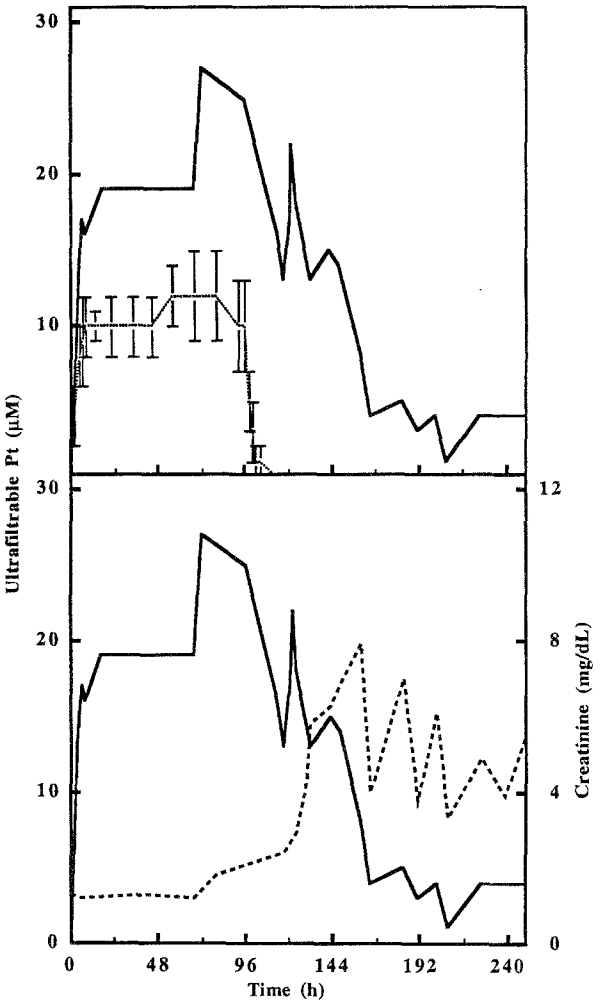

Fig. 2 *Upper panel* Time versus plasma uPt concentrations for patient X with acute renal failure (*solid line*) and eight similarly treated patients without renal failure (*dashed line*). *Bars* show patient-to-patient standard deviation. *Lower panel* Superimposed on uPt AUC curve (*solid line*) of patient X are the serum creatinine levels (*dashed line*). Although uPt levels were substantially elevated by 17 h from the start of chemotherapy, the serum creatinine had not risen above baseline at 56 h. The variations in creatine levels after 156 h reflect hemodialysis treatment sessions

dysfunction. For etoposide, levels from patient *X* paralleled those of the controls during and after the infusion.

Although ifosfamide and uPt levels were already substantially elevated by 18 h from the start of chemotherapy for the renally impaired patient, the serum creatinine did not yet reflect kidney injury. At 56 h, the serum creatinine remained at baseline; by 80 h, a 50% rise in creatinine was observed.

Discussion

Recently developed high-dose ICE regimens with ABMT have gained prominence in the treatment of such tumors as lymphomas, and lung, testis and

ovarian carcinomas [3, 4, 20]. Dose-escalation trials were initially performed for each individual agent, and then for combinations of agents, until non-hematologic dose-limiting toxicities were reached [2–4, 15, 20]. Common to each regimen that contained ifosfamide is the presence of dose-limiting renal insufficiency.

Experience with ifosfamide-containing regimens has revealed a consistent clinical pattern of renal toxicity. With escalating doses of a 96-h infusion of ifosfamide, renal toxicity is dose-limiting at 18 g/m^2 [2]. By 72–96 h after the start of chemotherapy, 24% of patients had developed reversible creatinine elevations ($>$ 2.0 mg/dl) at doses $\geq$ 12 g/m^2, and 68% exhibited a non-anion gap renal tubular acidosis (RTA). When a fixed dose of ifosfamide (12 g/m^2) was added to escalating doses of carboplatin (400–1600 mg/m^2), renal toxicity again was dose limiting (12% with irreversible creatinine $>$ 4.0 mg/dl) [3]. Elevated creatinine occurrs more commonly in those patients with prior cisplatin exposure.

There are two completed dose-escalation studies of ICE with ABMT [4, 20]. When given by 96-h infusion, Elias et al. determined the maximum tolerated doses (MTD) of the combination to be: ifosfamide 16000 mg/m^2, carboplatin 1800 mg/m^2, and etoposide 1200 mg/m^2 [4]. Overall, 22 patients (46%) developed creatinine elevations $\geq$ 1.5 mg/dl (one primary renal fatality), including nine (60%) at the MTD. The creatinine rise was observed by the completion of chemotherapy, peaked within 48–72 h, and then fell to baseline 4 days later. A proximal RTA, requiring $NaHCO_3$ supplementation, developed in all patients. Prior cisplatin exposure was again associated with increased risk of renal toxicity ($P = 0.01$). When given by short bolus (IE) and continuous infusion (C), Wilson et al. found the same MTDs of ifosfamide and carboplatin, but a slightly higher MTD of etoposide (1500 mg/m^2) [20]. Reversible creatinine elevations (2.0–7.6 mg/dl) developed in 29% and permanent renal damage at or below the MTD in 11%. Three patients of four died of acute tubular necrosis with multiorgan failure at doses above the MTD. A proximal RTA was seen by the completion of chemotherapy and lasted about 4 days.

The objective of this present study was to examine whether prompt evaluation of plasma drug levels might provide early warning of renal toxicity. Of nine patients receiving a 96-h infusion of high-dose ICE, one developed anuric renal failure requiring hemodialysis. Had plasma samples been analyzed by 24 h from the start of chemotherapy, high ifosfamide and uPt evels would have raised concern for potentially severe renal toxicity and would have led to early discontinuation of chemotherapy.

Significant and sharp rises in ifosfamide and uPt levels were evident by 17 h from the start of infusion in one patient who developed irreversible renal failure. At that time the plasma ifosfamide level was 200 μM. The corresponding mean ifosfamide level for those who did not develop renal failure was 127 μM (range 94–185). At 17 h, the uPt level in the patient with renal failure was 19 μM, with a corresponding mean level for the controls of 10 μM (range 6–13). The 95% confidence intervals suggest that at 16–22 h from the start of chemotherapy, ifosfamide levels $>$ 153 μM and uPt levels $>$ 14 μM might be predictive for the development of severe renal dysfunction. Although drug levels of ifosfamide and uPt were substantially higher at 56 h for the renally impaired patient, the serum creatinine level at that time did not yet reflect evidence of kidney injury. Etoposide levels were not significantly increased by the renal injury. Although normally about 35% of an etoposide dose is renally excreted, hepatic metabolism appeared to compensate for diminished renal clearance in the anuric patient.

No published studies of ifosfamide pharmacokinetics have examined a total dose as high as this (16 g/m^2) or this method and schedule of administration [8–12]. During the first 24 h (48 h in the renally impaired patient) of administration, plasma ifosfamide levels rose and then peaked. Looking specifically at total body clearance in the renally intact patients, during the first 24 h ifosfamide clearance was as expected for a 4 g/m^2 administered dose. With each subsequent day of the 96-h infusion, however, AUC progressively decreased, and thus clearance progressively increased, presumably due to activation (and self-induction) of cytochrome P450 enzymes [9, 11, 12]. Progressively increased clearances have also been shown for a fractionated schedule of standard-dose ifosfamide [11].

Previous non-ABMT studies have shown lower total body ifosfamide clearances in renally intact patients and have shown that while the volume of distribution increases with the dose, the clearance remains constant [8, 10]. Our data, which showed increasingly higher daily clearances of ifosfamide, might differ from previous studies for a variety of reasons. First, patients received a prolonged infusion, which presumably resulted in enhanced activation of cytochrome P450 enzymes. Usually ifosfamide is given daily by bolus, in lower (about fourfold) total and fractionated doses, which alter pharmacokinetic patterns. With the higher doses given with ABMT, the volume of distribution should plateau and clearance then increase with increasing doses. Second, the ABMT setting often influences the metabolic disposition of multiple drugs. Many medications (e.g. aminoglycosides, anticonvulsants) require dose adjustments upward to keep levels in the "therapeutic" range. Renal and hepatic clearances are increased due to enhanced activation from chemotherapy and other drug administrations, cytokine and interleukin release, comcomitant infections, etc. Fever, often seen during high-dose chemotherapy, commonly increases metabolism of many drugs. In this study, it was not possible to determine to what degree enhanced hepatic and/or renal clearances were responsible for the high total body clearances of

the chemotherapeutic agents seen in the renally intact patients.

Preexisting but unrecognized renal dysfunction, either from prior cisplatin and ifosfamide usage or from decreased vascular flow resulting from an inadequately treated SVC syndrome, could have predisposed patient X to acute renal failure after a nephrotoxic insult. However, a 24-h creatinine clearance showed no evidence of diminished glomerular filtration capability. It is also not clear which chemotherapeutic agent might have induced the renal injury. We have shown, however, that a severe renal insult can lead to the retention of renally excreted carboplatin, unidentified platinum species, and ifosfamide metabolites. Although ifosfamide metabolites fell below the level of detection in the NBP assay after multiple dialyses, uPt did not disappear. While uPt levels declined immediately after dialysis, their rebound suggested that a new equilibrium had been established between plasma and a third space compartment. The unidentified platinum species, possibly in combination with any ifosfamide metabolites which still remained, elicited caution and delay in marrow reinfusion in the patient with renal failure. This delay was justified since the plasma ultrafiltrates were potently cytotoxic (as shown by the low IC_{50}) to cryopreserved marrow.

This study suggests that plasma drug levels, analyzed early in the course of a 96-h continuous infusion of high-dose ICE, provides warning of severe and potentially fatal renal injury. Since ICE has substantial activity in a number of hematologic and solid tumor malignancies, but significant renal morbidity, real-time pharmacokinetic-guided dosing should be employed as an important modality to reduce treatment-related toxicity.

References

1. Dominici C, Petrucci F, Caroli S, Alimonti A, Clerico A, Castello MA (1989) A pharmacokinetic study of high-dose continuous infusion cisplatin in children with solid tumors. J Clin Oncol 7:100–107
2. Elias AD, Eder JP, Shea T, Begg C, Frei E III, Antman K (1990) High-dose ifosfamide with mesna uroprotection: a phase I study. J Clin Oncol 8:170–178
3. Elias AD, Ayash LJ, Eder JP, Wheeler C, Deary J, Weissman L, Schryber S, Hunt M, Critchlow J, Schnipper L, Frei E III, Antman K (1991) A phase I study of high-dose ifosfamide and escalating doses of carboplatin with autologous bone marrow support. J Clin Oncol 9:320–327
4. Elias AD, Ayash LJ, Wheeler C, Schwartz G, Tepler I, Gonin R, McCauley M, Mazanet R, Schnipper L, Frei E III, Antman K (1995) A phase I study of high-dose ifosfamide, carboplatin, and etoposide with autologous hematopoietic stem cell support. Bone Marrow Transplant (in press)
5. Gibaldi M, Perrier D (1982) Non compartmental analysis based on statistical moment theory In: Pharmacokinetics, 2nd edn. Marcel Dekker, New York, pp 409–417
6. Harland SJ, Newell DR, Siddik ZH, Chadwick R, Calvert AH, Harrap KR (1984) Pharmacokinetics of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum (II) in patients with normal and impaired renal function. Cancer Res 44: 1693–1697
7. Juma FD, Robers HJ, Trounce JR, Bradbrook ID (1978) Pharmacokinetics of intravenous cyclophosphamide in men estimated by gas-liquid chromatography. Cancer Chemother Pharmacol 1: 229–231
8. Lewis LD (1991) Ifosfamide pharmacokinetics. Invest New Drugs 9:305–311
9. Lewis LD, Fitzgerald DL, Harper PG, Rogers HJ (1990) Fractionated ifosfamide therapy produces a time-dependent increase in ifosfamide metabolism. Br J Clin Pharmacol 30:725–732
10. Lewis LD, Fitzgerald DL, Mohan P, Thatcher N, Harper PG, Rogers HJ (1991) The pharmacokinetics of ifosfamide given as long and short intravenous infusions in cancer patients. Br J Clin Pharmacol 31:77–82
11. Lind MJ, Margison JM, Cerny T, Thatcher N, Wilkinson PM (1989) Comparative pharmacokinetics and alkylating activity of fractionated intravenous and oral ifosfamide in patients with bronchogenic carcinoma. Cancer Res 49:753–757
12. Nelson RL, Allen LM, Creaven PJ (1976) Pharmacokinetics of divided dose ifosfamide. Clin Pharmacol Ther 19:365–370
13. Perrone R.K, Kaplan MA, Bogardus JB (1989) Extent of cisplatin formation in carboplatin admixtures. Am J Hosp Pharm 46:258–259
14. Reece PA, Stafford I, Russel, Grantley Gill P (1986) Reduced ability to clear ultrafilterable platinum with repeated courses of cisplatin. J Clin Oncol 4:1392–1398
15. Shea TC, Flaherty M, Elias A, Eder JP, Antman K, Begg C, Schnipper L, Frei E III, Henner WD (1989) A phase I clinical and pharmacokinetic study of carboplatin and autologous bone marrow support. J Clin Oncol 7:651–661
16. Sinkule JA, Evans WE (1984) High-performance liquid chromatographic analysis of the semisynthetic epipodophyllotoxins teniposide and etoposide using electrochemical detection. J Pharm Sci 73: 164–168
17. Sladek NE (1971) Metabolism of cyclophosphamide by rat hepatic microsomes. Cancer Res 31: 901–908
18. Teicher BA, Holden SA, Jacobs JL (1987) Approaches to defining the mechanism of enhancement by Fluosol-DA 20% with carbogen of melphalan antitumor activity. Cancer Res 47: 513–518
19. Wagner T (1989) Alkylating activity in serum, urine and CSF following high-dose ifosfamide in children – a comment. Cancer Chemother Pharmacol 24 [Suppl 1]:S7
20. Wilson WH, Jain V, Bryant G, Cowan KH, Carter C, Cottler-Fox M, Goldspiel B, Steinberg SM, Longo DL, Wittes RE (1992) Phase I and II study of high-dose ifosfamide, carboplatin, and etoposide with autologous bone marrow rescue in lymphomas and solid tumors. J Clin Oncol 10:1712–1722