Featured Article

Crossover Randomized Comparison of Intravenous *versus* Intravenous/Oral Mesna in Soft Tissue Sarcoma Treated with High-Dose Ifosfamide

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Abstract

Purpose: **We conducted our study to determine the pharmacokinetics (PK) and clinical efficacy of oral mesna in patients receiving ifosfamide for soft tissue sarcoma.**

Experimental Design: **Seventeen patients were enrolled in a randomized prospective Phase I/II study. Seventeen patients were exposed to study medication. Ifosfamide was given at a dose of 2 g/m^2/day for 5 days on a 21-day cycle. Before the first cycle, all patients were randomized onto a crossover design and received either the approved i.v. or i.v./oral mesna regimen, with crossover for the second cycle of chemotherapy. The i.v. mesna regimen consisted of dosings (20% ifosfamide dose) at 0, 4, and 8 h. The i.v./oral arm consisted of an i.v. mesna dosing (20% ifosfamide dose) at 0 h, followed by oral tablet dosing (40% ifosfamide dose) at 2 and 6 h. In-patient clinical monitoring and phlebotomy and urine sampling for mesna, dimesna, and ifosfamide PK were performed on all chemotherapy days.**

Results: **Thirteen patients were evaluable for PK and 17 for efficacy and toxicity. No significant differences were detected in the plasma PK of the concomitantly infused ifosfamide. Rates of hemorrhagic cystitis were similar across mesna schedules.**

Four of 10 evaluable patients demonstrated objective response.

Conclusion: **On the basis of our study, an i.v./oral mesna regimen is at least as uroprotective as the approved i.v. regimen. The i.v./oral regimen will improve patient tolerance and convenience, allow for a reduction in elective hospitalizations for ifosfamide chemotherapy, reduce the potential morbidity associated with inpatient administration of chemotherapy, and likely result in decreased costs of care.**

Introduction

First synthesized in 1965, ifosfamide [3-(2-chloroethyl)-2-[(2chloroethyl)-amino]tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide] is a member of the oxazaphosphorine family of alkylating agents (1, 2) and has a broad spectrum of activity. Early clinical studies of ifosfamide demonstrated its encouraging efficacy in a variety of tumor types, however, additional investigation was hampered by unacceptably high rates of dose-limiting urothelial toxicity (3–5).

The pharmacology of ifosfamide has been studied extensively (6–10). Ifosfamide differs from another oxazaphosphorine, cyclophosphamide, by the position of its two chloroethyl groups on the central ring (Fig. 1). This is responsible for the comparatively greater water solubility, antitumor activity, and toxicity profile of ifosfamide. Like cyclophosphamide, ifosfamide is administered as a prodrug, which requires activation by the hepatic cytochrome P450 mixed oxidase system 3A4 (Refs. 11 and 12; Fig. 2). The initial metabolic step is hydroxylation, producing an active alkylator, 4-hydroxyifosfamide, that is in spontaneous and balanced equilibrium with its tautomeric form, aldoifosfamide. Aldoifosfamide undergoes spontaneous β elimination, liberating acrolein to form the primary alkylating agent ifosforamide mustard. Acrolein has been proven to be a potent urothelial irritant and is currently accepted as the major cause of ifosfamide-induced hemorrhagic cystitis (6, 13).

Administration of ifosfamide for five or fewer daily doses of <1.2 g/m^2 modestly reduces the rates of hemorrhagic cystitis; however, significant numbers of patients continue to experience this complication, and without the efficacy benefit of dose escalation (14, 15). Several approaches have been studied in an attempt to control ifosfamide-induced urothelial toxicity and permit the clinical investigation of higher doses of this agent. Direct intravesicular injection of a variety of anti-inflammatory agents has been attempted but is logistically difficult and does not address the effects of acrolein on the pyelocalyceal system and ureters. Vigorous hydration, which both lowers the concentration of acrolein and 4-hydroxyifosfamide in the urinary tract and accelerates their transit time, continues to be a valuable tool. However, as a direct result of the development of the uroprotective agent mesna (sodium-2-mercaptoethane sulfonate; Refs.

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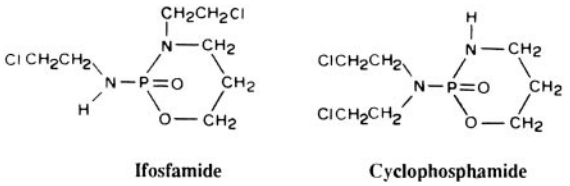

Fig. 1 Structure of ifosfamide and cyclophosphamide. (Reprinted with permission from Ref. 5.)

16, 7–10, 16–23), the study of ifosfamide, in particular at active high doses, could then be broadly pursued.

Mesna is hydrophilic, preventing its passage out of the vascular bed into cells. This results in efficient renal clearance and avoids any adverse impact on the cytotoxic effects of ifosfamide. After i.v. administration, mesna is rapidly oxidized in the plasma to dimesna (disodium 2,2′-dithiodiethyanesulfonate), which is the predominant circulating form (Fig. 2). After glomerular filtration, dimesna undergoes reabsorption in the proximal tubules. Before secretion in the distal tubules, one-third of the dimesna is rapidly converted back to the active thiol mesna by glutathione reductase in the cytoplasm of distal tubular epithelial cells. Mesna then readily detoxifies urinary 4-hydroxyifosfamide metabolites and acrolein (6, 9, 24, 25). The time to maximal urinary excretion is ~60 min after i.v. administration and, on average, ~150 min after oral administration (9, 25, 26). The minimum uroprotective concentration of mesna is ~1.7 μmol/liter or 100 μg/ml, which is achieved far more quickly with an i.v. dose (5.85 ± 2.16 h) compared with an oral dose (13.11 ± 6.11 h; Ref. 26).

Currently, the approved schedule for i.v. mesna in the United States is to administer 20% of the ifosfamide dose at the time of chemotherapy initiation, followed by repeat equivalent doses of mesna every 4 h thereafter, for a total of three to five doses (6, 9, 24). The use of this regimen has resulted in macrohematuria and microhematuria event rates of <5 and 20%, respectively (6). The i.v. mesna regimen has several drawbacks. Patients are subjected to prolonged stays at outpatient treatment facilities or are exposed to the inherent risks of hospitalization where such facilities are not available. In addition, the logistical and fiscal burdens placed on the healthcare facility are substantial. As a result, the use of oral mesna has become an appealing alternative that can facilitate the outpatient administration of ifosfamide.

The use of oral mesna for uroprotection in patients has been studied extensively by Goren *et al.* (27–29). In one study, normal human subjects received some oral tablets as we studied. In two other studies, predominantly of patients with lung cancer, oral mesna was given as either a solution in cola or as oral tablets. Goren *et al.* (27–29) concluded that their data showed the i.v./oral regimen should be at least as uroprotective as the i.v./mesna regimen. Oral administration of mesna solution significantly increases the rates of gastrointestinal distress, likely because of its poor palatability (11, 22). We, therefore, conducted a prospective, randomized Phase I/II study comparing the PK[6] and clinical efficacy of i.v. *versus* i.v. followed by oral mesna in tablet form in patients diagnosed with soft tissue sarcoma treated with ifosfamide.

Oral administration of mesna solution significantly increases the rates of gastrointestinal distress, likely because of its poor palatability (11, 22). We, therefore, conducted a prospective, randomized Phase I/II study comparing the PK and clinical efficacy of i.v. *versus* i.v. followed by oral mesna in tablet form in patients diagnosed with soft tissue sarcoma treated with ifosfamide.

Patients and Methods

Eligibility. This was a prospective, randomized Phase I/II multi-institutional crossover study comparing the PK and clinical efficacy of i.v., *versus* i.v. followed by oral mesna support in patients diagnosed with soft tissue sarcoma treated with ifosfamide. All patients were between 18 and 75 years of age. All patients had biopsy-proven soft tissue sarcoma. Pathology was reviewed at the respective participating institution. Additional requirements included an Eastern Cooperative Oncology Group performance score of ≤2, an estimated minimal prognosis of 4 weeks, hemoglobin ≥9 GM/dl, and the ability to provide informed, written consent. If prior therapy was administered, a minimum of 3 weeks was required before enrollment onto study. Patients were excluded from study participation if there was a history of autoimmune disease, allergy to ifosfamide or mesna, or any contraindication to ifosfamide administration, including hematuria >50 urinary erythrocytes/high power field. Patients with significant disease affecting the gastrointestinal tract that was felt to potentially affect the absorption of mesna were excluded. Patients with disease affecting the genitourinary tract or kidneys that was felt to potentially affect the excretion of ifosfamide, its metabolites, or mesna were also excluded. Women who were pregnant or breastfeeding were excluded from participation, and women of childbearing age were required to use an adequate method of contraception.

Pretreatment Studies. Pretreatment studies included a complete history and physical examination, assessment of the Eastern Cooperative Oncology Group performance score, complete blood count, comprehensive metabolic chemistry profile, urinalysis, manual urine microscopic analysis, and imaging confirming the presence of active malignant disease. All women of childbearing age underwent serum Beta Human chorionic Gonadotropin testing.

On-Study General Testing. While on study, all patients underwent weekly complete blood counts, serum chemistry profile, and urinalysis.

Design and Therapy. All patients received i.v. ifosfamide at a dose of 2 g/m^2/day for 5 days per 3-week cycle. Before starting therapy, all patients were randomized to receive either the standard i.v. mesna regimen (20% ifosfamide dose administered at the time of ifosfamide initiation and again 4 and 8 h later) or an i.v./oral regimen [20% ifosfamide dose administered i.v. at the time of ifosfamide administration, followed by oral mesna tablets (40% ifosfamide dose) 2 and 6 h later]. Each mesna tablet was a 400-mg formulation and was scored. After cycle 1, all patients then crossed over to receive the alternative mesna regimen for cycle 2 and, thus, served as internal controls for PK and clinical efficacy measures. All patients were admit-

[6] The abbreviation used is: PK, pharmacokinetic.

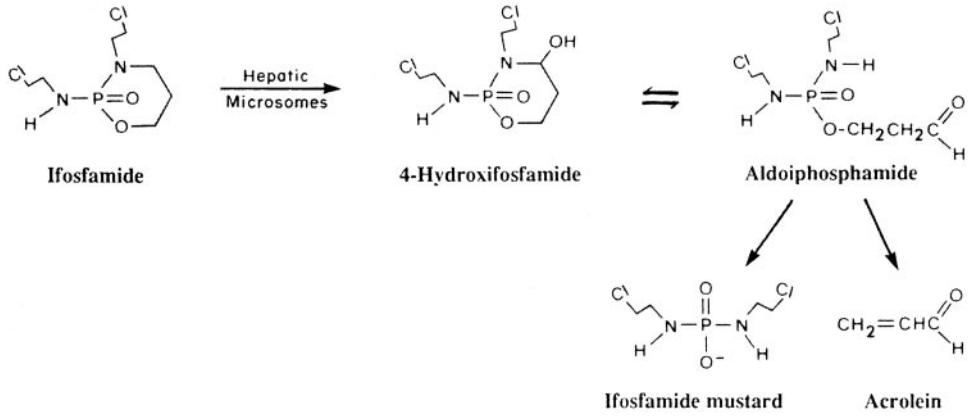

Fig. 2 Metabolism of ifosfamide and mesna. (Reprinted with permission from Ref. 5.)

ted to an inpatient treatment unit for both cycles of chemotherapy. PK, toxicity, and clinical efficacy data were collected for the first two cycles of ifosfamide. After two cycles, based on either radiographic or other measure of antitumor efficacy, patients could receive additional cycles of ifosfamide or initiate alternative and clinically appropriate sarcoma therapy. Patients who experienced emesis within 1 h of receiving oral mesna on days 1 or 5 were removed from the protocol and subsequently received clinically appropriate therapy (ifosfamide with i.v. mesna support) off-study.

PK Data Collection and Processing. To avoid contamination of study samples, blood and urine samples for ifosfamide and mesna were performed in separate locations within the processing area. Blood samples for mesna were collected into 5-ml graduated syringes and transferred immediately into prechilled sample tubes containing a 2 cc of solution of 700 μmol/liter DTT in 5% EDTA and placed on an ice bath. Within 30 min of obtaining blood samples, each sample tube was centrifuged at 10°C and 3cc of plasma was transferred into a prechilled sample tube containing 1.5 ml of a solution containing 1 M prechlroic acid and 1% EDTA. The remaining plasma from the initial sample tube was stored at −65 to −85°C, pending final analysis. Blood samples for ifosfamide were collected into 10-ml graduated syringes, and 2 cc were transferred into a sample tube containing 3 ml of sodium heparin. These tubes were then centrifuged within 60 min of collection at ambient temperature for 10 min. Plasma obtained was then stored at −65 to −85°C, pending final analysis. Urine samples were stored at 4–10°C during the collection period. Samples were transferred into 500-ml containers containing 8.25 ml of 6 M HCl and 12.5 ml of 10% (w/v) EDTA solution and were quantified. Two 2-ml aliquots of urine were transferred into sample tubes and stored at −65 to −85°C, pending final analysis.

On days 1 through 4, blood samples for mesna and ifosfamide were obtained before the administration of the ifosfamide and first mesna dose. On day 5, blood samples for patients on the i.v. mesna arm were performed at time 0 (start of ifosfamide and first dose of mesna), 15 and 30 min, 1 h, 2 h, 4 h, 4 h 15 min, 4 h 30 min, 5 h, 6 h, 8 h, 8 h 15 min, 8 h 30 min, 9 h, 10 h, 12 h, 14 h, 16 h, 20 h, 24 h, and 28 h. Blood samples for patients on the i.v./oral arm were performed at time 0 (start of ifosfamide and first dose of mesna), 15 and 30 min and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, and 30 h. Individual urine samples

Table 1 Patient characteristics

Patient	Age (yr)	Gender	Diagnosis	Metastatic (site)	Prior chemotherapy
1	64	F[a]	MFH	Y (lungs)	A + I
2	41	M	Liposarcoma	N	None
3	20	M	Ewing's sarcoma	Y (lungs + ST + B)	A + I + DTIC + VP16 + CP + CX + V
4	61	M	Angiosarcoma	N	None
5	58	F	MFH	Y (lungs)	A + I + DTIC
6	19	F	Ewing's sarcoma	Y (ST + B)	A + I + DTIC + VP16 + CP + CX
7	34	F	Synovial sarcoma	Y (lungs)	A + I, I, A + CX
8	45	M	Leiomyosarcoma	Y (lungs)	A + I
9	36	F	Cardiac sarcoma	Y (lungs + ST + P)	A + I
10	48	M	Synovial sarcoma	Y (lungs)	A + I + DTIC
11	30	F	ASPS	Y (lungs)	A + I, V + I + CP
12	52	F	RP sarcoma, NOS	Y (liver)	None
13	53	F	Synovial sarcoma	Y (lungs)	A + I
14	40	F	GI stromal tumor	Y (liver)	Temodar, A + I
15	73	M	Liposarcoma	Y (lungs + ST)	None
16	25	F	Synovial sarcoma	Y (lungs)	None

[a] F, female; M, male; MFH, malignant fibrous histiocytoma; NOS, not otherwise subclassafiable; ST, soft tissue; P, pancreas; A, doxorubicin; I, ifosfamide; DTIC, dacarbazine; CP, cisplatin; CX, cytoxan; V, vincristine; Y, yes; ASPS, alveolar soft part sarcoma.

Table 2 PK parameters of mesna regimens

	PK parameters of mesna, urine, iv/oral/oral							
	$Ucum_{0-12}$ (μmol)	$Ucum_{0-24}$ (μmol)	$Ucum_{0-24}$ (%)	R_{max} (μmol/h)	$t_{mid,\ max}$ (h)	R_{min} (μmol/h)	$t_{mid,\ min}$ (h)	CL_{ren} (l/h·kg)
Day 1								
No.	13	13	13	13	13	13	13	ne
Median	3589.99	4424.26	18.98	570.68	6.9	27.65	23.0	
Minimum	1641.43	1866.79	10.15	198.21	0.8	10.33	22.5	
Maximum	4878.72	6987.22	25.69	1115.96	11.0	110.23	23.2	
$Mean_{geo}$	3340.90	4204.81	18.21	526.77		30.78		
95% CI_{ln}	2786.73	3395.68	15.39	412.62		19.88		
*	4005.27	5206.73	21.55	672.50		47.68		
Day 5								
No.	13	13	13	13	13	13	13	13
Median	4229.26	5505.87	26.69	664.99	7.1	44.39	23.0	0.116
Minimum	3199.56	3383.75	14.03	448.71	0.8	5.92	22.5	0.047
Maximum	12558.59	17405.55	64.01	2694.34	11.0	138.33	23.1	0.328
$Mean_{geo}$	4796.54	5903.55	25.57	753.69	3.2	31.86	22.9	0.128
95% CI_{ln}	3806.53	4566.42	20.11	557.94	1.6	17.14	22.8	0.084
*	6044.04	7632.22	32.51	1018.10	6.6	59.21	23.0	0.194
Ratio day 5 *vs.* day 1 (ANOVA)								
Estimate	1.44	1.40		1.43		1.04		
90% CI[a]	1.24–1.66	1.21–1.64		1.21–1.69		0.63–1.70		
Day 1: ratio i.v.:oral:oral *vs.* i.v.:i.v.:i.v. (ANOVA)								
Estimate	1.01	1.23		0.82		7.45		
90% CI	0.89–1.14	1.08–1.39		0.71–0.96		4.31–12.89		
Day 5: ratio i.v.:oral:oral *vs.* i.v.:i.v.:i.v. (ANOVA)								
Estimate	1.44	1.71		1.29		4.81		1.13
90% CI	1.28–1.63	1.50–1.94		1.11–1.50		2.78–8.33		0.95–1.35

[a] CI, confidence interval.

were collected over 12 2-h periods on days 1 and 5 on both arms, starting 2 h before the first dose of mesna and ifosfamide. On days 3 and 4, a single 2-h sample was obtained on all patients starting 2 h before the first dose of mesna and ifosfamide.

Plasma PK parameters for mesna and ifosfamide were: maximum concentrations (C_{max}) of mesna and dimesna after each mesna administration (i.v. or oral) on day 5; C_{max} of ifosfamide at the end of infusion; time to reach maximum plasma concentration (t_{max}) after each oral mesna administration on day 5; area under the concentration-time curves ($AUC_{0\text{-last}}$ and $AUC_{0-24\ h}$) for i.v. and oral mesna on day 5 over all three mesna administrations; terminal half-lives ($t_{1/2}$) after the final mesna dose on day 5; and predose plasma levels on days 2–5. Urine PK parameters were: cumulative urinary excretion at times 0–12 h and 0–24 h as amounts and as a fraction of the daily mesna dose; maximum urinary excretion rates (R_{max}) after oral and i.v. mesna doses; time to reach maximum excretion rates (t_{max}); nadir excretion rates (R_{min}) at 22–24 h; and predose urine levels on days 2–5.

The sample size was determined on the basis of PK considerations. The study was not powered to detect differences in hematuria.

Results

Seventeen patients have been enrolled, 16 patients were exposed to study medication, with characteristics summarized in Table 1.

Three of the 16 patients (3, 5, and 12) did not complete the protocol. Patient 12 had extensive retroperitoneal sarcoma with hepatic involvement and experienced significant azotemia (serum creatinine, 3.8 mg/dl) associated with renal tubular acidosis (serum bicarbonate, 9 mg/dl) on day 3 of cycle 1. These adverse events were attributed to ifosfamide. Patient 5 experienced emesis shortly after receiving the first oral mesna dose on the first day of cycle 1. The patient subsequently admitted to consuming a heavy and fatty meal before initiating chemotherapy. Patient 3 experienced dyspnea because of tumor progression and was removed from protocol after completing one cycle of treatment.

Results of the day 5 PK analysis of the standard i.v. and i.v./oral mesna regimens are summarized in Table 2. The patient analysis of ifosfamide is detailed in Tables 3 and 4.

The exposure of mesna in plasma and urine is increased in the i.v./oral schedule. Prolongation of urinary mesna excretion is

Table 3 PK parameters of ifosfamide in plasma

Ratios for the ifosfamide predose plasma levels (ANOVA)				
	Day 5 *vs.* day 2			
	i.v.:i.v.:i.v.	i.v.:oral:oral	Day 2	Day 5
No. Estimate	12	12	12	12
Estimate	0.22	0.34	0.80	1.24
90% CI	0.15–0.34	0.23–0.52	0.52–1.25	0.80–1.94

Table 4 PK parameters of ifosfamide in plasma

	Ratio i.v.:oral:oral *vs.* i.v.:i.v.:i.v. (ANOVA)							
	C_{max} (μmol/l)	$t_{1/2}$ (h)	AUC_{0-12} (μmol·h/liter)	AUC_{0-24} (μmol·h/liter)	AUC (μmol·h/liter)	CL (liter/h·kg)	V_z (liter/kg)	$MRT_{ss,\ 2h\text{-}infus}$ (h)
Estimate	1.00	1.00	1.00	1.00	1.00	1.00	0.98	1.02
90% CI	0.91–1.10	0.95–1.05	0.92–1.09	0.93–1.08	0.93–1.08	0.92–1.07	0.90–1.07	0.98–1.06

observed in the i.v./oral regimen, with excretion rates at the end of the 24-h period above that seen in the standard i.v. regimen. No significant differences in the plasma PK of the concomitantly infused ifosfamide were detected between the two mesna schedules. One patient who showed visible blood in the first cycle with mesna/i.v./i.v. dosing had microhematuria only in the subsequent cycle with mesna i.v./oral/oral dosing. Overall, equal rates of microhematuria were observed with both dosing regimens (3 of 16 for i.v./i.v./i.v. dosing and 4 of 16 for i.v./oral/oral dosing). Of the 16 patients evaulable for safety, there were no serious adverse events attributed to oral or i.v. mesna. There was more nausea in the i.v./oral/oral arm with 14 of 16 patients experiencing this effect *versus* 9 of 16 in the i.v./i.v./i.v. arm. Seven patients in the oral schedule had emesis *versus* five patients on the i.v. schedule. Of 10 patients evaluable for tumor response, four demonstrated objective improvement, consisting of three partial responses (defined as a 50% reduction in clinically evident disease by cross-sectional imaging or physical examination) and one cytoreductive response that did not meet criteria for a partial response.

Discussion

Ifosfamide is an alkylating chemotherapeutic agent with significant activity in a variety of malignancies. Among its toxicities, irritation of uroepithelium by excreted 4-hydroxyifosfamide and spontaneously formed acrolein was dose limiting, before the development of mesna. The efficacy of this thiol in preventing ifosfamide-induced urotoxicity is well documented, as is its minimal toxicity profile. Both the i.v. as well as oral routes of mesna administration have been studied extensively, and both have demonstrated excellent and equivalent clinical results. The current study was undertaken to assess the clinical efficacy and PK properties of an oral tablet formulation of mesna.

Unique to the current study was the use of internal controls, with each patient receiving, in random order, the standard i.v. regimen as well as the i.v./oral regimen. This eliminates potential confounding by individual differences in cytochrome P-450 metabolic rates and strengthens the conclusions that can be drawn. PK data from this study demonstrate that the i.v./oral mesna regimen is at least as uroprotective as the standard i.v. regimen in patients receiving ifosfamide at doses of 10 g/m^2 over 5 days. Although oral administration requires higher doses to offset the slower accumulation in the urine, this does not seem to affect tolerance of the tablet formulation of the oral drug. Furthermore, the i.v./oral schedule prolongs the presence of mesna in the urinary tract and may actually improve the degree of uroprotection over that seen with the standard i.v. regimen.

In the setting of outpatient ifosfamide therapy, compliance with supportive medications is an important determinant for treatment success. The use of a tablet formulation of oral mesna will eliminate the issue of palatability seen with the oral administration of mesna solution. This, in turn, will improve patient compliance and may result in lower complication rates from outpatient therapy with ifosfamide. In addition, the i.v./oral regimen will improve patient convenience, decrease care costs associated with prolonged patient monitoring in infusion centers, and allow for a reduction in elective hospitalizations. The tablet formulation of oral mesna with the schedule described in this study has been approved by the U.S. Food and Drug Administration.

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