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Mesnum as a Protector Against Kidney and Bladder Toxicity with High-Dose Ifosfamide Treatment

Geoffrey Falkson, J. J. Van Dyk, René Stapelberg, and H. C. Falkson

Department of Cancer Chemotherapy, H F Verwoerd Hospital and the University of Pretoria, Pretoria 0002, South Africa

Summary. *Thirty-two patients with advanced cancer were treated in a phase I–II trial with ifosfamide plus mesnum. At doses up to 300 mg ifosfamide/kg the administration of mesnum prevented most of the expected kidney and bladder toxicity. With this high dose range hemopoietic dose-limiting. Only one of twelve evaluable patients with breast cancer showed definite therapeutic benefit. Complete remission or partial remission was seen in three patients with non-Hodgkin lymphoma and one patient with Hodgkin's disease.*

Introduction

A. Ifosfamide

Ifosfamide (2,3-(*N*,*N*^{1}-bis(2-chloroethyl)diamino-1,3,2-oxazaphosphoridinoxyd) is less toxic in experimental systems than cyclophosphamide, yet has a broader antitumor spectrum. In clinical trials, however, unexpected toxicity was encountered [16]; in addition to nausea, vomiting, alopecia and hemopoietic suppression, nephrotoxicity (lower nephron damage), and hematuria were prominent when single high doses of ifosfamide were administered. Subclinical nephrotoxicity also occured with small divided doses [16], and with doses of 0.6 g/m^2 on 5 consecutive days per week toxicity was just acceptable. However, therapeutic effects were only equivalent to those obtained with cyclophosphamide [11]. Results of a phase I–II trial combining ifosfamide with Etoposide (VP 16–213) were discouraging [10]. Ifosfamide at various dose ranges has been tested by several investigators in the United States. In lung cancer, ifosfamide alone [8, 9] or in combination with cisplatinum [14] showed activity. Ifosfamide was disappointing as a single agent or in combination with fluorouracil and adriamycin in breast cancer [1, 6]. When ifosfamide was used (instead of cyclophosphamide) in various other combinations for other diseases [7] no definite advantage could be shown. The only disease where ifosfamide appears to have a therapeutic advantage over equitoxic doses of cyclophosphamide is advanced pancreas cancer [13].

B. Ifosfamide and Mercaptoethane Sulfonate

Nephro- and bladder toxicity is the main obstacle when large doses of ifosfamide are delivered. Intravesicular administration of *N*-acethylhomocysteine-thiolactate and L-cysteine plus D-fructose by bladder catheter prevented hemorrhagic cystitis but did not protect the lower nephron [16].

Reprint requests should be addressed to G. Falkson

The urotoxicity of the oxazaphosphorine cytostatics (ifosfamide and cyclophosphamide) was subsequently shown to be due not to their alkylating activity but to the presence of acrolein, which is formed in the urine from the metabolites of the oxazaphosphorines. Following this clarification of the toxic mechanism, animal experiments confirmed that sodium 2-mercaptoethane sulfonate (mesnum) could act as a uroprotector by forming a non-toxic additive compound with acrolein [3, 4].

Clinical studies in Germany showed that mesnum significantly lowered the frequency of microhematuria during cytostatic therapy with ifosfamide at different divided dose schedules [2, 15]. Data were collected from various hospitals and some patients received other concomitant cytostatics or radiotherapy. In a recent report on eight patients, investigators in England concluded that mesnum enhances the therapeutic ratio of ifosfamide (2 g/m^2 at 2-weekly intervals) and may therefore increase its clinical efficacy [5]. Workers in Norway, using ifosfamide 50–60 mg/kg/day for 5 days monthly with and without irradiation, treated 15 patients with metastatic renal cancer and found that the urotoxicity could be controlled by mesnum (and intensive hydration) in some patients. They did not reconfirm previously reported high response rates to ifosfamide treatment of renal cancer [12]. Workers in Switzerland and Italy treated 27 patients, using two different mesnum schedules (one IV + PO and one PO schedule). Ifosfamide 1.8 g/m^2 was given daily for 5 days, repeated every 4 weeks. These workers conclude that mesnum given entirely PO does not provide sufficient uroprotection; that there is an important dose-limiting effect due to leucopenia (WBC less than 1,000 in 7/24 patients); that two cases of early death were possibly due to cardiac toxicity; and that only two patients showed a significant rise in serum creatinine but that this was reversible (M. Varini, 1981, personal communications). The same workers report a response rate of only 13% in patients with epidermoid cancer of the lung when this schedule is used.

The present study was undertaken to investigate the effects of mesnum in patients treated with single high doses of ifosfamide, the motivation being that the possible advantage of ifosfamide over other oxazaphosphorines is dependent on its concentration. This is limited by urotoxicity, which could be prevented by giving mesnum.

Materials and Methods

Thirty-two patients with histologically confirmed metastatic cancer were entered on study, 17 of whom were women and 15

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Table 1. Ifosfamide and mesnum scheduling and number of doses administered

Schedule	No. of patients	Dose of ifosfamide	Dose of mesnum as % of ifosfamide dose	No. of doses per patient									
				1	2	3	4	5	6	7	10	12	16
1	9	100 mg/kg d 1 q 21 d	20% hourly 0, 4 and 8	1	5	1	0	0	1	0	0	1	0
2	5	100 mg/kg d 1 q 14 d	20% hourly 0, 4 and 8	2	0	1	1	0	0	1	0	0	0
3	18	150 mg/kg d 1 and 3 q 28 d	30% hourly 0, 4, 8 and 12	0	4	3	2	4	1	2	1	0	1

men. One patient was under 30 and one was more than 69 years old. Twelve patients had breast cancer, four lung cancer (2 small cell), three non-Hodgkin's lymphoma, one Hodgkin's disease, three ovarian cancer, two prostate cancer, two malignant melanoma, and one each soft tissue sarcoma, bone sarcoma, thyroid cancer, pancreas cancer, and primary liver cancer. Thirteen patients had received no prior cytostatic treatment; the remaining patients had had at least one prior cytostatic or cytostatic combination treatment. Six patients had had three or more cytostatics or cytostatic combinations. Before ifosfamide was started patients were evaluated for performance status.

The performance status (PS) of the patients according to ECOG criteria[1] was as follows:
PSO, four patients; PS1, 15 patients; PS2, eight patients; PS3, four patients; PS4, one patient.

All neoplastic lesions were measured and these were re-evaluated at every clinic visit. The following special investigations were performed before treatment and at regular intervals thereafter: full blood counts, urinalysis (including microscopy), urea, uric acid, creatinine, and creatinine clearance. Serum protein electrophoresis pattern was determined as well as alkaline phosphatase, LDH, SGOT, bilirubin, and gamma-GT. For a patient to be eligible for this study normal values were considered essential except when serum protein patterns, alkaline phosphatase, LDH, SGOT, and gamma-GT were due to the malignant neoplastic disease per se.

Drug Administration. Three schedules of ifosfamide and IV mesnum administration were used.

Schedule 1: Ifosfamide 100 mg/kg IV on day 1 every 21 days, with mesnum, 20% of the ifosfamide dose, at 0, 4, and 8 h. Nine patients were treated at this dose level.

Schedule 2: Ifosfamide 100 mg/kg IV on day 1 every 14 days with mesnum, 20% of the ifosfamide dose, at 0, 4, and 8 h. Five patients were treated at this dose level.

Schedule 3: Ifosfamide 150 mg/kg on days 1 and 3 every 28 days, with mesnum, 30%, at 0, 4, 8, and 12 h on days 1 and 3. Eighteen patients were treated at this dose level. The drug administration and the number of doses given to patients at each drug dose level are shown in Table 1. A single dose of 300 mg/kg was not given as central nervous system side-effects were feared and it was felt that the dose should first be investigated in two divided parts on days 1 and 3.

Results

Toxic Effects. Of the 32 patients, 29 were evaluable for toxicity. The dose of ifosfamide was modified for toxicity in 18 of the 32 patients studied: Two of nine in schedule 1; one of five in schedule 2; 15 of 18 in schedule 3. The most commonly encountered toxic effects were nausea and vomiting in 26, leucopenia in 19, decrease in creatinine clearance in 13, demonstration of granular cylinders in the urine in 13, and microscopic hematuria in 13 patients. A decrease in hemoglobin and alopecia was documented in 10 patients. The data are shown in Table 2.

With schedule 1 leucopenia occurred in two of nine, decreased creatinine clearance in two of five, and alopecia in one patient. As this seemed tenable, the same drug dose was repeated in a further five patients at 14-day instead of 21-day intervals. At this dose level two of three patients with adequate measurements showed an increase in creatinine clearance, one patient showed mental confusion, and one patient developed granular casts in the urine. One patient developed alopecia. Of 12 patients evaluable for hemopoietic toxicity in schedule 1 and 2 only two developed leucopenia with WBC less than 4,500/mm^3, while four of eight with adequate follow-up showed a decrease of creatinine clearance. It was clear that if the dose of mesnum was increased and could protect against urotoxicity a larger dose of ifosfamide would be tolerated by the bone marrow. It seemed it would be safe to escalate the ifosfamide to 300 mg/kg if 150 mg/kg was given on days 1 and 3 every 4 weeks.

At 150 mg/kg given on days 1 and 3, with mesnum at 30% of the ifosfamide dose at 0, 4, 8, and 12 h, 17 of 18 patients were followed adequately for toxicity evaluation (see Table 2).

All 17 patients developed some degree of leucopenia, seven developing leucopenia with WBC less than 1,000/mm^3. It is clear that at 300 mg/kg the degree of hemopoietic toxicity is the dose-limiting factor. At this dose range nine patients showed worsening of creatinine clearance; except for one patient, this was not worse than 18–35 ml/min and was unaccompanied by changes in the blood urea and creatinine. Two patients, however, developed macroscopic hematuria and a further 12 microscopic hematuria, and these 12 patients showed an excess of granular casts in the urine, indicating renal tubular damage. It was therefore concluded that this was the maximum tolerated dose and probably not safe for general clinical use. A total of 182 doses of ifosfamide at 150 mg/kg were given during schedule 3. It is concluded that mesnum

1 Performance status key; 0 = Normal activity; 1 = Symptoms but ambulatory; 2 = In bed < 50% of time; 3 = In bed > 50% of time; 4 = 100% bedridden

Table 2. Side effects with ifosfamide plus mesnum at three different dose schedules (29 evaluable patients)

Side-effects	100 mg/kg every 21 days	100 mg/kg	150 mg/kg on days 1 and 3 every 28 days
Nausea and vomiting	6	3	17
Leucopenia	2	0	17
Thrombocytopenia	0	0	6
Anemia	0	0	10
Decreased creatinine clearance	2	2	9
Increased urea	0	0	1
Increased creatinine clearance	0	0	2
Macroscopic hematuria	0	0	2
Microscopic hematuria	0	1	12
Granular casts in urine	0	1	12
Stomatitis	0	0	1
Constipation	0	0	3
Alopecia	1	1	8
Infection	0	0	4
Mental confusion	0	1	2
Dermatitis	0	0	1

Table 3. Leucopenia following ifosfamide 150 mg/kg IV

	Grade				
	0	1	2	3	4
Leucopenia	$\geqq 4.5$	$3.0 - \leqq 4.5$	$2.0 - \leqq 3.0$	$1.0 - \leqq 2.0$	$\leqq 1.0$
Ifosfamide (150 mg/kg day 1) 24 patients [16]	4	3	9	6	2
				33.3%	
Ifosfamide (150 mg/kg days 1 and 3) plus mesnum 17 patients	0	3	3	4	7
				64.7%	

Table 4. Ifosfamide plus mesnum: therapeutic response

Total	CR	PR	NC	PD	Not evaluable
32	2	3	7	16	4

protects against the urotoxicity of ifosfamide, enabling the clinician to administer very large doses of ifosfamide. This protection is not absolute. When the toxic effects are compared with those obtained with single doses of ifosfamide 150 mg/kg given without mesnum [16] it is evident that urotoxicity is very much decreased but that there is little, if any, protective effect against the hemopoietic toxicity. Administering mesnum as a urotoxic protector makes it possible to give a dose of ifosfamide at which leucopenia becomes the dose-limiting factor. The leucopenia documented with ifosfamide 150 mg/kg and ifosfamide 150 mg/kg on days 1 and 3 with mesnum are shown in Table 3.

Therapeutic Effect

Complete remission was achieved in two patients, one with Hodgkin's disease (schedule 3) and one with low-grade lymphoma (schedule 1). Partial response was obtained in three patients (one each with breast cancer, high-grade lymphoma, and intermediate lymphoma, treated according to schedule 3, schedule 2, and schedule 1, respectively) (Table 4). Two patients (one with carcinoma of the prostate and one with broncho-alveolar carcinoma) showed definite improvement but are classified as no change, as this improvement did not meet the full criteria for partial remission. In the 12 evaluable patients with breast cancer only one partial response was observed. While the number of patients evaluable for response is too limited to draw finite conclusions it is clear that an optimistic outlook is not justified.

Discussion

Experimental data have suggested that ifosfamide may be superior to cyclophosphamide. The curative effect of ifosfamide in experimental animals depends on concentration rather than on total dose, while toxicity of the oxazaphosphorine is more related to total dose. In clinical use, urotoxicity is the dose-limiting side-effect of ifosfamide.

The present investigation was aimed at evaluating whether mesnum protects against ifosfamide-induced urothelial toxicity even at high dosage. However, at high dosage leucopenia becomes the dose-limiting side-effect. In this study the therapeutic efficacy of ifosfamide was disappointing, and this raises the question of whether ifosfamide plus mesnum has any advantage over cyclophosphamide. It would require prospective controlled clinical trials with optimal ifosfamide dosage versus high-dose cyclophosphamide to evaluate the relative value of these two alkylating agents.

Results from our study have not identified a tumor type where such a trial would be indicated. However, pilot trials reported in the literature suggest that pancreas carcinoma, malignant melanoma, sarcomas, and testis carcinoma may be disease types suitable for treatment with high-dose ifosfamide and mesnum. The dosage recommended for such trials is

ifosfamide 200 mg/kg plus mesnum, repeated at 3-weekly intervals.

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