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Toxicity of high-dose ifosfamide in children

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Summary. Ifosfamide has been shown to be an active agent in the treatment of several childhood cancers. However, the optimal dose and method of administration remains to be established. The dose/response relationship of ifosfamide suggests that a maximum tolerable, fractionated dose be given, and to reduce hospitalisation this dose should be given in the shortest possible time. A total of 20 patients aged 1–23 years received 124 courses (mean, 6 courses/patient; range, 1–16); 9 subjects had either relapsed or resistant disease, and all of these had previously received cyclophosphamide. A dose of 3 g/m^2 ifosfamide was given for 2 (five patients) or 3 (15 patients) successive days. In all, 9 patients received the drug twice daily as a bolus and 11 were given a continuous infusion. All patients received 3 g/m^2 mesna per day with ifosfamide and for 12 h there after, and hydration was maintained with 3 l/m^2 fluid daily. Myelosuppression occurred in all patients but was mild and reversible, with no toxic deaths. On four occasions in three patients treatment had to be delayed due to myelosuppression. Seven episodes of fever and neutropaenia were successfully treated with antibiotics. The mean glomerular filtration rate in 13 patients at the start of treatment was 104 ml/min per 1.73 m^2 and at the end was 92 ml/min per 1.73 m^2. In all, 19 patients had microscopic and 1 macroscopic haematuria, with no clinical sequelae. Two patients with grossly impaired renal function following previous cisplatin therapy may have been precipitated into terminal renal failure by the ifosfamide therapy. Only one person developed neurotoxicity, which recurred on further treatment with ifosfamide but was fully reversible. All patients had moderate to severe vomiting, which was controlled with anti-emetics. No abnormalities of liver or cardiac function were detected. We conclude that ifosfamide given by this schedule is safe in patients with normal renal function.

Introduction

The alkylating agent ifosfamide, an analogue of cyclophosphamide, has anti-tumour activity in a wide range of malignancies including soft-tissue sarcoma and lymphoma [12, 13]. The dose-response relationship of ifosfamide suggests that a maximum tolerable, fractionated dose be given and that to reduce hospitalisation it should be given in the shortest possible time [1, 11]. Several dose regimes have been described, the most frequent being five daily doses of 1.8 g/m^2, although an infusion of up to 8 g/m^2 over 24 h has also been reported [13]. Variations in administration include the individual dose, the number of doses in a course and the choice of administration by infusion or as a bolus, as well as the duration of therapy that can safely be given. The optimal dose and method of administration has yet to be determined. We report the results of giving 3 g/m^2 ifosfamide for up to 3 consecutive days in the Paediatric Oncology Unit, Newcastle upon Tyne.

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Patients and methods

From May 1985 to May 1987, 20 children (10 boys and 10 girls) aged 1–23 years (mean, 7.7 years) received 124 courses of ifosfamide (mean, 6 courses/patient; range, 1–16 courses). Diagnoses in the children are shown in Table 1. Nine patients were being treated for relapsed or resistant disease and all of these had previously received cyclophosphamide; eight had previously received radiotherapy, including 4 cases of pelvic radiotherapy. A total of 15 children received ifosfamide at a dose of 3 g/m^2 daily for 3 consecutive days; 5, all with rhabdomyosarcoma, received 3g/m^2 on 2 consecutive days. Ifosfamide was given in combination with vincristine and Adriamycin to 13 patients, with vincristine to 4, with Adriamycin to 1 and with VP16 to 1; 1 child was treated with ifosfamide alone.

Courses were repeated at 3-week intervals. In all, 9 children received ifosfamide twice daily as a bolus dose and 11 were given a continuous infusion. The uroprotective agent mesna (sodium 2-mercaptoethane sulfonate) was given at a dose of 3 g/m^2 per day on the days of treatment with ifosfamide and for 12 h afterwards. The mesna was given by infusion to 13 and by 3-h bolus doses to 7 patients. During treatment, hydration was maintained in all patients with 3 l/m^2 per day of intravenous fluid. Full blood count, urea, electrolytes, creatinine and serum liver enzymes were measured prior to each course of therapy, and in 13 children the plasma clearance of ^{51}Cr EDTA was measured regularly to monitor the glomerular filtration rate (GFR). All patients had normal urinalyses at the start of treatment.

Table 1. Malignant diagnoses in 20 children treated with ifosfamide

Disease	Number of children	
	Initial presentation	Relapse/resistant disease
Stage IV neuroblastoma	6	1
Rhabdomyosarcoma	3	2
Non-Hodgkin's lymphoma	–	2
Ewing's sarcoma	3	–
Disseminated retinoblastoma	–	1
Synovial sarcoma	1	–
Primitive neuroectodermal tumour	–	1

Results

No severe toxicity was observed in 18 of the patients; 2 had serious problems, some of which may have been related to ifosfamide treatment and are described in detail below. At the start of ifosfamide treatment all patients had normal plasma electrolytes and renal function, as indicated by serum creatinine in 19 children and ^{51}Cr EDTA clearance in 13.

Microscopic haematuria, measured by dip-stick testing, occurred at least once in 19 patients and recurred with every course of treatment in 12. One child who developed macroscopic haematuria that lasted for 1 day and did not warrant cystoscopy recovered completely, with no sequelae. Transient glycosuria unrelated to hydration fluids occurred in four patients and proteinuria, in two. The mean GFR before treatment was 104 ml/min per 1.73 m^2; at the completion of therapy it was 92 ml/min per 1.73 m^2.

Myelosuppression (WHO grade 2–4) [14] occurred after treatment in all patients but was usually reversible within 3 weeks. On four occasions in three patients, treatment was delayed for 1 week because the absolute neutrophil count was $< 1.0 \times 10^9$/l. Seven episodes of fever and neutropenia were successfully treated with intravenous antibiotics. No symptomatic thrombocytopenia occurred and no platelet transfusions were given. Eight patients required transfusion with red blood cells during the period of treatment.

Only one child developed clinical features of CNS toxicity during treatment, a 5-year-old girl with relapsed stage IV neuroblastoma. At 48 h after the completion of her first course of ifosfamide she became very drowsy, responsive only to vigorous stimulation. There were no focal signs and she recovered fully within 24 h. At 24 h after the second course of ifosfamide she again became "vacant" and sleepy, with marked tremor of the arms, although this did not develop into a generalised seizure. These symptoms again completely settled in 24 h. There was no evidence of any metabolic or biochemical disturbance or intracranial disease to account for these symptoms. The patient's serum albumin was normal and there was no bulky pelvic disease. She had previously been treated with cisplatin. Ifosfamide therapy was discontinued.

All patients suffered moderate to severe nausea and vomiting (WHO Grade 2–3) [14], which was controlled with anti-emetics (metoclopramide and chlorpromazine). No abnormalities of hepatic or cardiac function were detected.

There was no difference in toxicity between the 11 children who had a constant infusion and those who were given a bolus injection twice daily; it was no greater in patients with recurrent disease or in those previously treated with cyclophosphamide, and it did not appear to be cumulative. The frequency of treatment delay was unchanged after 6 months of therapy and as many as 12 3-day courses; 16 2-day courses were given successfully.

Two patients had more serious problems. The first had relapsed retinoblastoma, with heavy bone marrow infiltration. She had previously received treatment with cisplatin (total dose, 581 mg/m^2) and, as a result, had a GFR of only 24 ml/min per 1.73 m^2. She was given 3 g/m^2 ifosfamide on 2 days, after which she became severely neutropenic, with a proteus septicaemia. Her renal function deteriorated further and she died of renal failure as well as disseminated retinoblastoma. No autopsy was done.

The other patient had disseminated, relapsed neuroblastoma and had undergone previous chemotherapy that included cisplatin (total dose, 472 mg/m^2); she was described above as having an encephalopathy. Her ^{51}Cr EDTA clearance prior to ifosfamide was 51.9 ml/min per 1.73 m^2 and her serum creatinine, 156 mmol/l. Following the first course of ifosfamide (3 g/m^2 on 2 days), she developed the neurological problems described above. Her creatinine values fell to 79 mmol/l. After the second course, the creatinine level slowly rose to 684 mmol/l and she had high-output renal failure. The patient died 16 weeks later of disseminated neuroblastoma and renal failure.

Discussion

When ifosfamide was introduced into clinical practice, the limiting toxicity was haemorrhagic cystitis. The development of the effective uroprotector mesna has made dose escalation possible without unacceptable toxicity. Studies in mice [5] suggest that fractionation of the ifosfamide dose leads to better tolerance and a greater therapeutic effect than that achieved with a single bolus dose. This is supported by evidence that fractionation of an oral dose of ifosfamide may result in greater alkylating activity, probably due to the induction of metabolism, increasing the production of active metabolites [2].

Several schedules for ifosfamide administration have been described in paediatric patients (Table 2). Pinkerton et al. [9], Pratt et al. [10] and Magrath et al. [7] have given ifosfamide as a single agent. De Kraker and Voûte [6] have given ifosfamide with vincristine, and Gasparini [3] has used it as part of sequential chemotherapy including methotrexate, cytosine arabinoside, cisplatin, Adriamycin and actinomycin D. Our schedule was designed for maximal

Table 2. Previously described schedules of administration for ifosfamide

References	Total dose (g/m^2)	Method of administration	Number of days per treatment
[6]	6	Infused over 1 h	2
[3]	8	Continuous 24-h infusion	1
[9]	5	Continuous 24-h infusion	1
[7]	9	Continuous infusion for 5 days	5
[10]	8	Infusion over 15 min	5

efficacy with minimal toxicity and the shortest possible hospitalisation. Previous studies [7] have suggested that a total dose of 12 g/m^2 is only rarely tolerated and that a daily dose of 8 g/m^2 [13] leads to unacceptable nephrotoxicity in adults. Therefore, a total dose of 9 g/m^2 over 3 days was chosen, which was acceptable, with very little myelotoxicity even in heavily pre-treated patients. There was a high incidence of microscopic and low incidence of macroscopic haematuria, and no clinically significant bladder toxicity occurred with the administration of mesna at a dose to that of ifosfamide.

The incidence of neurotoxicity (5%) was lower in these patients than in previously published series of paediatric patients (22% [10], 8% [7] and 10% [9]). One patient who developed neurotoxicity had been pre-treated with cisplatin, which has been reported to be associated with an increased risk of toxicity [4]. The low incidence in the present study may be related to the near lack of other previously described predisposing factors to neurotoxicity in the children studied, i.e. bulky pelvic disease, low serum albumin and raised serum creatinine [8], or it may be a feature of this schedule of administration.

Two patients developed renal failure; both previously had grossly impaired renal function due to cisplatin therapy. Ifosfamide may have contributed to the severity of the neutropenia in one patient and the precipitation into complete renal failure in both. However, in such patients it is impossible to ascribe the renal failure and death definitively to the drug. Goren et al. [4] have shown the potentiation of ifosfamide toxicity in patients previously given cisplatin.

The approach to ifosfamide administration described in the present study is currently being used in the UKCCSG Ewing's sarcoma study. The current method of administration therefore appears to be safe in patients with normal renal function but should be used with caution in those with impaired renal function, particularly those who have previously received cisplatin. Whether or not it is more effective than other schedules in the eradication of tumours can only be determined by a randomised study, and this schedule of administration could be included in such a study.

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