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A phase II study of ifosfamide in paediatric solid tumours

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Summary. A total of 20 children with recurrent or unresponsive tumours (10 Wilms' tumours, 3 rhabdomyosarcomas, 4 Ewing's sarcomas, 1 osteosarcoma, 1 hepatoblastoma, 1 hepatoma) were given ifosfamide as a 24-h infusion (5 g/m^2), with mesna as a uroprotector. The number of courses ranged from 1 to 13 (median, 3), and the interval between them was 2–3 weeks. In all, 16 of these patients had previously received cyclophosphamide. Complete clinical responses (CRs) were seen in 3 cases (2 Wilms' tumours and 1 Ewing's sarcoma) and lasted 5, 7, and 9 months. Partial responses (PRs) were seen in 3 instances; mixed response or stable disease, in 4; and progressive disease, in 10. Treatment was well tolerated in most patients, with no cystitis or severe myelosuppression, but two children developed transient neurological symptoms and one became hypertensive. Nausea and vomiting were controlled by high-dose dexamethasone in most children.

Introduction

The oxazaphosphorine isophosphamide (iphosphamide, ifosfamide, IF) has been studied in a variety of tumours in adults [7]. The main advantages it offers over its close structural analogue cyclophosphamide (CP) are an apparent activity in some CP-resistant tumours and lower myelotoxicity, enabling the administration of higher doses.

This study was designed to determine the effectiveness of IF in children with relapsed sarcomas and, in particular, to assess the degree of cross-resistance in those who had previously received CP. These tumours were chosen because of the reported activity of the drug in adults with sarcomas. Stuart-Harris et al. [12] have reported a complete response rate of 15%, with 23% achieving a partial response. The 24-h infusion schedule chosen for this study was similar to that used by the Royal Marsden Hospital group and was based on evidence that a greater proportion of IF is metabolised to the active form after divided doses than after a single dose [1].

Patients and methods

A total of 20 children were studied. Their ages ranged from 2 to 14 years, and 7 were girls (Table 1). The group included 10 patients with Wilms' tumours who had relapsed either during or within 6 months of the end of treatment. With the exception of two cases, all had received CP either as part of their initial therapy or in an unsuccessful attempt to achieve a response after disease recurrence. Of the other 10 patients, 8 had received CP as initial therapy.

Drug administration. IF was given as a 24-h infusion at a dose of 5 g/m^2. In case 1, the dose was escalated to 7 g/m^2 by the third course but was reduced after a neurological complication (see below). IF was diluted in 4% dextrose 0.18% saline with 10 mEq KCl/500 ml. IF was added to each 500-ml infusion bag at a dose of 1 g/bag. Given at a rate of 2.5 l/m^2, this provided the appropriate dose of IF plus hydration. 2-Mercaptoethane sodium sulphonate (mesna) was given in the same infusion fluid to give a 100% equivalent dose to IF, but the former was infused over 48 h. An initial sedative cocktail of diazepam (5 mg/m^2), chlorpromazine (12.5 mg/m^2) and dexamethasone (10 mg/m^2) was given i.v. 30 min before IF. Dexamethasone (10 mg/m^2) was repeated every 8 h for 24 h. Courses of IF were initially given at 21-day intervals, but as prolonged myelosuppression was not apparent, the interval was reduced to 14 days. In all cases the neutrophil count was required to be $>1.0\times10^9$/l and platelets, $>100\times10^9$/l prior to each course.

Clinical assessment. The extent of disease at the time of relapse and after treatment with IF was assessed according to site: chest – X-ray, fluoroscopy, computerized axial tomographic (CAT) scan; bone – X-ray, isotope scan; abdomen and pelvis – ultrasonography, CAT scan. Blood counts were done weekly in the first few patients and subsequently at 14 days after each course. Urea, creatinine and serum electrolytes were estimated at each course and liver function tests (bilirubin, AST, ALT), at varying intervals during treatment.

Unless there was obvious clinical progression of disease after the first course, patients received two courses of IF and were reassessed at the time of the third. If disease was stable or there was evidence of a response, IF was continued. After a total of ten courses, consolidation with surgery or radiotherapy was considered, and in two patients local irradiation was given to the original site(s) of relapse.

A complete clinical response (CR) was defined as the absence of detectable disease for at least 4 weeks; a partial

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Table 1. Patients' diagnosis, duration of response, time of relapse and response to ifosfamide

Diagnosis	Patients (*n*)	Time of relapse	Response to ifosfamide (months)
Wilms' tumour	10	On treatment, 7 patients	1 CR(5), 1 PR(2), 5 NR
		Off treatment, 3 patients	1 CR(7), 1 PR(2), 1 NR
Rhabdomyosarcoma	3	On treatment	3 NR
Ewing's sarcoma	4	On treatment, 3 patients	1 CR(9), 1 PR(4), 2 NR
		Off treatment, 1 patient	1 NR
Hepatoma	2	On treatment	2 NR
Osteosarcoma	1	On treatment	1 NR

response (PR) was a reduction of at least 50% in maximal tumour diameter in two dimensions on X-ray or ultrasonography, for at least 4 weeks. No response (NR) was recorded in patients who had stable disease (SD), a small or mixed response (MR), or progressive disease (PD).

Results

Drug tolerance

In general, IF was well tolerated and there were few acute side effects. Nausea and vomiting were effectively controlled in all but three patients by means of the sedative cocktail and dexamethasone. As mesna was used for uroprotection, forced diuresis was not induced, although i.v. fluids were given liberally during IF infusion. Macroscopic haematuria was not seen in any patient during the study. One child had previously developed severe haemorrhagic cystitis when given IF without mesna at another centre, but this did not occur during the present study with concurrent mesna administration.

Acute neurological complications were seen in two patients. One developed generalised convulsions 7 h after starting IF; they lasted 5 min and responded to i.v. diazepam. The infusion was stopped immediately. The convulsions appeared to be directly related to IF, and no metabolic, infectious or other drug-related factors were apparent. However, this child had received 7 g/m^2 as part of an initial, escalating dose schedule that was subsequently discontinued. No such problems occurred with later doses of 5 g/m^2, and there were no detectable clinical sequelae. Severe facial spasms and trismus developed in one case during IF infusion. This was not related in time to the administration of chlorpromazine and resolved with i.v. diazepam. There was no recurrence with further IF therapy.

Shortly after the beginning of IF infusion, transient hypertension occurred in a child with bilateral hydronephrosis due to a bladder rhabdomyosarcoma. His blood creatinine, urea, and electrolyte levels remained normal during and after the episode, which resolved after the administration of i.v. frusemide. In this case, the rise in blood pressure was probably as much related to fluid load as to any direct nephrotoxic effect of IF.

Severe myelosuppression was not a problem, and in most patients IF infusion could be repeated after an interval of 14 days. There were no episodes of infection or haemorrhage.

Response

The overall response (CR + PR) was 30% (6/20). A CR was achieved in 3 patients, but in one of these the duration of remission may have been influenced by consolidation with radiotherapy. CRs were achieved in two patients with relapsed Wilms' tumours and one with relapsed Ewing's sarcoma. A boy with a pulmonary metastasis of Wilms' tumour, which had occurred during treatment that had included CP (600 mg/m^2), was radiologically disease-free after three courses of IF. A girl with Wilms' tumour, which had relapsed in the pleura 3 months after the completion of treatment and was resistant to subsequent four-drug therapy including CP (600 mg/m^2), had a complete radiological response after five courses of IF. The child with Ewing's sarcoma had relapsed at metastatic sites in bone 4 months after treatment that had included CP (1 g/m^2); she had rapid resolution of bone pain, and after ten courses of IF there was radiological evidence of bone healing.

Discussion

Despite intensive chemotherapy with CP, vincristine, doxorubicin and actinomycin, cure rates in children with advanced sarcomas, such as rhabdomyosarcoma, Ewing's sarcoma and Wilms' tumour (with unfavourable histology) [2] remain disappointing. This four-drug regimen has been used in various combinations for several years, and new agents are urgently required. IF has been widely used in adults, and as a first-line single agent in adults with non-small-cell carcinoma of the lung [6] and advanced soft-tissue sarcoma [12], it has yielded response rates of 24% and 38%, respectively. In combination with vincristine, a 25% CR rate has been described in a variety of childhood tumours [9]; a dose of 6 g/m^2 was split into two 1-h infusions on consecutive days and repeated at 3 weekly intervals. A combination of IF and cisplatin has produced CRs in two of four patients with relapsed Ewing's sarcoma [8]. IF has now been adopted by a number of European paediatric centres as first-line therapy for rhabdomyosarcoma, Ewing's sarcoma and neuroblastoma, in combination with vincristine and actinomycin (IVA) or doxorubicin (IVAD).

The present study was designed to assess the efficacy of IF in childhood tumours when given as a 24-h infusion [10]. After encountering neurotoxicity in one patient at 7 g/m^2 during a dose-escalation study, we subsequently used 5 g/m^2 in all patients. In adults with soft-tissue sarcomas, no further responses were seen when the dose was increased above 5 g/m^2, and myelosuppression was more marked [12]. In addition to neurotoxicity, nephrotoxicity may be a problem at higher doses.

Mesna was highly effective in preventing bladder toxicity. It has been suggested that a higher dose of mesna is necessary in children than in adults. In our experience, however, the incidence of bladder toxicity with CP in the dose range of 600–1,000 mg/m^2 is not high and may in fact be lower than in adults. The recommended dose of mesna is extremely variable, ranging from 50% to 200% of the dose of CP or IF [5]. Maintenance of adequate concentrations of mesna in the bladder for the duration of metabolic excretion appears to be a crucial factor; a dose of mesna equal to the IF dose and infused over 48 h gave ef-

fective protection. Oral administration of mesna has obvious attractions, and the parenteral preparation has been given mixed with palatable flavours. The comparative effectiveness of this route has not been documented in children, but oral administration has been successfully used in adults [5].

All of the children in this study were in relapse, 15 having initially responded to CP-containing regimens. The overall response rate with IF (30%) is therefore encouraging. The patients previously treated with CP had received doses ranging from 600 mg to 1.5 g/m^2 per course. The cytotoxic dose comparability of IF and CP in animal studies is approximately 2:1 [4]. The responsiveness in CP-resistant tumours could simply have been due to the higher relative dose of IF, but a genuine lack of cross-resistance seems likely in some cases [3].

There is a rapid decline in plasma IF concentrations after the completion of infusion, which is attributable to a composite of metabolism and excretion of the parent compound [1]. The $t_{½}$ in children appears to be shorter than that reported in adults, but this may be due to differences in assay method rather than to a genuine age-related difference.

Although IF has gained popularity and has even replaced CP in several regimens, a number of question remain unanswered. The superiority of the divided dose or infusion schedule over bolus administration has not been clearly demonstrated in a randomised study, and although in adult soft-tissue sarcomas response rates for IF appear to be superior to those for CP [3], this has not been similarly tested in paediatric tumours. In most current schedules, IF is given on an in-patient basis for hydration and parenteral mesna. The single-dose schedule of CP was ideal for out-patient treatment and therefore economical and convenient for the patient and family. The wider spectrum of toxicity must also be considered. Although neurotoxicity is less common in children than adults [11], nephrotoxicity, with tubular leak syndromes, is increasingly seen, particularly with high-dose IF (9 g/m^2). In the Wilms' tumour patient with only one functioning kidney this is of particular relevance.

In conclusion, these data demonstrate activity for IF in a variety of relapsed tumours (especially Wilms' tumour), some of which are clearly resistant to CP. Because of the inconvenience of IF administration and its extramedullary toxicity, further comparative studies are needed in children to clarify its superiority over CP in untreated patients and to determine the optimal method of administration with regard to efficacy and toxicity.

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