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# A phase II study of ifosfamide in children with recurrent solid tumours

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**Summary.** Twenty children with recurrent or unresponsive tumours (10 Wilms', 3 rhabdomyosarcoma, 4 Ewings's, 1 osteosarcoma, 1 hepatoblastoma, 1 hepatoma) and one untreated patient with renal carcinoma were given ifosfamide as a 24-h infusion (5 mg/m$^2$), with mesna as uroprotective. The number of courses ranged from 1 to 13 (median 3), and the interval between them was 2–3 weeks. Sixteen of these patients had previously received cyclophosphamide. Complete clinical responses were seen in 3 cases (2 Wilms' and 1 Ewing's) and lasted 5, 7, and 9 months. Partial responses were seen in 3 instances, mixed response or stable disease in 4, and progressive disease in 11. Treatment was well tolerated in most patients, with no cystitis or severe myelosuppression, but 2 children developed transient neurological symptoms and 1 became hypertensive. Nausea and vomiting were controlled by high-dose dexamethasone in most children.

Plasma ifosfamide levels were estimated by means of gas-liquid chromatography in 10 patients. Peak concentrations ranged from 38 to 125 μg/ml (median 80). The elimination half-life, at 2.5–5.2 h (median 3.2) was shorter than previously reported in adults.

Future studies should test the possibility that ifosfamide-containing combination chemotherapy may be more effective than the regimens, usually including cyclophosphamide, that are currently used as front-line treatment of embryonal and Ewing's sarcoma.

## Introduction

The oxazaphosphorine isophosphamide (iphosphamide, ifosfamide, IF) has been studied in a variety of tumours in adults [7]. The main advantages it has over its close structural analogue cyclophosphamide (CP) are first, an apparent activity in some CP resistant tumours and secondly, lower myelotoxicity allowing higher doses to be given. A 1-h infusion of IF (3 g/m$^2$) given on 2 consecutive days in combination with vincristine is effective in some childhood tumours [5], but there has been no previous study of the drug as a single agent in this age group.

This study was designed to the determine the effectiveness of IF in children with relapsed sarcomas and, in particular, to assess the degree of cross-resistance in those that had previously received CP. These tumours were chosen because of the reported activity of the drug in adults with sarcomas. Stuart-Harris et al. [11] reported a complete response rate of 15%, with 23% achieving 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 after divided doses a greater proportion of IF is metabolised to the active form than after a single dose [1].

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## Patients and methods

In all 21 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 stopping treatment. With the exception of 2 cases (13 and 15) all had received CP either as part of their initial therapy or in an unsuccessful attempt to achieve a response after disease recurrence (pts 3 and 19). Of the other 11 patients, 8 had received CP as initial therapy.

*Drug administration.* IF (Boehringer Ingelheim) 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 per 500 ml. IF was added to each 500-ml infusion bag at a dose of 1 g/bag. When given at a rate of 2.5 l/m$^2$ this provided the appropriate dose of IF plus hydration. 2-Mercaptoethane sodium sulphonate (mesna, Boehringer Ingelheim) was administered in the same infusion fluid to give a 100% equivalent dose to IF, but was infused over 48 h (Fig. 1). Because of the severe vomiting reported in adults after IF (uncontrolled by phenothiazines in 50% [10]) an aggressive antiemetic policy was adopted. An initial sedative cocktail of diazepam (5 mg/m$^2$), chlorpromazine

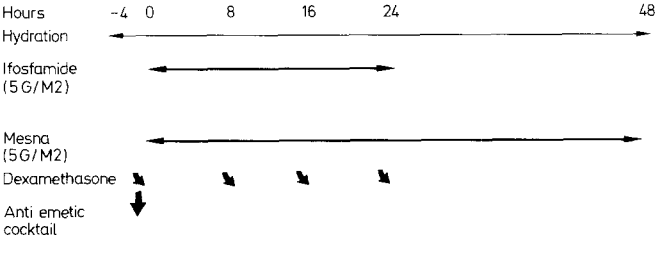


**Fig. 1.** Regimen for IF administration

**Table 1.** Details of patients, previous chemotherapy and response to ifosfamide

| Case | Age (years) | Sex | Diagnosis | Stage | Previous chemotherapy (reinduction) | Relapse sites | Timing of relapse | Number of IF doses | Mean interval between doses (days) | Response | Duration (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 12 | F | Ewing's | III | CVAAd (VP 16, Cisplat Ad) | Chest | On Treatment | 10 | 14 | PR | 4 |
| 2 | 4 | M | Rhabdomyosarcoma | III | VAC (VAC int) | Bladder | On treatment | 3 | 16 | NR (lungs PR) | |
| 3 | 2 | M | Wilms' | III[a] | VAAd (CVAAd) | Lungs | On treatment | 4 | 17 | PR | 2 |
| 4 | 3 | M | Wilms' | III[b] | CVAAd | Lungs | On treatment | 8 | 20 | CR | 5 |
| 5 | 12 | M | Wilms' | III[b] | CVAAd (CVAAd) | Abdomen | 3 Mo. off treatment | 2 | 21 | PR | 2 |
| 6 | 7 | F | Rhabdomyosarcoma | III | VAC int | Lungs | On treatment | 2 | 21 | NR (PD) | |
| 7 | 11 | F | Ewing's | III | CVAAd | Femur & spine | 4 Mo. off treatment | 10 | 14 | CR | 9 |
| 8 | 3 | M | Hepatoblastoma | III | CVAAd, Cisplat, IF | Liver | On treatment | 3 | 21 | NR (SD) | |
| 9 | 9 | M | Wilms' | IV[b] | CVAAd | No response | – | 1 | – | NR (PD) | |
| 10 | 5 | M | Wilms' | IV[a] | CVAAd | Lungs & abdomen | On treatment | 2 | 14 | NR (PD) | |
| 11 | 3 | M | Rhabdomyosarcoma | III | VAC int | Lungs, nasopharynx | On treatment | 3 | 14 | NR (lungs PR) | |
| 12 | 8 | M | Wilms' | III[a] | CVAAd | Liver | On treatment | 3 | 14 | NR (PD) | |
| 13 | 8 | M | Wilms' | III[a] | VAAd | Lungs | 1 Mo. off treatment | 4 | 16 | NR (MR) | |
| 14 | 14 | M | Osteosarcoma | III | MTX, Cisplat, Ad | Lungs | 16 Mo. off treatment | 4 | 14 | NR (PD) | |
| 15 | 6 | F | Wilms' | I (IV)[a] | VA (VAAd) | Lungs | On treatment | 6 | 14 | NR (PD) | |
| 16 | 12 | M | Renal carcinoma | IV | – | – | – | 2 | – | NR (PD) | |
| 17 | 3 | F | Ewing's | III | CVAAd | Tibia | 1 Mo. off treatment | 3 | 14 | NR (PD) | |
| 18 | 12 | M | Hepatoma | IV | Cisplat, Ad | Initial PR only | | 3 | 28 | NR (PD) | |
| 19 | 3 | F | Wilms' | I (IV)[a] | V (CVAAd) | Lungs | 3 Mo. off treatment | 13 | 14 | CR | 7 + |
| 20 | 13 | M | Ewing's | II | CVAAd | Lungs | On treatment | 5 | 14 | NR (PD) | |
| 21 | 4 | F | Wilms' | IV | CVAAd | No response | – | 1 | – | NR (PD) | |

[a] Favourable histology [b] Unfavourable histology [2]

Chemotherapy details:

C, cyclophosphamide; V, vincristine; A, actinomycin; Ad, adriamycin; Cisplat, cisplatinum; MTX, methotrexate; VAC: V, 1.5 mg/m$^2$; A, 1 mg/m$^2$; C, 500 mg/m$^2$, every 21 days; VAC int: V, 1.5 mg/m$^2$ days 1&5; A, 0.5 mg/m$^2$ days 1, 3&5; C, 500 mg/m$^2$ days 1, 3&5, every 21 days; CVAAd (Wilms'): V, 1.5 mg m$^2$; C, 600 mg/m$^2$, and alternating; A, 1.5 mg/m$^2$ or Ad 40 mg/m$^2$, every 21 days; CAAd (Ewing's): V, 1.5 mg/m$^2$, C, 1 g/m$^2$; Ad 40 mg/m$^2$ till 400 mg/m$^2$ then A, 1.5 mg/m$^2$, every 21 days

(12.5 mg/m$^2$), and dexamethasone (10 mg/m$^2$) was given IV 30 min before IF. Dexamethasone (10 mg/m$^2$) was repeated 8-hourly 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 $\geqslant 1.0 \times 10^9$/l and platelets $> 100 \times 10^9$/l prior to each course.

*Drug concentrations.* Blood was taken at varying intervals during the 24-h period following IF infusion. The number of samples ranged from three to seven, and in most cases samples were taken from the infusion site after thorough flushing with saline. Repeated venepunctures were not considered justified. In 6 patients samples were also taken during the IF infusion.

IF concentrations were estimated by means of gas liquid chromatography [12]. To each 0.2 ml plasma were added: 10 µl 500 µg/ml trifosphamide (internal standard), 0.1 ml 0.1 NaOH, 0.5 ml ethylacetate. The mixture was vortexed for 10 s and centrifuged for 30 s at 10 000 *g* (Eppendorf Microfuge). Then 1–3 µl of the ethylacetate layer was injected into the chromatogram. A standard curve was prepared by 'spiking' 0.2-ml aliquots of blank plasma with 5–80 µg/l IF. Samples were passed through a Shimadzu GC9A chromatogram with an FDT detector and fitted with a 5% SE30 column 1 m × 3 mm. The carrier gas was nitrogen flowing at 50 ml/min with a column temperature at 230 °C and an injection temperature of 240 °C.

*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, CT scan; Bone – X-ray, isotope scan; Abdomen and pelvis – ultrasound, CT scan.

Blood counts were performed 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 (5 and 7) local irradiation was given to the original site(s) of relapse.

Complete clinical response (CR) was defined as no detectable disease for at least 4 weeks, partial response (PR) was a reduction of at least 50% in maximum tumour diameter in two dimensions on X-ray or ultrasound, for at least 4 weeks. No response (NR) was recorded in the case of patients in whom there was 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 liberal fluids were given IV during IF infusion. Macroscopic haematuria was not seen in any patient during the study. One child (no. 8) had previously developed severe haemorrhagic cystitis when given IF without mesna at another centre, but this did not occur during the study with concurrent mesna.

Acute neurological complications were seen in two patients. Patient 1 developed generalised convulsions 7 h after starting IF; they lasted 5 min and responded to IV 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 which 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 patient 5 during IF infusion. This was not related in time to the administration of chlorpromazine and resolved with IV diazepam. There was no recurrence with further IF therapy.

Transient hypertension occurred shortly after commencing IF in patient 2, a child with bilateral hydronephrosis due to a bladder rhabdomyosarcoma. His blood creatinine, urea, and electrolytes remained normal during and after the episode, which resolved after administration of IV frusemide. It is probable that in this case the rise in blood pressure was 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 could be repeated after an interval of 14 days. There were no episodes of infection or haemorrhage.

### *Response*

The overall response (CR + PR) was 29% (6/21). CR was achieved in three patients, but in one of these (no. 7) the duration of remission may have been influenced by consolidation with radiotherapy.

Case 4, a 3-year-old boy with Wilms' tumour, developed a single pulmonary metastasis during chemotherapy including CP (600 mg/m$^2$ 3-weekly). The lesion was no longer apparent on X-ray after three courses of IF, and he remained disease-free during a further six courses. Prior to consolidation with lung irradiation, multiple pulmonary deposits developed.

Case 7, and 11-year-old girl with Ewing's sarcoma, developed metastatic disease in the femur and T4 vertebral body 4 months after completing therapy including CP (1 g/m$^2$ 3-weekly). During IF treatment there was complete resolution of bone pain, and X-rays and bone scan showed changes consistent with early healing; after ten courses of IF, radiotherapy to both sites was given. She remained disease-free with gradual normalisation of bone scan changes, but after 9 months multiple bony deposits recurred.

Case 19 is a 4-year-old girl with Wilms' tumour, who relapsed 3 months after discontinuation of treatment with vincristine alone for stage 1 disease. Despite four-drug

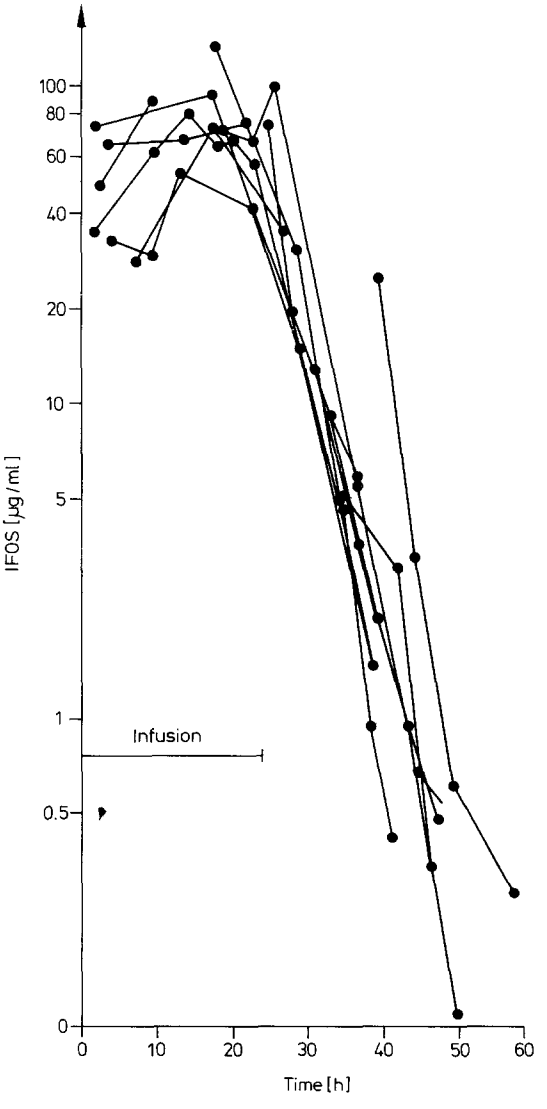


**Fig. 2.** Plasma IF concentrations during and following infusion

**Table 2.** Analysis of plasma IF concentrations taken during and following a 24 h infusion

| Case | Peak concentration (μg/ml) | Elimination $t_{1/2}$ (h) |
|---|---|---|
| 1 | 85.8 ; * | 4.2 ; 3.4 |
| 2 | 52.2 | 3.2 |
| 3 | 71.1 ; 89 | 3.2 ; * |
| 6 | 37.9 ; 71.5 | 2.9 ; 3.0 |
| 7 | 85.9 | * |
| 8 | 80.6 | 3.5 |
| 9 | 78.5 | * |
| 10 | 69.4 | 2.5 |
| 11 | 125 | 3.0 |
| 14 | 90.5 | 5.2 |

In three patients samples were taken during two separate courses
* Sample timing not appropriate

therapy (Table 1) and local irradiation, extensive (biopsy-proven) pleural disease was found at L thoracotomy undertaken to remove a large single metastasis. The latter was resected and 7 months later, after 13 courses of IF, she remains clinically and radiologically disease-free.

*Ifosfamide pharmacokinetics*

Plasma IF profiles in ten patients are illustrated in Fig. 2. Peak values were determined in the six cases from whom samples were taken during or at the end of the 24-h infusion. Where samples were taken during the 24-h period after completion of IF infusion the elimination half-life ($t_{1/2}$) was calculated with reference to log linear regression analysis (Table 2).

In one child urinary concentrations of IF were estimated on two separate occasions. Recovery of IF was 26% and 32% of the infused dose over the first 24 h and 44% over 48 h.

## Discussion

Despite intensive chemotherapy with CP, vincristine, adriamycin, and actinomycin cure rates in children with advanced sarcomas, such as rhabdomyosarcoma, Ewing's sarcoma and Wilms' tumour (patients with unfavourable histology in particular) [2], remain disappointing. This four-drug regimen, in various combinations, has been in use for several years, and new agents are urgently required. Although IF has been widely used in adults, its use has only recently been considered in children. As a first-line single agent in adults with non-small-cell carcinoma of the lung [6] and advanced soft tissue sarcoma [11], 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 [5], including Wilms' (1 CR/2), Ewing's (1 PR/4) and rhabdomyosarcoma (2 CR and 4 PR/16); 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 cisplatinum produced CR in two of four patients with relapsed Ewing's sarcoma [9]. IF has recently been adopted by a number of European paediatric centres as first-line therapy for rhabdomyosarcoma in combination with vincristine and actinomycin (IVA).

The present study was designed to assess the efficacy of IF in childhood tumours when given as a 24-h infusion. 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 [11]. In addition to neurotoxicity, nephrotoxicity may be a problem at higher doses.

Mesna was highly effective in preventing bladder toxicity, as clearly illustrated by the child who developed severe cystitis at another centre prior to entering this study. This uroprotection has previously been demonstrated to be more effective and safer than bladder washout [6], and superior to forced diuresis [8]. It has been suggested than 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 600–1000 mg/m$^2$ does not appear to be particularly high, and may in fact be less than in adults. The recommended dose of mesna is very variable, ranging from 50% to 200% of the dose of CP or IF [4]. Maintenance of adequate concentrations of mesna in the bladder for the duration of metabolite excretion appears to be a crucial factor; a dose of mesna equal to the IF dose and infused over 48 h gave effective protection. Oral administration of mesna has obvious attractions and we have recently used the parenteral preparation 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 [4].

All but 1 of the children in this study were in relapse, 15 having initially responded to CP-containing regimens. The overall response rate with IF (29%) is therefore encouraging. The patients already 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 [3]. The responsiveness in CP-resistant tumours could have been simply due to the higher relative dose of IF, but it seems likely that there is a genuine lack of cross-resistance in some cases [7].

The rapid decline in plasma IF concentrations after completion of the infusion is a composite of metabolism and excretion of the parent compound [1]. Although the $t_{1/2}$ is considerably shorter than that reported in adults this may be due to differences in assay method rather than a genuine age-related difference. The rather low urinary recovery in the one patient studied is similar to that described in adults after a split-dose regimen and is consistent with a high degree of drug metabolism [1].

Resistance to the four 'best' agents often develops, and unfortunately there are few promising new drugs for therapy of paediatric sarcomas. Cisplatinum and the epidophyllotoxins have some activity, but response rates are generally lower than 15% in patients with resistant or recurrent disease. 'Megatherapy' approaches, e.g., high-dose melphalan and total-body irradiation, seem worthy of further investigation in children, but the toxicity of this strategy is inevitably high, and better 'standard dose' agents are needed. The response rate observed in children with highly resistant disease, along with its acceptable toxicity, suggests that IF may be useful in combination therapy, and possibly superior to CP.

A number of details concerning the administration of IF require standardisation. It is not known, for example,

whether prolonged infusion is superior to short infusion or whether there is any advantage in a split schedule over several days. Ultimately, when these points have been clarified, controlled clinical studies – possibly with a crossover design – will be required to determine whether IF or CP is the superior agent in the management of childhood sarcomas.

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