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Ifosfamide/etoposide alternating with high-dose methotrexate: evaluation of a chemotherapy regimen for poor-risk osteosarcoma

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Summary Fifteen patients with relapsed osteosarcoma were treated with an intensive combination chemotherapy schedule. Ifosfamide 2.5 g m^{-2} daily and etoposide 150 mg m^{-2} daily coincidentally for 3 days and high-dose methotrexate 8 g m^{-2} (with folinic acid rescue) on days 10–14 in a planned 21-day cycle. Feasibility, toxicity and response to this alternative combination for the treatment of relapsed osteosarcoma was assessed. There were 98 evaluable cycles for toxicity and tolerability. The majority of cycles were well tolerated. Haematological toxicity of grade 3/4 (common toxicity criteria) was seen in all courses. Renal tubular loss of electrolytes, particularly magnesium, occurred in 71% of cycles. Thirteen per cent of cycles were repeated within 21 days and 61% within 28 days. In the thirteen patients evaluable for response, a partial response rate of 31% was seen after two cycles. However, patients with stable disease continued on therapy, and an overall consequent response rate of 62% was observed. Four patients were alive with no evidence of disease at 8–74 months. Three are alive with disease (at 8–19 months). There were six deaths, all disease related. This regimen exhibits an encouraging response rate in a group of children with poor prognosis disease, with a tolerable toxicity profile.

Keywords: relapsed osteosarcoma; ifosfamide; etoposide; high-dose methotrexate

The development of treatment for patients with non-metastatic osteosarcoma limb primaries over the past 20 years has led to impressive improvements in survival with reported long-term relapse-free survival rates of 55–76% (Link et al, 1990; Bramwell et al, 1992; Meyers et al, 1992; Bacci et al, 1993). There are, however, recognized groups of patients who continue to have a poor outcome. These include patients with unresectable primary disease; those with metastatic disease at presentation; and those who relapse either locally or with distant metastases. Long-term disease-free survival for the first two groups is approximately 0–20% (Schaller et al, 1982; Goorin et al, 1985; Parham et al, 1985; Cassano et al, 1991; Bacci et al, 1992), and 5-year survival after metastatic relapse has been reported as ranging from 17% to 50% with metastatectomy and/or chemotherapy (Goorin et al, 1984; Huth and Eilber, 1989; Solheim et al, 1992; Tabone et al, 1994; Saeter et al, 1995).

Single-agent and multiagent chemotherapeutic trials have demonstrated the efficacy of a number of agents in the treatment of osteosarcoma – including doxorubicin (Cores et al, 1972), cisplatin (Nitschke et al, 1978), methotrexate (Jaffe et al, 1973) and ifosfamide (Marti et al, 1985). More recent phase II studies reveal roles for other agents in combination, most notably etoposide (Kung et al, 1985; Grana et al, 1989).

Since 1983, first-line therapy in the UK for children with non-metastatic limb primaries has been based on cisplatin/doxorubicin combinations within a series of Medical Research Council trials (Bramwell et al, 1992; Ornadel et al, 1994). In an attempt to provide an intensive chemotherapeutic approach for those failing conventional first line therapy, we have developed a schedule whereby other active agents, ifosfamide, etoposide and high-dose methotrexate, could be incorporated in an intensive manner. Ifosfamide and etoposide combinations have been evaluated previously in patients with recurrent paediatric sarcomas (Miser et al, 1987; Goorin et al, 1994; Tabone et al, 1994). High-dose methotrexate has evidence of activity both as a single agent and within multiple agent trials (Grem et al, 1988; Rosen, 1993). Of importance, high-dose methotrexate with folinic acid rescue can be given to neutropenic patients, thereby allowing another agent to be delivered during the myelosuppressive phase of the chemotherapy cycle and thus providing a degree of treatment intensification. This strategy has been successfully used in the intensification of treatment of non-Hodgkin's lymphoma (Muller-Weihrich et al, 1985).

This report describes the feasibility, toxicity and early response data of this combination.

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METHODS AND PATIENTS

Treatment

The protocol was planned to deliver ifosfamide 2.5 g m^{-2} over 24 h with mesna uroprotection at the same dose on 3 consecutive days. Coincident infusions of etoposide 150 mg m^{-2} daily for 3 days were administered over 4 h. High-dose methotrexate (8 g m^{-2} according to age) was given over 24 h on days 10–14 of a planned 21-day cycle (10% of dose in the first hour and 90% of dose infused over next 23 h) with appropriate hydration. Folinic acid

Table 1 Outcome of treatment with ifosfamide/etoposide alternating with high-dose methotrexate (IEM) related to primary treatment details in relapsed, evaluable patients

Patient no.	First-line therapy	Age at dx relapse	Months from primary dx	Site of relapse	Assessment after two cycles	Best outcome of IEM	No. of courses at best assessment	Surgery	Outcome after surgery	Max no. of courses	Current status	Survival in months from relapse
1	Cisplatin/doxorubicin	15	9	Lung	SD	PR	11	Bilateral thoracotomies	CR	11	NED	12
2	Cisplatin/doxorubicin	14	13	Lung	SD	CR	10	–	–	12	NED	74
3	Cisplatin/doxorubicin	12	19	Lung	PR	PR	2	Thoracotomy	CR	3	DOD	30
4	Cisplatin/doxorubicin	14	10	Lung	PR	PR	6	Bilateral thoracotomies	CR	7	AWD	8
5	Cisplatin/doxorubicin	15	19	Lung	SD	SD	4	Bilateral thoracotomies	CR	5	NED	8
6	Cisplatin/doxorubicin	15	16	Lung	PR	PR	2	Thoracotomy	CR	6	NED	8
7	Cisplatin/doxorubicin	10	8	Lung	SD	SD	4	–	–	6	DOD	11
8	Cisplatin/doxorubicin	16	11	Lung	PR	PR	2	–	–	6	DOD	13
9	Cisplatin/doxorubicin	8	6	Lung	[a]	PD	3	–	–	3	DOD	7
10	Cisplatin/doxorubicin	15	11	Lung, bone	SD[a]	PR	6	Bilateral thoracotomies	PR	11	AWD	19
11	Cisplatin/doxorubicin	15	12	Lung, bone, CNS	SD	PR	6	–	–	11	DOD	18
12	EOI multidrug	12	26	Bone	SD	SD	3	Above knee amputation	–	3	DOD	8
13	Cisplatin/doxorubicin	16	11	Local	–	SD	1.5	–	–	2	AWD	9

dx, diagnosis; NED, no evidence of disease radiologically; AWD, alive with disease; DOD, dead of disease. [a]Assessment after three courses to suit patient circumstances.

rescue was started 36 h after the start of the methotrexate infusion at a dose of 15 mg m^{-2} every 3 h from hour 36 to hour 48, and then 15 mg m^{-2} 6 hourly until the methotrexate level was below 1.0×10^{-7} M with appropriate adjustments according to methotrexate level monitoring (minimum ten doses.) Second and subsequent cycle scheduling were dependent on regain of haematological function, namely neutrophils > 1.0×10^{-9} and platelets > 100×10^{-9}. Dose reduction was driven by cytopenia (grade 4) causing major sepsis or delays to haematological recovery requiring treatment delay of greater than 1 week.

For clarification of description, one course of ifosfamide/etoposide plus one course of high-dose methotrexate constitutes one cycle of chemotherapy.

Tumour surgery was scheduled on an individual basis when response to chemotherapy appeared maximal.

Patients

Sequential patients treated with the new combination schedule had relapsed either with recurrent local disease or distant metastatic disease. Appropriate local Ethical Committee approval was acquired in each of the participating centres.

Assessment at entry

Disease assessment at entry included physical examination with measurements of the diameter of known disease when appropriate. Imaging studies included plain radiographs of the primary lesion, and computerized tomography (CT) and/or MRI scans of the primary, in all those who had not previously had amputation of the primary site. All had CT scans of the chest and radionuclide bone scans.

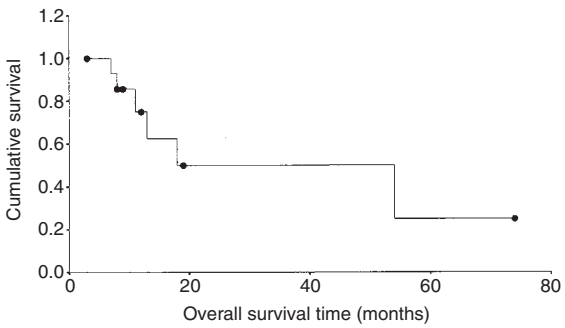

Figure 1 Survival from commencement of combination regimen

Laboratory investigations included evaluation of the full blood count (FBC), serum electrolytes, urea and creatinine, liver function tests, calcium, magnesium and phosphate. The glomerular filtration rate was also assessed using [^{99m}Tc] DTPA (diethylene triamine penta-acetic acid).

Assessment of response

Response of pulmonary metastases was assessed radiologically by CT scan and/or plain radiographs. Isotope bone scans were also performed to monitor bone metastases. Assessments were usually performed after two and six complete cycles. Definitions of response were as follows: complete response (CR), radiological disappearance of all evidence of tumour; partial response (PR), greater than or equal to 50% reduction radiologically in the tumour diameters at all sites; stable disease (SD), < 25% decrease in size

of one or more lesions; and progressive disease (PD), progression of one or more of the tumours by greater than or equal to 25% of the diameter, or appearance of disease at a new site.

Toxicity

Toxicity was assessed using the CTC (common toxicity criteria) (Franklin et al, 1994), with grade 3 indicating severe and grade 4 indicating unacceptable or life-threatening toxicity (excluding myelosuppression).

RESULTS

Patient characteristics

Thirteen patients with relapsed osteosarcoma were treated with the regimen and were evaluable for response. A further two patients had had tumour surgery at presentation and, consequently, were additionally evaluable for toxicity assessment.

There were seven males and eight females aged between 6 and 16 years (median 15 years). All fifteen patients had recurrent disease.

In those patients diagnosed with measurable relapsed disease, the time interval from initial presentation to diagnosis of recurrent disease ranged from 6 to 26 months. Lung metastases alone accounted for disease in nine patients. Three patients had bone secondaries, one in isolation, one in combination with both CNS and lung disease and the third patient had a combination of bone and lung recurrence. One child had a recurrence of his axial primary disease.

Twelve of these patients had been pretreated on cisplatin/doxorubicin schedules and one patient had received a multidrug regimen (methotrexate–vincristine–doxorubicin plus doxorubicin–cisplatin plus bleomycin–cyclophosphamide–dactinomycin) according to EOI guidelines (Souhami et al, 1997).

Toxicity

There were 98 evaluable cycles, the majority of which were well tolerated. Myelosuppression of grade 3 or 4 was recorded in 80% of cycles and febrile neutropenic episodes requiring hospital admission occurred in 45% of cycles. Only three cycles caused severe sepsis (grade 4) necessitating subsequent dose reduction. Three patients required dose reduction of ifosfamide ± etoposide because of unacceptable haematological toxicity.

Significant renal toxicity was not common. Creatinine levels of greater than three times normal or a measured glomerular filtration rate (GFR) of < 40 ml min^{-1} 1.73 m^{-2} were seen in only four cycles and were reversible. Renal tubular loss of electrolytes, in particular magnesium, was common. Magnesium levels of < 0.8 mmol l^{-1} (normal range 0.65–1.05 mmol l^{-1}) were recorded in 61% of cycles, but were correctable with oral supplementation. However, late-onset glomerular dysfunction (Prasad et al, 1996) was beyond the scope of this study in view of the limited follow-up interval.

Hepatotoxicity was limited to transient elevations of transaminases. Mucositis occurred in both the upper and lower GI tract in some patients, but was generally mild and short lived.

The consequent mean in-patient stay was 11.1 days per cycle (range 5–27 days). This figure includes both administration of chemotherapy and inpatient admissions with febrile neutropenic episodes.

An assessment of the tolerability of the first four cycles of treatment in terms of the ability to proceed on time to subsequent courses is conveyed by the finding that 13% of the first four cycles were administered within the prescribed 21 days, 33% within 25 days and 61% were given within 28 days.

Responses

Thirteen patients with relapsed disease were evaluable for response (Table 1). The response rate after two cycles of chemotherapy was 31%. Patients with responsive or stable disease continued on therapy, achieving a best outcome after a further number of courses and thus giving an overall response rate of 62% (95% confidence interval 32–86%).

Eight out of 11 patients with pulmonary metastases achieved PR after 2–10 cycles (patient numbers 1–4, 6, 8, 11, 15). Two patients remained with stable disease (patients 5 and 7) and one had progressive disease (patient 9). Out of the group with partial response/stable disease, five were converted to CR with thoracotomy.

In the group with bony metastases, two patients out of three had a PR after 3–6 cycles. Both of these patients had combined lung and bone recurrence, PR was essentially judged on the basis of serial chest CT scans, both patients however demonstrated concomitant reductions in isotope bone scan activity. One patient had stable disease after two cycles, but refused further treatment because of side-effects. One child's disease progressed after three cycles of treatment.

Within the group of patients with relapsed disease, four patients are alive with no evidence of disease 8–74 months after entry into the study. Three patients are alive with radiological evidence of disease 8–19 months later. Six patients have died from their disease 7–30 months later. There were no toxic deaths.

Figure 1 details Kaplan–Meier analyses of overall survival from commencement of the chemotherapy regimen in evaluable patients. The median survival time was 18 months from commencement of the regimen, with 95% confidence intervals ranging from 0 to 54 months.

DISCUSSION

The outlook for children and young adults with recurrence of osteosarcoma or primary metastatic disease remains poor. When the lung is the only site of disease recurrence, a surgical approach in which all resectable deposits are removed has been advocated as potentially curative, with a reported 5-year survival rate from first thoracotomy of 23–50% (Schaller et al, 1982; Meyer et al, 1987; Belli et al, 1989; Snyder et al, 1991; Skinner et al, 1992; Ward et al, 1994; Saeter et al, 1995; Han et al, 1996). Development of bony metastases carries a worse prognosis with a 0% 4-year survival rate (Ward et al, 1994).

The place of chemotherapy in the management of recurrent or advanced osteosarcoma is not of proven benefit, especially in those already heavily pretreated (Han et al, 1981; Meyer et al, 1987; Cassano et al, 1991). However, a number of regimens have been reported to have been used in this situation (Morgan et al, 1984; Solheim et al, 1992; Ward et al, 1994); including ifosfamide and etoposide in combination (Miser et al, 1987; Goorin et al, 1994; Tabone et al, 1994; Gentet et al, 1997).

Ifosfamide is considered by some authors to be one of the most effective treatments in osteosarcoma, with response rates recorded in the region of 67% (Chawla et al, 1990). Other phase II studies

confirm its efficacy as a single agent and in combination schedules (Marti et al, 1985; Harris et al, 1995). Etoposide has been used in a number of phase II trials in children with recurrent malignant solid tumours, and has shown a high proportion of complete and partial responses (Chard, 1979; O'Dwyer et al, 1985); however, single-agent usage in osteosarcoma has been disappointing. Support for its efficacy in combination with ifosfamide is provided by the results of the Rizzoli institute's second neoadjuvant study in which it was used as salvage therapy (Bacci et al, 1993), and the results of the Children's Cancer Group (Miser et al, 1987). The tolerability of this combination is aided by the fact that their non-haemopoiotic toxicities do not overlap.

There is a considerable body of evidence supporting the role of high-dose methotrexate in the treatment of osteosarcoma since its first use in the 1970s, both as a single agent and as part of multi-agent trials (Grem et al, 1988; Rosen, 1993). The advantages of adding high-dose methotrexate to an ifosfamide/etoposide combination include that, individually, it has an impressive single-agent profile; myelotoxic schedules can be resumed after only 1 week of administering HDMTX; and, properly administered, there is minimal toxicity. In addition, especially latterly, current MRC protocols for first-line treatment of osteosarcoma do not include high-dose methotrexate and therefore relapsing patients have not had prior experience of this drug.

The toxicity profile overall was tolerable. There was no treatment-related mortality. The renal tubular electrolyte loss related to ifosfamide chemotherapy required close monitoring and oral supplementation, but no patient required dose reduction because of renal complications. Haematological toxicity resulted in febrile neutropenia events that required inpatient stay and occasional dose-reduction consequently. But the majority of courses were well tolerated.

The results of this retrospective analysis suggest an encouraging response rate of 62%, in a group of children with poor prognosis disease. We have observed a delayed response rate to this regimen in patients who had stable disease at reassessment after two cycles. Patients with SD had radiological PR or CR by 6–10 cycles, indicating that classic phase 2 methodology of assessment after two cycles may not always be adequate. The number of patients evaluated are obviously too few to be considered statistically significant and the period of follow-up is limited. However, the regimen deserves consideration for an appropriate multi-institutional evaluation.

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