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Pilot Study of a Rapid Etoposide-cisplatin Regimen in Paediatric Soft Tissue Sarcomas

Marianne B. Phillips and C. Ross Pinkerton

10 patients with refractory or relapsed soft tissue sarcoma were treated with weekly etoposide (150 mg/m^2 on days 1, 2 and 3) and cisplatin (60 mg/m^2 on day 2). Toxicity was mainly myelosuppression which resulted in deviation from planned weekly chemotherapy scheduling. With this rapid dose-delivery schedule the tolerated median dose intensities were 161 mg/m^2 per week for etoposide and 49 mg/m^2 per week for cisplatin. In 9 evaluable patients there were 7 responses, 2 complete and 5 partial, giving a response rate of 78% (confidence interval 51–100%). The combination of etoposide and cisplatin in this schedule produced a higher response rate than reported with previous schedules and is worthy of further evaluation.
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INTRODUCTION

THE SURVIVAL of children with soft tissue sarcoma has improved over the past decade with 3 year event free survival (excluding stage IV disease) of 53%, overall survival 69%, using combined chemotherapy, radiotherapy and surgery in the SIOP MMT 1984 trials [1], and 70% 5 year survival for this group in the IRS II study [2].

Refractory disease (approximately 10% of cases) and local or metastatic relapse remain problems and further efforts at improving chemotherapy are warranted. Potential new agents are limited and it is therefore important to optimise the scheduling of existing drugs.

Single agent etoposide has achieved response rates of 20% in intensively pretreated children with rhabdomyosarcoma [3].

Cisplatin has been shown to have 15% response rate as a single agent in refractory rhabdomyosarcoma and undifferentiated soft tissue sarcoma in phase II trials [4].

Etoposide inhibits DNA synthesis with little effect on RNA and protein synthesis, whereas cisplatin also causes inhibition of RNA and protein synthesis [3, 4]. This may explain the synergy which exists experimentally and clinically between these two agents. Additionally repair of the DNA damage induced by cisplatin cross linking may be inhibited by the anti-topoisomerase II effect of etoposide [5]. A previous phase II trial of etoposide and cisplatin achieved a response rate of 33% in relapsed paediatric rhabdomyosarcoma [6], though another study achieved only a 12.5% response and the efficacy of such a drug combination was questioned [7]. A heterogeneous pretreated group of patients receiving higher dose intensities achieved a response rate of 62% [8], and subsequently the incorporation of both agents, with differing schedules, into first-line therapy for children with soft tissue sarcoma showed encouraging response rates of 80, 87 and 100% [8–10], though not without appreciable toxicity.

Dose escalation of cisplatin to 200 mg/m^2 is possible using a 5 day schedule [11] but the toxicity is probably less if a similar total dose is administered weekly over 2 weeks [12, 13]. The least effective way to give etoposide in small cell lung cancer is as a single dose [14, 15]. The higher response rates achieved with weekly administration of the same dose divided over 3 days may be obtainable for other tumours. This reasoning provided

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the rationale for the weekly schedule in the present regimen which, in addition to allowing an increase in dose intensity, produces a rapid delivery of drugs with a minimum period during which tumour cells are not exposed to treatment. The latter philosophy has recently been applied to malignant germ cell tumours [16], non-Hodgkin lymphoma [17] and neuroblastoma [18].

PATIENTS AND METHODS

10 patients under 15 years of age with histologically proven soft tissue sarcoma were entered into the study. There were 7 girls and 3 boys with median age at initial diagnosis of 2.75 years (range 0.75–12.25 years) and a median age of treatment with regimen under evaluation of 3.8 years (range 0.9–14.25 years). There were 7 cases of histologically proven rhabdomyosarcoma (6 embryonal and 1 mixed alveolar/embryonal), 2 of undifferentiated soft tissue sarcoma and 1 of soft tissue Ewing's sarcoma. Assessment at diagnosis showed two stage II; four stage III and four stage IV tumours.

Patients treated with etoposide/cisplatin had either presented with widely metastatic disease; had refractory or progressive disease on first line chemotherapy or had relapsed (4–14 months) after completion of first-line treatment modalities. All patients had been previously treated prior to receiving etoposide/cisplatin regimen (Table 1). One child with stage IV disease with an extensive nasopharyngeal primary not amenable to surgery, felt to be at high risk of relapse, received etoposide/cisplatin as consolidation of a complete response (CR) prior to megatherapy with autologous bone marrow rescue and was evaluable for toxicity alone.

Pretreatment investigations included clinical evaluation, radiological assessment of measurable disease, bone marrow/trephine evaluation and assessment of renal function, in addition to baseline haematological and biochemical status. Measurable disease, clinical and/or radiological, was reassessed at 3–6 week intervals and reassessment of renal function, with monitoring of haematological/biochemical variables, was repeated at intervals throughout.

Informed verbal consent regarding the novel drug scheduling was obtained from the parents of all the children entered into the study.

Treatment

Etoposide at a dose of 100 mg/m^2 was infused intravenously over 1 h on days 1, 2 and 3. Cisplatin, given as a bolus intravenously at 60 mg/m^2 on day 2, was administered with intravenous hydration at 3 l/m^2/24 h of alternating N saline plus 20 mmol KCl/l and 5% dextrose + 20 mmol KCl/l for 24 h pre- and post-cisplatin bolus. To ensure adequate urine output 100 ml/m^2 10% mannitol was given intravenously, over 30 min, 30 min prior to cisplatin and 6 hourly for 24 h thereafter. The drug combination in this schedule was repeated weekly as tolerated.

Evaluation of response

Antitumour responses were defined as: (a) complete response (CR)—the disappearance of all clinically and radiologically evaluable disease; (b) partial response (PR)—at least 50% reduction in measurable lesions; (c) no response (NR)—any response of less than 50% reduction in disease; (d) progressive disease (PD)—progressive disease on treatment.

RESULTS

Responses

Of the 10 children entered on study, 9 had evaluable disease prior to etoposide/cisplatin. 1 patient with stage IV embryonal rhabdomyosarcoma was in clinical and radiological CR prior to the regimen and remained so until disseminated relapse after 9 months off treatment. She was evaluable only for toxicity. Among the other 9 patients there were 2 CR and 5 PR with a response rate of 78% [95% confidence interval (CI) = 51–100%]. 1 patient with stage III embryonal rhabdomyosarcoma had no measurable response to two courses of treatment and 1 case with stage IV embryonal rhabdomyosarcoma progressed and died after only one course. Both children had failed to respond to previous vincristine, doxorubicin, cyclophosphamide (VAC) chemotherapy. All responses were in cases who had previously achieved CR or PR to prior treatment, except 1 case (no. 5) who had disseminated Ewing's sarcoma, failed treatment at presentation with daunorubicin and vincristine (thought to have had non-Hodgkin lymphoma), and had a PR to the etoposide/cisplatin regimen (Table 1).

The CRs were obtained in one case with locally relapsed rhabdomyosarcoma and in 1 patient with metastatic undifferentiated soft tissue sarcoma. The PRs were achieved in 3 cases of relapsed rhabdomyosarcoma, two local, one nodal; one locally relapsed undifferentiated soft tissue sarcoma and one disseminated Ewing's sarcoma (Table 1).

The durations of response in the 2 patients with CR were 5 and 15 months, both cases subsequently relapsed and died. In the 5 patients with PR, 3 children relapsed at 3, 5 and 5 months and have since died; 1 remains well, off treatment, in PR with stable disease at 20 months and one is well, disease-free (rendered CR with radiotherapy) at 22 months.

Compliance

A total of 39 courses of the regimen were given to the 10 study patients. Weekly scheduling of the drugs was adhered to provided the neutrophil count was $>0.5 \times 10^9$/l and platelet count $>50 \times 10^9$/l. As expected, myelosuppression proved to be the main reason for schedule violation or variability. 1 patient who progressed on treatment received one course only; 1 patient with NR received two courses; 1 patient received only two courses due to severe myelosuppression; 7 patients completed three courses and 3 patients completed six courses (Table 1).

The median drug intensities achieved in patients who received at least three courses of the drug combination was 23 mg/m^2/day (range 15.8–56.3 mg/m^2/day) for etoposide and 7 mg/m^2/day (range 3.3–13.8 mg/m^2/day) for cisplatin, i.e. 43 and 54% of planned intensities of 53 and 13 mg/m^2/day, respectively. Both drugs were scheduled at, and in most cases achieved, higher intensities than in previous phase II trials with the same drug combinations where intensity deliveries were 23 mg/m^2/day etoposide with 6.4 mg/m^2/day cisplatin [6] or 21 mg/m^2/day etoposide with 6.4 mg/m^2/day cisplatin [9].

Toxicity (Table 2)

The regimen was tolerated well with myelosuppression, often severe, the main dose limiting toxicity and the reason for variability from a planned interval between courses of 7 days. In one patient myelosuppression was of sufficient severity to cease further courses.

The interval between courses ranged from 6–36 days with a median of 12 days, the degree of myelosuppression correlated (as expected) with the intensity of prior chemotherapy (Table 3).

Table 1. Patients' characteristics

Patient	Stage, site and pathology	Previous treatment	Status at time of etoposide/cisplatin	No. courses etoposide/cisplatin	Response	Duration of response
1	St.IV embryonal rhabdomyosarcoma forearm	Rapid VAC × 6	CR	3	NE	14/12
2	St.IV undifferentiated sarcoma	Rapid VAC × 6	PR	3	CR	15/12
3	St.III embryonal rhabdomyosarcoma vagina	Rapid VAC × 5	PD	2	NR	9/12
4	St.IV embryonal rhabdomyosarcoma of abdominal wall	Rapid VAC × 6 + surgery	PD	1	PD	—
5	St.IV Ewing's sarcoma chest	VCR/daunorubicin	NR	6	PR	4/12
6	St.III intraspinal undifferentiated sarcoma	Rapid VAC × 6 + surgery + radiotherapy	Local relapse 4/12 off treatment	6	PR	SD at 20/12
7	St.III embryonal rhabdomyosarcoma neck	Rapid VAC × 6, + HD Melph.	Local relapse 14/12 off treatment	6	PR	CR with DXT CR at 22/12
8	St.II embryonal rhabdomyosarcoma face	Rapid VAC × 6 VP16 × 3 + HD Melph.	Local relapse 12/12 off treatment	5	PR	5/12
9	St.III embryonal rhabdomyosarcoma pelvis	Rapid VAC × 6 + surgery + HD Melph.	Nodal relapse 5/12 off treatment	2	PR	5/12
10	St.II alveolar/embryonal rhabdomyosarcoma forearm	Rapid VAC × 6 + radiotherapy + HD Melph.	Local relapse 9/12 off treatment	5	CR	5/12

Rapid VAC = weekly vincristine, doxorubicin and cyclophosphamide; HD Melph. = high dose melphalan with autograft; DXT = local irradiation.

Overall, despite severe neutropenia, the incidence of severe infection was low. 2 patients experienced episodes of severe bacterial infection—one a case of *Brahamella catarrhalis* septicaemia and the other a case of *Escherichia coli* septicaemia, but both responded to appropriate antibiotics and supportive measures. One patient experienced an episode of severe mucositis with oesophagitis leading to stricture formation that required surgical dilatation.

Renal toxicity was experienced by 2 patients, with reductions in ^{51}Cr EDTA glomerular filtration rate of greater than 50%, though this recovered in both cases in the absence of further courses and nephrotoxicity did not prove a schedule limiting factor.

The regimen was emetogenic but this was readily controllable in all but 1 patient, using a 4–6 hourly schedule of standard dose metochlopramide and dexamethasone with or without chlorpromazine.

Table 2. Toxicity

No. of patients (10 evaluable) with WHO grade 3 or 4 toxicity on one or more occasions	
Haematological:	
Neutropenia	8
Thrombocytopenia	6
Renal	2
Emesis	1
Infection	2
Mucositis	1

Table 3. Time interval between courses of treatment

		Interval (days)	
Courses	*n*	Median	Range
1–2	9	7	7–24
2–3	7	21	6–36
3–4	5	13	7–25
4–5	5	22	7–29
5–6	3	7	7–21

No symptomatic hearing impairment was observed but serial audiograms were not performed.

DISCUSSION

Despite the small numbers in this study, the response rate of 78% in this group of pretreated patients with refractory or relapsed soft tissue sarcomas is encouraging and compares favourably to a response rate of 26% in a previous etoposide/cisplatin combination phase II trial in a similar, though larger, cohort of 27 patients who received lower dose intensities [6]. In that study responses were only seen in patients with rhabdomyosarcoma whereas in this study responses were also seen in undifferentiated soft tissue sarcoma and soft tissue Ewing's sarcoma though no responses were seen in any patient with primary refractory disease. The study confirms the efficacy of rapid delivery etoposide/cisplatin combination in such patients in contrast with a previous study which achieved only two PRs in 16 children using a schedule of less frequent administration of similar drug doses [7].

The strategy of this particular regimen of rapid dose delivery at high intensity requires further evaluation as an improvement in rate and quality of response remains desirable for this difficult group of patients.

Rapid delivery schedules appear well tolerated and are effective. The rapid-VAC regimen achieved response rates of 78% in rhabdomyosarcoma [19] and it is possible that improved responses might be seen with the addition of rapid etoposide/cisplatin to this regimen either concurrently, as alternating courses, or sequentially.

Alternative strategies to optimise the efficacy of etoposide are dose escalation, in order to further increase dose intensity, or continuous low dose administration as it is known that efficacy may increase when tumour cells are exposed to prolonged low serum etoposide levels [20, 21]. Studies with high dose etoposide combined with autologous bone marrow rescue demonstrate maximum dose tolerated to be 2.4 g/m^2 (800 mg/m^2/day × 3)—further dose increases being limited by extramedullary toxicity [22].

Cisplatin dose escalation may be desirable as the dose–response relationship is often linear [23]. Single total doses above 200 mg/m^2 are not feasible due to unacceptable toxicities despite vigorous hydration to overcome nephrotoxicity. Myelosuppression and peripheral neuropathy become dose-limiting at lower total doses but the introduction of other pharmacological agents to protect against extrarenal cisplatin toxicities, e.g. sodium thiosulphate or WR2721, may allow some escalation [24].

The value of adding etoposide to cisplatin as intensification of conventional first-line chemotherapy regimens was evaluated in a pilot study using low dose intensity etoposide [9]. A clear benefit in response rate had previously been shown with the addition of etoposide to cisplatin [25]. Subsequently IRS III has shown higher overall survival than in IRS II [26] although the role of additional chemotherapy remains unproven.

An attractive concept for patient management is the potential to give etoposide and cisplatin on an outpatient basis [27]. This facility would not only improve patient quality of life but would have resource implications by avoiding frequent hospitalisation. Outpatient administration is feasible as orally administered etoposide is readily absorbed [28] and more rapid infusion of cisplatin *per se* does not appear more nephrotoxic [29].

Cisplatin analogues such as carboplatin with retention of therapeutic benefit but decreased toxicity are under evaluation in phase II and III trials. Initial studies with high dose carboplatin–etoposide (JET) regimen in a phase II study in soft tissue sarcomas in children showed response rate of 64% [30].

In conclusion, the rapid etoposide/cisplatin regimen appears well tolerated and achieves a high response rate in a heterogenous group of pre-treated soft tissue sarcomas in children with previous chemotherapy sensitivity. With further dose intensity and scheduling manipulations, the response rates achieved may be increased and this regimen is worthy of consideration for use in first line therapies.

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Targeting Chemotherapy for Hepatoma: Arterial Administration of Anticancer Drugs Dissolved in Lipiodol

T. Konno

In targeted cancer chemotherapy, Lipiodol Ultrafluid (Lipiodol) was used as a carrier of anticancer drugs, these drugs were termed as "oily anticancer agents". This arterial injection therapy with oily anticancer agents was performed for 323 patients with hepatoma. Serum alpha-fetoprotein (AFP) levels decreased in 165 (93%) of 177 AFP-positive patients. Reduced tumour size was observed in 210 (regression over 50% in 96 and less than 50% in 114) of 222 evaluable patients with unresectable hepatoma. In patients who preoperatively received a dose of styrene maleic acid neocarzinostatin (SMANCS)/Lipiodol of more than 0.7 mg/cm^2 of maximal cut surface area of the tumour, complete necrosis or necrosis of almost the entire area of tumour was found, and non-cancerous liver tissue and the gallbladder remained unaffected. The survival period of 277 patients with unresectable hepatoma who were treated with oily anticancer agents is thought to be prolonged, especially of 147 patients, excluding those with Child C liver cirrhosis, with tumour occupying all segments of the liver, or with extrahepatic spread. The 1-, 2-, 3-, and 5-year survival rates were 84, 47, 37, and 34%, respectively.
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INTRODUCTION

SURGICAL RESECTION [1], transarterial embolisation [2], bolus or continuous arterial infusion of anticancer agents, and systemic chemotherapy [3] have mainly been used to treat hepatocellular carcinoma (HCC). Because 80% of the patients with HCC had liver cirrhosis and extended spread of the tumour was observed in many patients, about 15% [4] of the patients were candidates for tumour resection, and about 50% [1] of these patients underwent curative resection. Recurrence of the tumour was observed 1 year postoperatively in 50% of the patients who underwent hepatic resection. Therefore, the majority of patients with HCC had received the other treatment modalities just mentioned. However, the results of these treatments were not satisfactory. Clear antitumour activity and reduction of damage to the cirrhotic liver are thought to be essential for successful treatment of HCC. It is thought that targeting of the anticancer agent to the tumour, which results long-lasting, selective high concentrations of the drug in the tumour, may achieve improved results.

A lipid lymphograhic agent, Lipiodol Ultrafluid (lipiodol), has been found to be selectively retained in sites of hepatic tumours and other malignant solid tumours when it is injected arterially [5, 6]. Targeted chemotherapy was attempted by using this characteristic of lipiodol. The form of the dose that is

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