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Phase II Study of Rapid-scheduled Etoposide in Paediatric Soft Tissue Sarcomas

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Twenty three patients with paediatric soft tissue sarcomas who had relapsed or refractory disease were treated with a rapid schedule of intravenous etoposide (100 mg/m^2 daily on three consecutive days, weekly over 3 weeks). The regimen was well tolerated with predictable myelotoxicity. In 19 patients with rhabdomyosarcoma, there was a response rate of 42%. This appears to be better than previously reported with conventional three weekly schedules. These data indicate that for rhabdomyosarcoma, as for some other tumours, a divided dose regimen may be the optimal schedule and is worthy of further evaluation.

Key words: etoposide, rapid-schedule, dose intensity, rhabdomyosarcoma, sarcoma, childhood tumours
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INTRODUCTION

THE SURVIVAL of children with soft tissue sarcomas has improved over the past decade with 5-year event-free survival for non-metastatic disease in the region of 70% for the major collaborative groups such as the American Intergroup Rhabdomyosarcoma Study Group (IRS) [1], International Society of Paediatric Oncology (SIOP) [2] and German Cooperative Soft Tissue Sarcomas Group (CWS) [3].

However, refractory disease (approximately 10% of cases) and local or metastatic relapse (30%) remain problems, and survival in those with metastatic disease remains less than 20%. Further efforts to improve chemotherapy regimens are thus warranted. The number of potential new drugs is limited and it is, therefore, important to optimise the scheduling and/or combinations of existing drugs.

Single-agent etoposide has previously been shown to have activity in relapsed rhabdomyosarcoma, although with conventional scheduling only comparatively low response rates are achieved (20%) in intensively pretreated children [4, 5].

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The cytotoxic effect of etoposide shows marked dependence on schedule with *in vitro* studies demonstrating a clear direct relationship between duration of exposure of cells to etoposide and the degree of cell kill [6, 7]. In small cell lung cancer, the least effective way to give etoposide is as a single dose, and weekly divided dose administration has been shown to be a more effective schedule [8, 9]. In particular, high response rates were achieved with administration of a dose given divided over 5 days [10]. These studies provided the rationale to evaluate a weekly schedule in paediatric sarcomas. Potential advantages of this schedule also include allowing an increase in dose intensity and the rapid delivery of drugs in a minimum period.

PATIENTS AND METHODS

23 patients, 14 male, 9 female, with a median age of 4 years 9 months (range 8 months–18 years), were entered into this phase II study. The histopathological diagnoses in this group of patients with soft tissue sarcomas were 19 rhabdomyosarcoma, 2 fibrosarcoma, 1 synovial sarcoma and 1 undifferentiated soft tissue sarcoma. SIOP TNM stages at initial diagnosis were 2 stage I, 10 stage II, 5 stage III and 6 stage IV [11]. The indications for inclusion in the study were residual or progressive disease after first-line chemotherapy (9), relapse 3–24 months off treatment (13) and initial progressive disease (1). 11 patients had previously received etoposide and teniposide as part of their

conventional first-line treatment modalities (Table 1). These regimens comprised either 300–450 mg/m^2 of etoposide given every 3 weeks in combination with cisplatin or etoposide or teniposide 150 mg/m^2 every 3 weeks in combination with carboplatin and vincristine.

Pretreatment investigations included full clinical evaluation and radiological assessment of all measurable sites of disease, bone marrow/trephine evaluation, assessment of renal function and baseline haematological and biochemical status. Measurable disease, clinical and/or radiological, was reassessed after one full cycle of chemotherapy (i.e. nine doses of etoposide) with renal function, haematological and biochemical parameters repeated at intervals throughout the treatment.

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

Treatment

Single-agent etoposide 100 mg/m^2 was given daily on 3 consecutive days, weekly for 3 weeks and repeated as tolerated. Each dose was infused intravenously over 1 h on days 1, 2, 3, 8, 9, 10, 15, 16 and 17, regardless of the degree of myelosuppression and in the absence of other severe toxicities. This regimen of a total of nine doses of etoposide per cycle was repeated on full recovery of the neutrophil ($>1.0 \times 10^9$/l) and platelet ($>100 \times 10^9$/l) counts and as indicated by clinical and disease reassessment.

Evaluation of response

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

RESULTS

All 23 patients received at least one full course of nine doses of etoposide; 7 patients subsequently completed two courses; 3 patients three courses and 1 patient five courses. Dose intensity (DI) was calculated for the first cycle of treatment only, with a median DI in the whole group of 40 mg/m^2/day. A reduction in the maximum planned dose intensity of 43 mg/m^2/day occurred in 9 patients due to myelosuppression (in these cases, DI range from 19 to 31 mg/m^2/day).

Responses

All patients were assessable for response. Within this group of high-risk pretreated patients, there were four CR, four PR, five NR and 10 PD, giving an overall response rate of 35%. All responses occurred in patients with rhabdomyosarcoma, and amongst this histological group alone the complete response rate was 21%, with an overall response rate of 42% (Table 1).

In the patients who achieved CR, 2 had refractory disease following a regimen with six courses of vincristine, doxorubicin and cyclophosphamide [12]. 2 patients had local nodal relapses—1 after 4 months off treatment with four courses of IVA (ifosfamide, vincristine and actinomycin); two courses of CEV (carboplatin, epirubicin and vincristine) and two courses of IVE (ifosfamide, vincristine and etoposide) and the other 2 years off treatment with IVA, cisplatin-doxorubicin and double autologous bone marrow transplantation (ABMT) following megatherapy which included etoposide. Of those who achieved a PR, all 4 cases were relapses 3–12 months off treatment with IVA chemotherapy; alone in 1 patient, plus cisplatin-doxorubicin in 2 patients and following VINCAEPI (vincristine, carboplatin

Table 1. Clinical details including prior epipodophyllotoxins and response

Diagnosis	Initial stage	Measurable disease	Prior VP16/VM26	Response
RMS pelvis	IV	Residual marrow disease	N	CR
RMS retro-orbital	II	Residual disease	N	NR
RMS pelvic	IV	Residual primary disease	N	CR
RMS temple	III	Residual disease	N	NR
STS sacral	II	Relapse, local (2 years off)	N	PD
RMS nasopharynx	III	Relapse, local (4 months off)	Y	CR
RMS buttock	II	Relapse, pulmonary (11 months off)	Y	PR
RMS vaginal	III	Residual disease	N	PD
RMS leg	IV	Residual pulmonary disease	Y	NR
RSM arm	IV	Relapse, pulmonary (1 year off)	N	PR
RMS audit. meatus	II	Relapse, local (2 years off)	Y	CR
RMS paravertebral	IV	Residual primary disease	Y	PD
FBS inguinal	IV	Residual primary disease	Y	PD
RMS paravesical	I	Relapse, local (6 months off)	N	PR
RMS ethmoidal	II	Relapse, axillary (3 months off)	N	PR
RMS scapular	III	Relapse, pulmonary (2 months off)	Y	PD
SYS synovial	II	Relapse, popliteal (8 months off)	N	NR
RMS dorsolumbar	III	Relapse, pulmonary (3 months off)	N	PD
FBS temporal fossa	II	Residual disease	Y	PD
RMS nasopharyngeal	II	Progressive disease	Y	PD
RMS pterygoid	II	Relapse, local (3 months off)	Y	PD
RMS abdominal	I	Relapse, local (3 months)	Y	PD
RMS orbit	II	Relapse, pulmonary (15 months off)	N	NR

RMS, rhabdomyosarcoma; SYS, synovial sarcoma; FBS, fibrosarcoma; STS, soft tissue sarcoma; CR, complete response; NR, no response; PD, progressive disease.

Table 2. Toxicity associated with first cycle of etoposide

	Toxicity (WHO grading) (n = 21)				
	0	I	II	III	IV
Anaemia	12	2	5	2	0
Neutropenia	10	3	0	5	3
Thrombocytopenia	16	1	2	2	0
Infection	17	1	3	0	0
Nausea/vomiting	19	0	2	0	0
Oral	20	0	1	0	0
Hepatic	20	1	0	0	0
Skin	20	1	0	0	0
Renal	21	0	0	0	0

and etoposide) in 1 patient. 3 of the 8 patients responding to this regimen had, therefore, previously been exposed to epipodophyllotoxins at conventional doses and schedules.

Toxicity

The regimen was generally well tolerated by all patients, with 21 patients evaluable for toxicity (Table 2). The primary toxicity of this rapid dose delivery schedule was myelosuppression. Thirty-eight per cent of patients experienced WHO grade III–IV neutropenia and 10% grade III–IV thrombocytopenia. Almost half of the cases had no myelosuppression, despite heavy pretreatment. Reflecting the lack of severe neutropenia, the incidence of infection was low, with only four episodes of infection associated with neutropenia (neutrophil count $<0.5 \times 10^9$/l) in 3 patients. All responded to broad spectrum antibiotics and supportive measures, with recovery of the neutrophil count. 2 patients experienced WHO grade II nausea/vomiting, readily controlled with antiemetics. One patient developed grade II mucositis and 1 patient transient mild elevation of hepatic enzymes and grade I hepatic toxicity.

DISCUSSION

Etoposide is a useful agent in the management of a variety of paediatric tumours. It is usually given as a 3- or 5-day schedule of once daily intravenous doses to a total dose of 300–500 mg/m^2/course, repeated every 3–4 weeks, thus providing a DI of 14–24 mg/m^2/day. A weekly divided dose schedule provides the potential to increase dose-intensity. This rapid delivery philosophy has been applied to other tumours such as neuroblastoma [13], non-Hodgkin's lymphoma [14] and malignant germ cell tumours [15]. In the schedule chosen for this phase II study, a maximum DI of 43 mg/m^2/day was possible and was achieved in almost 60% of patients entered on to the study.

The potential value of adding etoposide as intensification of first-line chemotherapy regimens in paediatric soft tissue sarcomas was evaluated in a pilot study using low DI etoposide [16]. A randomised study by the American Intergroup Rhabdomyosarcoma Study Group (IRS III) evaluating etoposide in addition to the VAC regimen (vincristine, actinomycin, cyclophosphamide) has shown higher overall survival than in the IRS II in the study patients as a whole, but the role of the additional agent remains to be analysed and published.

The likely synergistic effect of combining etoposide and cisplatin has been widely applied [17], and it has been shown that a weekly combination of these drugs is both feasible and effective in paediatric sarcomas [18]. The response rates in the present study compare favourably with previous studies on smaller numbers of relapsed or resistant sarcomas in which response rates of 19 and 21% were reported [4, 5]. The study confirms the efficacy and tolerability of a rapid schedule and justifies further work with increased DI regimens of etoposide in soft tissue sarcomas. One point of caution, however, is the increasing evidence of a schedule-dependent leukaemogenic effect of the epipidophyllotoxins [19]. The risk with conventional 3-weekly scheduling, particularly with a low total cumulative dose is minimal but it seems likely that repeated doses, i.e. twice/thrice weekly may be associated with secondary acute myelocytic leukemia. It would seem prudent to limit evaluation of this regimen to high-risk or relapsed patients, in whom potential benefits would outweigh the small risks of late effects.

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