Eur J Cancer, Vol. 29A, No. 16, pp. 2223–2225, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00
Pergamon Press Ltd

21-Day Schedule Oral Etoposide in Children—a Feasibility Study

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To determine the feasibility and toxicity of prolonged oral etoposide in children, 22 patients with relapsed or refractory disease were commenced on etoposide 50–100 mgs/m² per day for 21 days. A second course was administered after full blood count recovery, followed by disease reassessment. In total, 72 courses were evaluable for toxicity, with 10% of completed courses complicated by febrile neutropenia. 15 patients were evaluable for response, with 1 partial response, 10 stable disease and 4 progressive disease. This schedule was well tolerated with acceptable toxicity when doses of less than 80 mg/m²/ day were administered and warrants further evaluation.
Eur J Cancer, Vol. 29A, No. 16, pp. 2223–2225, 1993.

INTRODUCTION

THE OPTIMUM schedule for clinical etoposide use remains unknown, and usually 100–200 mg/m² is given intravenously daily for 1–5 days [1–6]. However, there is increasing evidence that smaller daily doses given orally over longer periods may be at least as effective without increased toxicity [7–9]. In adults there was a superior response rate when the same dose was divided over 5 days instead of a single dose [10]. Although response rates were similar when an 8-day schedule was compared with a 5 day schedule, there was less myelotoxicity with the 8-day schedule [11]. Studies of the pharmacokinetic profiles showed that the only major difference in the divided dose arm was longer exposure to a relatively low drug concentration (1 μg/ml) [12]. This study was undertaken to determine the feasibility and toxicity of prolonged schedule etoposide in children.

PATIENTS AND METHODS

22 patients with relapsed or refractory disease were entered in the trial between June 1990 and June 1991. Informed parental consent was obtained. Patient details are shown in Table 1.

Table 1. Patients' details

Diagnosis	
Relapsed neuroblastoma	6
Refractory neuroblastoma	5
Relapsed soft tissue sarcoma	4
Refractory soft tissue sarcoma	1
Relapsed leukaemia	4
Relapsed Hodgkin's disease	1
Relapsed germ cell tumour	1
Age (years)	
Median	7
Range	2–19
Sex	
Male	12
Female	10
Prior etoposide treatment	19
Bone marrow disease at time of study	11

Disease assessment was performed appropriate to the tumour type. Measurable disease was estimated in two maximum dimensions. Bilateral bone marrow aspirates and trephines and urinary catecholamines were performed in children with metastatic neuroblastoma. A unilateral aspirate was examined in cases of leukaemia.

The recommended schedule of 50–75 mg/m²/day for 21 days was based on adult studies [13]. To allow accurate drug dosage it was recommended that intravenous (i.v.) preparation was used orally for smaller children. Twice daily dosage was preferred, to maximise the time when serum concentrations were in excess of 1 μg/ml.

During the first course full blood counts (FBC) were performed weekly in conjunction with clinical review. Liver function tests (LFT) were documented and mucositis recorded if present. The dose was reduced if severe myelosuppression leading to hospital admission occurred.

Patients were formally reassessed after two 21-day courses. Complete response (CR) was defined as no evidence of residual disease, partial response (PR) as a greater than 50% reduction in measurable disease, stable disease (SD) as a less than 50% reduction in measurable disease and progressive disease (PD) as a greater than 25% increase at disease site(s).

Neuroblastoma was staged according to the International Neuroblastoma Staging System (INSS) recommendations [14], which includes mixed response (MR) defined as no new lesions; greater than 50% reduction of any measurable lesion (primary or metastases) with less than 50% reduction in any other; less than 25% increase in any existing lesion.

RESULTS

22 patients started 72 courses. Sixty-eight courses were completed. Four courses were terminated early, two after 3 and 14 days because of vomiting and two because of disease progression. These courses were not evaluated for haematological toxicity.

The initial dose received, the drug preparation and the schedule used are shown in Table 2. In 4 cases the investigator electively gave greater than 75 mg/m².

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Revised 1 July 1993; accepted 6 Sept. 1993.

Table 2. Etoposide dose and schedule

	No. of patients
Dose (mg/m²)	
50	13
60	5
80	2
90	1
100	1
Preparation and schedule	
Intravenous route o.d.	1
oral capsules o.d.	8
oral capsules b.d.	4
intravenous preparation orally o.d.	4
intravenous preparation orally b.d.	5

b.d., twice a day; o.d, once daily.

Toxicity

Ten per cent (7/68) of completed courses, including 11 patients with marrow disease, were complicated by febrile neutropenia.

In 13 patients who had a normal FBC on starting therapy the median nadir neutrophil count following course one was 1.05×10^9/l (range 0–2.7) and that of platelets 110×10^9/l (range 30–273). Overall, 8/53 courses which started with a normal FBC were complicated by a white blood cell count (WBC) of less than 1.0×10^9/l, and 7/53 by thrombocytopenia of less than 50×10^9/l.

Dose modification was necessary because of haematological toxicity in 6 patients, with contributing factors such as higher dose or marrow disease in 5 patients. Nausea and vomiting (grade II or IV) complicated 11 out of 72 courses. Mucositis occurred in four out of 68 evaluable courses.

16 patients were evaluable for alopecia after two courses. 6 patients had total alopecia, 5 had patchy and 5 had none.

2 of 9 patients who had serial evaluation of LFTs had a two-fold rise in liver enzymes accounted for by progressive disease in both cases. One had a transient rise in serum creatinine when dehydrated during an admission with mucositis.

Response

20 patients were evaluable. 2 others were non-evaluable, 1 who was withdrawn because of vomiting and 1 who was inadequately assessed. 16 patients completed two courses, but only 15 of these were evaluable for response. 5 patients [acute lymphocytic leukaemia (ALL) 2; acute myeloid leukaemia (AML) 2 and rhabdomyosarcoma 1] had clinically progressive disease after one course and can be regarded as treatment failures.

The method of assessment in the evaluable cases comprised computed tomography (CT) scan of primary or metastatic site ($n = 6$), marrow examination ($n = 6$), bone scan ($n = 1$) and X-ray ($n = 2$). Responses were one PR (neuroblastoma), six MR (neuroblastoma), four SD (three soft tissue sarcoma, one germ cell tumour) and eight PD (three neuroblastoma, one soft tissue sarcoma, four leukaemia). The patient achieving a PR was unable to tolerate the oral drug and received an equivalent daily intravenous dose.

Useful palliation was documented in 11/15 patients who had pain prior to commencement of therapy.

DISCUSSION

Overall, this treatment was well tolerated and a suitable oral preparation, either capsule or intravenous ampoule, was able to be taken over a prolonged period even by young children. As expected, the major toxicity was haematological, with myelosuppression comparable to that described in adult studies [8, 9]. Higher doses were not well tolerated with 3 of 4 patients who received 80 mg/m² or more requiring dose reduction because of myelosuppression, but with lower doses two children completed eight and nine courses with good palliative effect.

Other toxicities were mild with the exception of moderate to severe nausea and vomiting in a minority of patients, but underlying abdominal disease may have been responsible for some of the symptoms. Mucositis only occurred in conjunction with severe myelosuppression, and all 3 patients who suffered mucositis tolerated a further course with dose reduction without complications.

Response rates at sites of measurable disease were unimpressive but these patients were heavily pretreated and some had advanced disease. Most had received prior etoposide therapy in standard schedules. There was no relationship between prior etoposide therapy and response. Response according to disease category did vary and it is worth noting that all four children with leukaemia (two ALL and two AML) progressed during the first course of therapy. Symptomatic relief for prolonged periods with minimal toxicity was striking, however.

Compliance was excellent in this study, and if a 14–21-day course of oral etoposide were shown to be effective it would probably be preferred to the more toxic conventional schedules. A phase II study is underway within the U.K. Children's Cancer Study Group, with strict dosage (50 mg/m²/day), twice daily scheduling and incorporating pharmacokinetic studies. It has been suggested that the leukaemogenic effect of epipodophyllotoxins is schedule-dependent [15], and it is likely that this schedule would ultimately be used for poor prognosis disease.

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Eur J Cancer, Vol. 29A, No. 16, pp. 2225–2231, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

A Phase I/II Study of a Stepwise Dose-escalated Regimen of Cisplatin, Etoposide and Ifosfamide plus Granulocyte–Macrophage Colony-stimulating Factor (GM-CSF) in Patients with Advanced Germ Cell Tumours

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In order to improve the survival of patients with metastatic advanced disease germ cell tumours (according to Indiana University classification), 77 patients were treated by a stepwise dose-escalated combination regimen of platinum (P), etoposide (E) and ifosfamide (I) (PEI) followed by application of granulocyte–macrophage colony-stimulating factor (GM-CSF) (10 μg/kg subcutaneously per day at levels 2 and 3) starting the first day after chemotherapy for 10 consecutive days. The maximally tolerated dose was reached at the third dose level with P 30 mg/m², E 200 mg/m² and I 1.6 g/m², all given for 5 days, once every 21 days, for a total of four cycles. Sixty-seven per cent of patients had three or more metastatic sites. Twenty-two per cent of patients had extragonadal primary tumours. 49 (65%) patients achieved complete remission, and 9 additional patients (12%) achieved marker normalisation with unresectable residual disease. After a median follow-up of 27 months, the overall survival is 80%, with 67% of patients remaining free from progression. The dose-limiting toxicities were WHO grades 3/4 mucositis/enteritis in 33% of patients and prolonged thrombocytopenia < 20.000/μl (> 10 days). Adverse reactions to GM-CSF occurred in 13% of patients. The use of a single haematopoietic growth factor allowed only a moderate increase in dose intensity (factor 1.37). Peripheral blood stem cells will be additionally incorporated into the treatment protocol in order to deliver multiple cycles of an upfront dose-intensified PEI regimen in patients with "poor risk" germ cell tumours with less toxicity.

Key words: advanced germ cell tumours, dose intensity, platinum/etoposide/ifosfamide, GM-CSF
Eur J Cancer, Vol. 29A, No. 16, pp. 2225–2231, 1993.

INTRODUCTION

WITH THE introduction of effective combination chemotherapy, testicular cancer has become a model for a highly curable malignant disease [1]. About 80% of all patients with metastatic testicular cancer will achieve a durable complete remission (CR) [2]. The application of prognostic factors enables one group of patients with an exceptionally high chance of cure to be distinguished from another subset of patients, designated "poor risk", in whom only a complete response rate of 40–70% can be achieved with standard chemotherapy regimens [3]. Different strategies have been investigated to improve the unsatisfactory results in these poor-risk patients, including the incorporation of additional agents to the three drug regimens, the rapid alternation of drug regimens or the increase of dose intensity [4–8].

A dose–response relationship was shown for patients with germ cell tumours treated with cisplatin doses between 60 and 120 mg/m² and this prompted the investigation of cisplatin administered at 200 mg/m² per cycle (double-dose cisplatin) [4]. A benefit for double-dose cisplatin in combination with etoposide, bleomycin and vinblastin over standard PEB (platin/etoposide/bleomycin) was suggested in a randomised trial for patients with poor-risk germ cell tumours performed at the National Cancer Institute (NCI) of the U.S.A. [5]. However, a