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Chronic Daily Administration of Oral Etoposide in Refractory Lymphoma

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In a phase II study, 25 patients with previously treated lymphoma received oral etoposide for 21 consecutive days. All patients were considered incurable with standard therapy. Etoposide was administered at 50 mg/m² per day: courses were repeated every 28–35 days, depending on myelosuppression. 15 patients (60%) had partial responses (95% CI 41–77%), while 10 patients had no response. Median time to disease progression was 5 months (range 2–13 months). Oral etoposide was active against indolent and aggressive (intermediate and high grade) lymphomas; however, median time to progression was only 3 months in aggressive lymphoma compared with 8 months in indolent lymphoma. Myelosuppression was the major side-effect; 7 patients (28%) had a leucocyte nadir below 1000/μl during the first course, and 11 patients required dose reduction during subsequent courses due to unacceptable leukopenia. All patients had total alopecia, but other side-effects were uncommon. These results highlight the importance of schedule in the administration of etoposide.
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INTRODUCTION

ETOPOSIDE has a wide spectrum of antineoplastic activity and is part of the combination chemotherapy for several neoplasms, including the non-Hodgkin's lymphomas (NHL) and Hodgkin's disease [1, 2]. Etoposide is frequently used in first-line or salvage regimens for these malignancies [3–5]. Although dosage varies, the schedule is standard: divided intravenous doses over 3–5 days. In murine L1210 leukaemia, divided daily doses were more effective than intermittent large doses [6]. In extensive-stage small cell lung cancer, etoposide for 5 consecutive days gave a higher response rate than did the same total dose over 24 h [7].

An oral etoposide preparation is now available, which facilitates the investigation of a prolonged dosing schedule. Our phase I study demonstrated that oral etoposide could be given safely at 50 mg/m² for 21 consecutive days [8]. The dose-limiting toxicity was myelosuppression; all patients had total alopecia, but other side-effects were rare. Antitumour activity was observed in patients with soft tissue sarcoma, NHL, breast cancer, and ovarian cancer, despite previous treatment with several other chemotherapeutic agents. We then started a series of phase II trials to investigate chronic oral etoposide in several malignancies, including refractory lymphomas.

PATIENTS AND METHODS

25 patients at Vanderbilt University Medical Center entered this study between July 1988 and July 1989. All patients had biopsy-documented NHL (23 patients) or Hodgkin's disease (2 patients). The patients with either aggressive (intermediate or high grade) NHL or Hodgkin's disease had relapsed or progressed after at least one previous multidrug regimen, and were considered incurable. The patients with indolent NHL had to have received at least one previous chemotherapy regimen. All patients had bidimensionally measurable tumour masses, and met the following criteria: (1) Eastern Cooperative Oncology Group (ECOG) performance status 0–2; (2) estimated life expectancy of 12 weeks or more; (3) serum creatinine below 2.0 mg/dl; (4) serum bilirubin below 2 mg/dl; (5) white blood cell count 3000/μl or more; and (6) platelets 100,000/μl or more. No patient received antineoplastic therapy in the fortnight before entry. Patients who had previously received intravenous etoposide were eligible. All patients gave informed consent before entry.

At entry, the following studies were done: complete blood counts and differential, electrolytes, biochemistry, and chest X-ray. Computerized tomography of the chest and/or abdomen was done when indicated for tumour measurement.

Patients received oral etoposide for 21 consecutive days at 50 mg/m² per day. The daily dose was approximate, since etoposide was available only in 50 mg capsules. For example, if a patient should have received 85 mg per day, the drug was administered at 100, 100 and 50 mg on 3 consecutive days and the schedule was repeated for 21 days (average daily dose 83 mg).

During each 21 day course, complete blood counts were measured weekly. Etoposide was discontinued if the total leucocyte count fell below 2000/μl or platelets fell below 75,000/μl. After 21 days, etoposide was discontinued for a week and each patient was re-evaluated on day 28. Subsequent courses were begun as soon as total leucocyte count had risen over 3000/μl. Patients received two 21 day courses before being re-evaluated for response. Responding patients received 4–6 courses, depending on their tolerance of treatment.

Patients who had leucocyte nadirs of less than 2000/μl or who required discontinuation of daily dosing before 21 days, received a dosage reduction to 75% on the subsequent cycle. No patient had dosage escalation.

Responses were assessed by standard criteria. Complete

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response was disappearance for at least 4 weeks of all evidence of tumour by physical examination and X-ray. Partial response was 50% reduction for at least 4 weeks in the product of perpendicular diameters of each indicator lesion. Patients who failed to achieve either complete or partial response were classified as non-responders. Time to disease progression was calculated from the first day of treatment.

RESULTS

Age range was wide, but 18 patients were 60 or older (Table 1). All patients had advanced lymphoma involving multiple sites. Most patients had received two or more previous chemotherapy regimens; 9 had received etoposide.

Clinical characteristics of patients with indolent lymphoma are compared with those of patients with aggressive lymphoma in Table 2. The 2 patients with Hodgkin's disease are included in the low grade lymphoma group. The median ages of the two groups were similar, since most of our young patients with aggressive lymphoma were included in other studies. The median interval from diagnosis to treatment with oral etoposide was much longer in the indolent group (35 vs. 10 months). Both groups were heavily pretreated, and had received a similar number of previous chemotherapy regimens; as expected, treatment regimens differed in accordance with standard practice in the treatment of these disorders. Most patients were resistant to the chemotherapy received before entry. 6 patients, all in the indolent group, had responded to previous therapy and had been off treatment for more than 6 months before entry.

15 patients (60%, 95% CI 41–77%) achieved partial response with oral etoposide. 8 patients had no response and were removed after one or two courses. 2 other patients received less than one course and were removed due to toxicity; they were included as treatment failures. 5 of the 9 patients who had previously received etoposide achieved partial response. Median time to disease progression was 5 months; 2 patients continue to respond at 7 and 8 months, respectively.

Oral etoposide was active against indolent and aggressive lymphomas (Table 2). However, the time to disease progression differed. 4 of the 5 responses in patients with aggressive lymphoma were brief; 3 patients progressed after only 3, 3 and 4 months, respectively. The fourth responder had a partial response after one course and was withdrawn with severe nausea and vomiting. This patient progressed during the next month while receiving treatment with intravenous etoposide 100 mg/m^2 for 3 consecutive days. The fifth responder with high grade lymphoma remains in partial response 7 months after beginning treatment and is continuing therapy. Responses in patients with indolent lymphomas were more durable; time to progression ranged from 4 to 13 months. The median duration of response was 8 months; 1 patient remains in an unmaintained partial remission at 8 months. Responding patients with indolent lymphoma received a median of four courses of etoposide (range 2–9).

All 3 patients with indolent lymphoma who had previously received intravenous etoposide responded again to oral etoposide, while 2 of 6 patients with aggressive lymphoma responded. These 2 responding patients with aggressive lymphoma provided the strongest evidence for schedule dependency of etoposide. 1 patient had developed diffuse recurrence in skin and lymph nodes within a month of receiving an intensive combination containing intravenous etoposide. She had nearly a complete resolution of her skin lesions after one course of oral etoposide, and remained in remission for 3 months. The other patient had received etoposide 1200 mg/m^2 on two occasions as part of an intensive combination, to which he had only minimal response. He then received cyclophosphamide/prednisone with no response. When treated with oral etoposide (3 months after receiving intravenous etoposide), he had a partial response which persists after 7 months.

Myelosuppression was the most serious side-effect. Median leucocyte nadir following the first course (during which all patients received full dosage) was 2400/μl; 7 patients had nadirs below 1000/μl, while 4 patients had nadirs between 1000 and 2000/μl. Nadirs occurred between days 21 and 28; most patients were able to begin the subsequent course on day 28 or day 35. In general, patients who had nadirs above 2000/μl during the first cycle were able to continue subsequent cycles at full dose, with no evidence of cumulative toxicity. 11 patients required dose reductions after the first course; no further nadirs below 1000/μl occurred in patients receiving 75% of the starting dose.

Table 1. Patients' characteristics

	No. of patients
Median age (range)	67 (31–82)
M/F	9/16
Histology	
Low grade NHL	13
Follicular, predominantly small cleaved cell	10
Small cell lymphocytic	2
Cutaneous T cell	1
Hodgkin's disease	2
Intermediate and high grade NHL	10
Large cell, diffuse	8
Large cell, immunoblastic	1
Small noncleaved	1
No. of previous regimens	
1	4
2	7
3	12
4 or more	2
Previous intravenous etoposide	9

Table 2. Comparison of clinical characteristics and results in indolent versus aggressive lymphoma

	Low grade lymphoma (includes Hodgkin's disease)	Intermediate and high grade lymphoma
Median age (yr)	67	68
Median interval, diagnosis to study entry (mo)	35	10
Mean No. of previous regimens	2.6	2.3
Median interval, most recent treatment to study entry (mo)	4	1
With lymphoma progression on previous regimen	62%	70%
Response rate	67%	50%
Median time to progression (mo)	8	3

7 patients were admitted for treatment of neutropenia and fever, all after receiving the full dose during the first course. 5 of these 7 patients were successfully treated with subsequent courses of oral etoposide at reduced dosage, with no further admissions. 2 patients were removed from treatment after only one course, because of severe myelosuppression. No treatment-related deaths occurred.

8 patients had platelet nadirs below 50,000/μl and four required platelet transfusions. After dose reductions, only 1 patient had a recurrence of severe thrombocytopenia; this patient was withdrawn after two courses because of prolonged thrombocytopenia. No clinically significant bleeding occurred. Anaemia was common and cumulative with repeated courses. 13 patients required transfusions of at least two units (range 2–8).

All patients had total alopecia. Other side-effects were uncommon. 5 patients had mild to moderate mucositis (4 in the setting of neutropenia and fever), 2 had diarrhoea, and 2 had nausea and vomiting. In 1 of these patients, nausea and vomiting were severe enough to require withdrawal after one course.

DISCUSSION

Oral etoposide administered at low doses for 21 consecutive days was active in patients with refractory lymphoma. High response rates were observed in both indolent and aggressive lymphomas, most of which were refractory to previous combination chemotherapy. Responses were observed in 5 of 9 patients who had previously received intravenous etoposide, and 2 of these patients responded shortly after failing to respond to a combination regimen containing intravenous etoposide. In addition, rapid progression was seen in 1 patient who responded to oral etoposide but was switched to intravenous etoposide (3 day schedule) because of intolerance. As anticipated, response durations were brief in patients with aggressive lymphomas; however, median time to progression was 8 months in patients with low grade lymphoma, with 8 patients having remission of 6 months or more.

Several studies have documented etoposide activity as a single agent [1, 9–14]. Our 65% overall response rate compared favourably with these studies, and suggested an advantage for the chronic dosing schedule.

The importance of schedule in the antineoplastic activity of etoposide is supported by its mechanism of action, as well as by data from animal [6] and clinical studies in the treatment of small cell lung cancer. Etoposide interacts with DNA topoisomerase II, an enzyme that catalyses DNA topoform interconversions by introducing a transient enzyme-bridged double-stranded break in one of the DNA segments [15]. This interaction is reversible after withdrawal of etoposide, which suggests that prolonged exposure would enhance efficacy [16].

The most convincing evidence for schedule dependency of etoposide in the treatment of human malignancy is in extensive-stage small cell lung cancer [7, 17]. The response rate of patients who received a 5 day schedule was 89%, compared with 10% when a 24 h infusion was administered. The total areas under the concentration vs. time curves (AUCs) were equivalent in both regimens. However, patients receiving the 5 day regimen maintained levels of etoposide greater than 1 μg/ml for approximately twice as long as did patients receiving the infusion. It was speculated that time of exposure to etoposide was more important than concentration; similar results have been suggested in small cell lung cancer lines incubated with etoposide [18].

Our preliminary results showed daily peak serum etoposide levels at 4–6 μg/ml and trough concentrations ranging from 0.4 to 5.3 μg/ml. Our patients may therefore have achieved about 1–5 μg/ml for many hours during the 21 days.

Miller *et al.* reported 17 patients with germ cell tumours who were treated with etoposide 50 mg/m^2 daily until progression or toxicity not ameliorated by dose adjustment was observed [19]. 6 of 16 patients showed objective evidence of response to oral etoposide; 3 patients had partial response while 3 had decreased markers with stable radiographic disease. Similar activity was noted in a small group of patients with recurrent small cell lung cancer [20].

In heavily pretreated patients, it is doubtful that other myelosuppressive agents could be safely combined with the dose and schedule of etoposide that we used; however, treatment with an effective single agent is often appropriate in patients with low grade lymphoma. About half the patients in this group will be unable to tolerate the dose of 50 mg/m^2 per day, but usually tolerate reduced dosages for repeated cycles. Although active in aggressive lymphomas, chronic oral etoposide as a single agent makes little impact on the course of this disease. However, incorporation of this schedule of oral etoposide into combination regimens used for initial therapy may increase the efficacy of these regimens. Our preliminary results with combinations indicate that full doses of cisplatin or carboplatin in combination with this dose and schedule of etoposide are well tolerated in previously untreated lung cancer patients.

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Pirarubicin in Advanced Breast Cancer: A French Cooperative Phase II Study

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79 patients with advanced breast cancer were given Pirarubicin 20–25 mg/m² during 3 consecutive days every 3 or 4 weeks. 78 were evaluable for response (41 without previous chemotherapy and 37 with only one previous regimen). The overall response rate was 35% (95% CI 24–45) and the complete response rate was 8%. In previously untreated patients, the response rate reached 41.5%. The limiting toxicity was a non-cumulative granulocystopenia, sometimes severe at these high doses, with a prompt recovery. The non-haematological toxicities were mild, and included 13% with grade 3 alopecia.
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INTRODUCTION

PIRARUBICIN (4'-0-tetrahydropyranyl-doxorubicin) has a higher preclinical therapeutic index than doxorubicin[1,2] with low cardiotoxicity in different animal models[3–5]. Pharmacokinetic studies show a half-life shorter than that of doxorubicin with an earlier cellular uptake and a higher cellular concentration of the drug[6,7]. Phase I studies have shown that the limiting toxicity was granulocystopenia and that the optimal dose was between 45 and 75 mg/m² every 3 weeks.

In Japanese phase II reports, the spectrum of activity of pirarubicin was close to that of doxorubicin with less toxicity, especially alopecia[8]. Mathe *et al.*[9] reported a response rate of 28% in 50 patients with advanced breast cancer, mostly heavily pretreated. They suggested that a 3 day schedule gave a better tolerance than bolus administration. We have done a cooperative phase II study of pirarubicin in non-heavily pretreated advanced breast cancer.

PATIENTS AND METHODS

Eligibility criteria

All female patients with a pathologically proven advanced breast cancer (metastatic and/or with locoregional relapse), aged under 70, had been enrolled if they had at least one measurable or evaluable site of evaluation (except isolated bone disease), and either no previous chemotherapy or only one previous regimen containing less than 300 mg/m² doxorubicin (or equivalent) at least 1 year before inclusion. Performance status (ECOG) under 2 was required, as well as white cell counts over 4×10^9/l, platelets over 120×10^9/l, serum bilirubin under 35 μmol/l, and serum creatinine under 135 μol/l. All patients gave oral informed consent.

Exclusion criteria

Congestive heart failure, previous myocardial infarction, severe rhythm abnormalities or left ventricular ejection fraction