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CLINICAL TRIAL REPORT

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Prolonged daily administration of oral etoposide in lymphoma following prior therapy with Adriamycin, an ifosfamide-containing salvage combination, and intravenous etoposide

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Abstract Prolonged daily administration of oral etoposide has been reported to be active in refractory lymphoma. The purpose of this phase II trial was to confirm the activity of this schedule of etoposide in a selected group of heavily pretreated patients with non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD). A total of 26 patients (20 with NHL and 6 with HD) were entered in the trial; all had previously been treated with an Adriamycin-based chemotherapy, an ifosfamide-containing salvage combination, and i.v. etoposide. Etoposide was given in a fixed oral daily dose of 100 mg over 3 weeks; the weekly dose (500–700 mg) was selected such that the average daily dose was approximately 50 mg/m^2. Cycles were repeated on day 29. An objective response was seen in 16 patients (62%; 95% confidence interval, 42%–80%), with a complete response (CR) being observed in 3 cases (12%) and a partial response (PR), in 13 (50%). The median duration of PRs was 3 months. CRs lasted for 15 months in one patient and continue at 12+ and 20+ months in the remaining two patients. The overall actuarial survivial for the entire group was 40% at 2 years; the median survival time was 12 months. The main toxicity was myelosuppression; WHO grade 3 or 4 leukopenia and thrombocytopenia developed in 31% and 12% of the patients, respectively. There was no drug-related death. We conclude that oral etoposide is an effective and tolerable palliative treatment for heavily pretreated lymphoma patients.

Key words Oral etoposide · Refractory lymphoma · Salvage chemotherapy

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Introduction

Etoposide is an active drug for lymphoma [10] and appears to act by causing breaks in DNA by interaction with DNA topoisomerase II [12]. The efficacy of etoposide has been found to be schedule-dependent, with more prolonged i.v. administration (5 days versus 24 h) being better for patients with small-cell lung cancer [11]. Prolonged daily administration of low-dose oral etoposide (50 mg/m^2 per day for 21 consecutive days) has been demonstrated in a phase I study to be relatively safe [3], and subsequent phase II studies have confirmed the activity of this schedule (oral etoposide) in previously treated patients with metastatic small-cell lung [7], testicular [7], breast [8], and ovarian cancers [5]. Hainsworth et al. [4] investigated oral etoposide in refractory lymphoma and observed partial responses in 15/25 patients (60%), including 5/9 individuals who had previously been treated with i.v. etoposide.

Additional studies are required to confirm the activity of oral etoposide in refractory lymphoma, as patient selection can significantly influence the results. Furthermore, i.v. etoposide is often used in front-line and salvage regimens in lymphoma and, therefore, it is important to confirm the activity of the oral regimen following prior exposure to standard etoposide-containing i.v. regimens.

At our center, lymphoma patients who develop refractory or relapsing disease following Adriamycin-containing chemotherapy are routinely treated with a salvage combination of dexamethasone, etoposide, ifosfamide, and cisplatin (DVIP) [2] or a similar combination containing i.v. arabinofuranosylcytosine (Ara-C) instead of etoposide (DAIP). The latter combination was given to some patients who had received prior i.v. etoposide.

In this phase II study we evaluated the activity of oral etoposide in lymphoma as the next line after DVIP or DAIP, i.e., following prior therapy that included Adriamycin, ifosfamide, cisplatin, and i.v. etoposide, in all patients.

Patients and methods

The DVIP combination [2] has been used at our center since November 1989 as a standard salvage therapy for patients with refractory or relapsing non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) who have received previous therapy including Adriamycin. Since March 1992, DAIP instead of DVIP has been given to lymphoma patients who develop progressive disease following prior therapy including both Adriamycin and i.v. etoposide. Other eligibility criteria include: (1) a WHO performance status of 0–2, (2) normal serum creatinine and bilirubin levels, (3) an interval of ≥3 weeks from the last chemotherapy, and (4) a WBC of ≥4,000/mm^3 and a platelet count of ≥100,000/mm^3.

Baseline staging procedures were carried out as indicated for evaluation of response. These included a chest X-ray in all patients and computerized tomography of the chest, abdomen, and pelvis and a gallium 67 scan in most patients.

Etoposide was given in a fixed oral daily dose of 100 mg over 3 weeks. The weekly dose was selected such that the mean daily dose given during the cycle was approximately 50 mg/m^2. For example, if a patient was to receive 90 mg per day, six daily doses of 100 mg were given per week. Complete blood counts were performed weekly, and etoposide was discontinued if the WBC count was <2,000/mm^3 and/or the platelet count was <75,000/mm^3. Cycles were repeated on day 29 if the WBC count was ≥4,000/mm^3 and/or the platelet count was ≥100,000/mm^3. The dose was reduced by 25% in subsequent cycles if the nadir WBC count was <1,000/mm^3 and/or the nadir platelet count was <50,000/mm^3 or if discontinuation of etoposide before the end of the cycle was required due to myelotoxicity. Responding patients received two cycles after a maximal response had been documented but were given no less than six cycles unless disease progression or unacceptable toxicity had occurred or unless consolidation with high-dose chemotherapy and autologous bone marrow transplantation was planned.

WHO response and toxicity criteria were used [9]. Survival analysis was performed using the method of Kaplan and Meier [6]. Survival was determined from the onset of therapy. The response duration was measured from the date on which a partial response (PR) or complete response (CR) was first documented. The time to tumor progression was defined as the period ranging from the date of the start of treatment to the date of progression. Response was usually assessed after the second cycle.

Results

Between February 1992 and July 1994, 26 patients were entered into the study. The patients' characteristics are shown in Table 1 and details of prior therapy are given in Table 2. The numbers of responding patients in various subgroups are also shown in Tables 1 and 2. Most of the patients (58%) had histologically aggressive NHL, and half had received three or more chemotherapy regimens in the past. Prior Adriamycin-containing regimens were CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone, 12 patients), ProMECE/MOPP (prednisone, methotrexate, calcium leucovorin, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine, 7), MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, 6), and MACOP-B (methotrexate, calcium leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin, 1 patient). The last chemotherapy regimen was DVIP in 21 patients and DAIP in 5. The cumulative dose of prior i.v. etoposide ranged between 180 and 2,400 mg/m^2 (median, 558 mg/m^2).

Table 1 Characteristics of 26 lymphoma patients treated with oral etoposide and the response to etoposide according to patients' characteristics[a] (*LDH* Lactic dehydrogenase)

Characteristic		Number of patients	Number of responders
Sex (M/F)		12/14	
Median age (range): 50 (18–75) years			
WHO performance status:			
	0 + 1	11	7
	2	15	9
Histology:			
	Hodgkin's disease	6	3
	Low-grade NHL	5	3
	Intermediate and high-grade NHL	15	10
Extranodal involvement:			
	Yes	18	10
	No	8	6
"B" symptoms:			
	Present	12	7
	Absent	14	9
Maximal diameter:			
	≥10 cm	5	3
	<10 cm	21	13
Serum LDH:			
	Elevated	11	6
	Normal	15	10

[a] The Working Formulation classification was used for NHL. Intermediate-grade histological subtypes included diffuse, large-cell (6 patients) and diffuse, mixed small- and large-cell (3 patients). The high-grade subtype was large-cell immunoblastic (6 patients)

The number of oral etoposide cycles given varied from 1 to 8 (median, 2). The planned weekly dose ranged between 500 and 700 mg (median, 600 mg). Therapy was continued until disease progression was seen in 20 patients. Treatment was stopped after three cycles in a patient who achieved a PR but developed severe and prolonged myelotoxicity. In the remaining five patients, treatment was discontinued after a maximal response had been documented.

All patients were evaluable for response and toxicity. Objective responses were observed in 16 patients (62%; 95% confidence interval, 42%–80%) and included CRs in 3 patients (12%) and PRs in 13 (50%). Rapid symptomatic relief was noted in all the nine responders who had been symptomatic prior to the onset of therapy. The duration of PRs ranged from 1 to 11+ months (median, 3 months). CRs continue as 20+ months in a patient with aggressive NHL and lasted for 15 months in the second complete responder with aggressive NHL. A CR was recorded in a patient with HD at 3 months after the beginning of etoposide treatment; 1 month later this patient underwent consolidation with high-dose chemotherapy with autologous bone marrow transplantation. The CR continues in this patient at 12+ months (i.e., 15 months after the initiation of oral etoposide). The median time to tumor progression for nonresponders, responders, and the entire group was 3 weeks, 4 months, and 2.5 months, respectively. The median survival duration was 12 months for the entire group and 4 months

Table 2 Characteristics of prior therapy in 26 lymphoma patients treated with oral etoposide and the response to etoposide according to prior treatment characteristics

Characteristic	Number of patients	Number of responders
Number of previous regimens:		
2	13	9
3	10	5
>3	3	2
Prior radiation therapy:		
Yes	14	7
No	12	9
CR to last chemotherapy:		
Yes	7	5
No	19	11
Response to prior i.v. etoposide-containing combination:		
Yes	18	12
No	8	4
Median interval from last chemotherapy (range): 1.5 (1–36) months		

for nonresponders; the median survival time for responders cannot yet be evaluated. The overall actuarial survival for the entire group was 40% at 2 years.

The number of patients was too small to allow firm conclusions to be drawn regarding a correlation between the response to treatment and various prognostic factors (Tables 1, 2). It is noteworthy, however, that a CR to oral etoposide was seen in 3/7 patients who had achieved a CR to their last chemotherapy versus 0/19 patients who had failed to achieve a CR. The efficacy of oral etoposide in disease refractory to i.v. etoposide-containing regimens could be evaluated in ten patients who had disease progression within 1 month of the last DVIP treatment. Five of these patients responded to oral etoposide with PRs lasting for 1–3 months (median, 1.5 months).

The main toxicity encountered was myelosuppression (Table 3). Nadir counts were observed between days 11 and 32 (median, 22 days). WHO grade 3 or 4 leukopenia developed in 8 patients (31%) and WHO grade 3 or 4 thrombocytopenia developed in 3 patients (12%). Only 5/81 cycles (6%) were associated with neutropenic fever. Due to myelosuppression, the first cycle was not completed in 6 patients (23%), and dose reduction during the second cycle was required in 4/20 patients (20%) who had received two cycles or more. The median interval between the first two cycles was 33 days (range, 28–50 days), and most of the delays were due to myelosuppression.

Table 3 Myelotoxicity of oral etoposide: 81 courses given to 26 patients

Median nadir counts:	
WBC/mm^3	2,700
Platelets/mm^3	105,000
Hemoglobin (g/dl)	9.8
Leukopenia (number of patients):	
WHO grade 3	5 (19%)
WHO grade 4	3 (12%)
Thrombocytopenia (number of patients):	
WHO grade 3	1 (4%)
WHO grade 4	2 (8%)
Hospitalization due to granulocytopenic fever (number of courses):	5 (6%)
Platelet transfusions (number of courses):	1 (1%)
Red blood cell transfusions (number of patients):	7 (27%)

Nonhematological side effects encountered (WHO grades 2 and 3) included nausea and vomiting in 5 patients (19%), mucositis in 9 (35%), and alopecia in 15/18 (83%). Alopecia was nonevaluable in eight patients due to preexisting alopecia from previous chemotherapy. There was no drug-related death.

Discussion

As compared with the patients included in the series of Hainsworth et al. [4], our patients were more selective regarding prior therapy. In the former series, patients had to have received at least one previous chemotherapy regimen. The type of prior therapy was not specified by the authors, but only 9/25 patients had received previous i.v. etoposide. On the other hand, the patients included in the current series had received at least two previous combinations, including an Adriamycin-based regimen and an ifosfamide-/cisplatin-containing salvage combination. Furthermore, all the patients had previously been exposed to i.v. etoposide. The objective response of 16/24 patients (62%), including CRs in 3/26 (12%), observed in the current series is similar to that reported by Hainsworth et al. [4] and confirms the activity of oral etoposide in lymphoma even after previous exposure to active front-line and salvage regimens.

Although durable CRs were observed in patients who had responded with CRs to their last chemotherapy, the activity of oral etoposide as observed in the current study was modest in general as compared with that of other salvage regimens in lymphoma [1]. It should be noted, however, that the effectiveness of salvage therapy in lymphoma depends on the extent of prior therapy and, therefore, a better response to oral etoposide can be anticipated in less heavily pretreated patients.

Although all our patients had previously been exposed to i.v. etoposide, our data do not prove the superiority of the oral schedule over the i.v. schedule, as most of the patients had responded to prior i.v. etoposide and may have responded again to etoposide given on a standard i.v. schedule. In addition, the PRs noted in 5/10 patients with disease that was clearly resistant to an i.v. etoposide-containing regimen may have been attributable to the higher dose intensity of etoposide given on the oral schedule (263 mg/m^2 per week versus 100 mg/m^2 per week in the DVIP combination).

As observed in other studies of oral etoposide [3–5, 7, 8], myelosuppression, especially leukopenia, was the major

toxicity of oral etoposide in the present study. Bone marrow suppression, however, was reversible and there was no drug-related death. Furthermore, hospitalization due to treatment complications was required in only 6% of all courses of therapy.

In conclusion, oral etoposide is an effective and tolerable palliative treatment for heavily pretreated lymphoma patients. These results, obtained in a poor-risk group of lymphoma patients, are encouraging and warrant further investigation of this schedule of etoposide given alone or in combination in patients with lymphoma.

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