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Oral Etoposide in Lymphoma

F. Anthony Greco

Sarah Cannon Cancer Center, Centennial Medical Center, Nashville,Tennessee, USA

Abstract

Etoposide is one of the most active agents for the therapy of lymphomas. Oral etoposide has proven to be active in and clearly beneficial for patients with previously treated lymphomas. The optimal dose and schedule of oral etoposide for use in combination chemotherapy are still uncertain, but low daily doses (50 to 100mg) for 10 to 14 days may be near optimal. Studies in previously untreated patients using combination chemotherapy that includes oral etoposide are needed, since preliminary data suggest that this agent has excellent activity and tolerability when combined or alternated with methotrexate, calcium folinate (calcium leucovorin), cyclophosphamide, vincristine, and prednisone in the elderly and medically unfit patient. Combination therapy approaches may also be helpful in HIV-related lymphomas. Additional studies are warranted.

Etoposide is one of the most active drugs for the treatment of patients with lymphoma.[1] However, with a few exceptions, etoposide has not been widely administered as a part of initial combination chemotherapy. Etoposide has gained a prominent role as a component of secondary or salvage therapy, both in standard dose combination chemotherapy and high dose stem cell transplantation regimens. Most patients initially receive cyclophosphamide and doxorubicin as components of combination chemotherapy in a cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) regimen or as a modified variation. Oral etoposide has only rarely been used in refractory or medically unfit patients or the elderly.[2-4]

Since etoposide is very active and can be combined with many other agents, it has the potential to become even more important in the treatment of lymphoma. The development of prolonged schedules using low daily doses of oral etoposide has encouraged its use in lymphomas. The impressive schedule dependency seen in small cell lung cancer and germ cell tumours is likely to be as profound in lymphomas.

We have investigated the use of oral etoposide as a single agent in previously treated patients with lymphoma and as an integral component of initial combination chemotherapy for elderly and unfit patients. This review will discuss these and other related issues.

1. Single Agent Phase II Study in Refractory Lymphoma

The first prolonged oral etoposide schedule developed in a phase II study used doses of 50 mg/m^2 daily for 21 days.[5] These results have been previously published.[2]

25 patients with refractory lymphoma were treated. Patient characteristics are detailed in table I. All patients with intermediate or high grade histological findings and with Hodgkin's disease were considered incurable, having relapsed after receiving at least one previous multidrug regimen. All patients with indolent non-Hodgkin's lymphoma (NHL) had received at least one prior

Table I. Patient characteristics[a] in a phase II study of prolonged oral etoposide in refractory lymphoma[5]

Characteristics	No. of patients (n = 25)
Gender (male/female)	9/16
Histology	
intermediate/high grade NHL	10
low grade NHL	13
Hodgkin's disease	2
No. previous regimens	
1	4
2	7
3	12
≥4	2

a Median age, 67 years (range, 31 to 82 years).

NHL = non-Hodgkin's lymphoma.

chemotherapy regimen. Nine patients had received previous intravenous etoposide as part of a combination regimen. All patients had measurable disease; responses were assessed using standard criteria. Patients received two 21-day courses of oral etoposide before their responses were evaluated. The average daily dose for each individual patient could only be approximated, since etoposide was available only in 50mg capsules. For example, if a patient required 85 mg/day, the drug was administered at 100, 100, and 50mg on 3 consecutive days, and this schedule was repeated for 21 days (average daily dose, 83mg).

Overall, 15 patients (60%; 95% confidence interval, 41 to 77%) had a partial response to oral etoposide. One patient, classified as a partial responder in our original report, subsequently became a complete responder. This patient, who was lost to follow-up, remained disease-free for 50 months after beginning the treatment. Five of 9 patients who had previously received etoposide had partial responses. Median time to disease progression was 5 months (range, 2 to >26 months).

The clinical characteristics and treatment results in patients with low grade and higher grade lymphomas are compared in table II. Clinical characteristics of the 2 groups were similar. The median age of the group with aggressive NHL was relatively old (68 years). Most of the younger patients with intermediate or high grade lymphomas were included in trials using high dose salvage therapy. Oral etoposide was active in both indolent and aggressive lymphomas (67 and 50% overall responses, respectively). However, the median response duration was longer in the indolent group (8 *vs* 3 months). Two patients with Hodgkin's disease, one of whom had a partial response, were included in the low grade group.

Treatment-related toxicity was similar to that reported for other groups of previously treated patients receiving this dose and schedule.[6] Although myelosuppression was severe in 7 patients [white blood cell count (WBC) nadirs $<1.0 \times 10^9$/L], 14 of 25 patients maintained WBCs $>2.0 \times 10^9$/L. Most patients who experienced severe myelosuppression were able to tolerate subsequent courses using 75% of the original dose. All patients developed total alopecia; other adverse effects, however, were unusual.

The overall response rate of 60% in this small study was encouraging and appeared higher than reported for refractory patients receiving single agent intravenous etoposide.[7,8] However, definitive conclusions regarding the comparative efficacy of intravenous and oral etoposide schedules cannot be made from comparisons of studies that may have varied with respect to patient selection and characteristics. In previously treated patients, it is unlikely that this oral etoposide schedule could be safely used with other myelosuppressive agents. Single agent therapy, however, is often appropriate for patients with indolent NHL. This schedule is convenient and well tolerated by most patients. Others have also confirmed these good response rates in patients with lymphoma.[9-11] Although the short duration of response in patients with aggressive NHL limits the usefulness of etoposide in single agent salvage therapy, incorporation of etoposide into a multi-agent first-line regimen may improve the efficacy of initial therapy.

While the high response rate obtained with long term oral etoposide in patients with refractory lymphoma is impressive, it does not prove the

Table II. Clinical characteristics and treatment results: low grade versus intermediate/high grade non-Hodgkin's lymphoma (NHL)[5]

Characteristics	Low grade NHL + Hodgkin's disease (n = 15)	Intermediate and high grade NHL (n = 10)
Mean no. of previous regimens	2.6	2.3
Median age (years)	67	68
Patients with progressive lymphoma while receiving previous regimen (%)	62	70
Median interval, most recent treatment to study entry (months)	4	1
Overall response rate (%)	67	50
Median response duration (months)	8	3

superiority of this schedule. The achievement of responses in patients previously treated with intravenous etoposide suggests a difference in efficacy between the 2 schedules. Most of the patients who received long term oral etoposide, however, did not start therapy immediately after disease progression while receiving intravenous etoposide. These patients may not actually be refractory to intravenous etoposide, and may have responded equally well to re-treatment with intravenous etoposide.

Two patients demonstrated a response to the extended schedule immediately after progression on the standard 3-day schedule. These patients responded to the 21-day schedule after definitive disease progression with an etoposide-containing combination regimen. In both of these patients, long term oral etoposide produced remissions immediately after they had demonstrated resistance to, and progression with, combination regimens containing standard (or higher) doses of intravenous etoposide given over a 3-day schedule. These results support the superiority of the long term oral schedule compared with the standard dose and schedule.

2. Phase II Study of a Long Term Oral Etoposide-Containing Combination Regimen for Elderly or Unfit Patients with Aggressive NHL

Combination chemotherapy in elderly and unfit patients with intermediate or high grade NHL remains inferior, with most investigators reporting cure rates of less than 30%.[12] Many trials in aggressive lymphoma excluded patients aged more than 65 years. The disappointing results are due, at least in part, to the difficulty of administering standard combination regimens to patients in this age group. We therefore conducted a phase II study to evaluate the tolerability and efficacy of a long term oral etoposide-containing combination regimen in this patient population. These results have been reported previously.[4]

In this study, combination chemotherapy was used, with the following modifications specific to patients who were elderly or who had severe coexistent medical illnesses: (i) short duration of treatment; (ii) avoidance of agents known to be poorly tolerated by elderly patients; and (iii) incorporation of a low dose, long term schedule of oral etoposide.

Considered for this study were all patients with intermediate or high grade NHL who were older than 65 years or who had severe coexisting medical problems precluding treatment with standard regimens. Other eligibility requirements included the following: (i) stage II, III, or IV disease; and (ii) no previous chemotherapy. Performance status was not used as a criterion for patient exclusion. 31 patients were treated.

The design of the 15-week chemotherapy regimen is shown in table III. Blood cell counts were measured weekly during oral administration of etoposide. The etoposide dose was decreased by 50% if the total WBC was 2 to 3×10^9/L and was stopped if the WBC was $<2 \times 10^9$/L. 75% of the original dose of etoposide was administered during the second course for patients who required its pre-

Table III. A 15-week combination regimen[a] for the treatment of elderly or unfit patients with aggressive non-Hodgkin's lymphoma[4]

Agent + dose	Week									
	1	2	3	4	5	6	7	8	9	9
50 mg/m^2 etoposide orally per day	→	→	→							
40 mg/m^2 methotrexate IV (with folinic acid rescue)	X	X								
60mg prednisone orally per day	→					→				
500 mg/m^2 cyclophosphamide IV						X				
12 mg/m^2 mitoxantrone IV						X				
1 mg/m^2 vincristine IV						X				

a Schedule repeated once starting week 9.

IV = intravenous; → = for 1 week; **X** = single dose.

mature discontinuation during the first course or who developed fever as a result of neutropenia. Cyclophosphamide, mitoxantrone, vincristine, and prednisone were administered at full dose. These drugs were delayed 1 week if the WBC was <2 $\times 10^9$/L on day 35.

Patients were evaluated after completion of treatment, and were categorised by treatment response according to standard criteria. Standard guidelines were used to assess toxicity.[13]

Patient characteristics are illustrated in table IV. The median age of the patients was 71 years, and 12 patients (39%) were aged ≥75 years. 24 patients (77%) had one or more than one characteristic generally considered indicative of a poor prognosis. 26 patients (84%) had one or more than one severe coexisting medical problem, including cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, chronic renal insufficiency, or history of malignancies.

28 of 31 patients completed the 15-week course of treatment and were evaluable for response and toxicity. Three patients discontinued therapy during the first 10 days: 2 patients were unable to swallow oral etoposide capsules, and one patient moved to another city. 18 patients (64%) who completed treatment achieved a complete response, and the remaining 10 patients (36%) had a partial response. One of the partial responders achieved a complete response following radiation therapy to a single residual radiographic mass.

Ten (56%) of the complete responders remained in continuous complete remission for a median of 28 months (range, 16 to 41 months). Two patients who had complications arising from pre-existing cardiovascular disease died at 13 and 26 months without evidence of relapse. The other 6 patients

Table IV. Patient characteristics[a] in a phase II study of a long term oral etoposide-containing combination regimen for elderly or unfit patients with aggressive non-Hodgkin's lymphoma (from Young et al.,[4] with permission of Oxford University Press)

Characteristic	No. (%) of patients
ECOG performance status	
0	3 (10)
1	14 (45)
2	8 (26)
3	6 (19)
Gender	
male	17 (55)
female	14 (45)
Stage	
II	12 (39)
III	4 (13)
IV	15 (48)
Histological type	
large, noncleaved cell	18 (58)
large, cleaved cell	8 (26)
immunoblastic sarcoma, B cell	2 (6)
peripheral T cell	2 (6)
small, noncleaved cell	1 (3)
Extranodal sites	
0-1	20 (64)
≥2	11 (35)
Tumour bulk >10cm	7 (23)
Fever, sweats or weight loss >10%	14 (45)
Elevated lactic dehydrogenase level (≥250 IU)	11 (35)

a n = 31; median age, 71 years (range, 59 to 84 years).

ECOG = Eastern Cooperative Oncology Group.

with complete remission relapsed at a median of 16 months (range, 2 to 24 months). Two of these patients achieved a second complete remission, and 1 of these 2 patients was treated again with the same regimen. 17 patients (10 with disease in first complete remission) remained alive. The progression-free survival for the entire group was 47% ± 10% (mean ± SE) at 28 months.

The 28 evaluable patients received a median of more than 90% of the planned treatment doses. Treatment was delayed in only 3 instances, when the administration of cyclophosphamide, mitoxantrone, vincristine, and prednisone was postponed for 1 week. No treatment-related deaths occurred. Eight patients required brief hospitalisations for treatment of fever related to neutropenia. The median WBC nadirs during courses 1 and 2 were 3.4×10^9/L and 2.8×10^9/L, respectively. No grade 4 thrombocytopenia occurred; 9 patients required red blood cell transfusions during therapy. Other than alopecia, nonhaematological toxic effects were mild except in one patient, who developed grade 4 mucositis in conjunction with neutropenia.

This combination regimen was feasible and relatively well tolerated in this group of patients. The complete response rate and the survival rate with this regimen in this small study may be superior to those with other reported regimens for this patient group.[12] Unlike other reported regimens,[12] however, this regimen resulted in mild to moderate myelosuppression and rarely required dose reductions. In addition, no treatment-related mortality occurred with this regimen, and other nonhaematological toxic effects were mild to moderate.

Definitive comparisons with other standard regimens cannot be made on the basis of this limited phase II study. However, because of the observed efficacy and limited toxicity, this regimen or modifications of it deserve continued evaluation in the treatment of elderly patients with large cell and other aggressive NHLs. This approach may also be particularly applicable to HIV-related lymphoma.[14]

3. Prolonged Administration of Low Dose Intravenous Etoposide in Lymphoma – Attempt to Define an Optimal Dose

Administration of 100mg of oral etoposide produces peak plasma concentrations of 1.8 to 3 mg/L.[15] Myelosuppression with etoposide appears to depend on peak etoposide serum concentrations, while antitumour effects are related to duration of tumour exposure to relatively low etoposide concentrations (about 1 mg/L). A study was carried out using a long term, low dose continuous infusion schedule as a method of avoiding high peak serum etoposide concentrations, and steady-state concentrations of etoposide were measured.[16] The objectives of this study were to determine an etoposide concentration necessary for cytotoxicity against sensitive neoplasms and to confirm our belief that this schedule is not myelosuppressive.

15 patients with etoposide-sensitive neoplasms, including 10 patients with NHL, were treated in this phase I/II study. Etoposide was mixed in saline (maximum concentration of 0.4 g/L) and was administered as a continuous infusion by a portable infusion pump. A dose of 25 mg/m^2/day was selected as the initial dose level, since this infusion rate should produce a constant serum etoposide concentration of 0.5 to 1.0 mg/L. A 21-day infusion was planned, followed by a 1-week rest period, similar to our experience with the long term oral etoposide schedule. We learned that infusions of more than 21 consecutive days were possible in most patients. Patients were subsequently treated continuously as long as their WBC remained $>2 \times 10^9$/L, platelet count $>75 \times 10^9$/L, and tumour progression was not evident. Those who developed myelotoxicity, necessitating an interruption of therapy, were usually restarted at 75% of the initial dose.

The median duration of therapy was 17 weeks (range, 3 to 80 weeks). The total dose administered ranged from 525 to 8838 mg/m^2 (median, 1620 mg/m^2). Myelosuppression was the major toxicity, but it was relatively mild in most patients. Two heavily pretreated patients developed grade 4 leu-

copenia after infusion durations of less than 28 days. Grade 4 leucopenia occurred in 2 other patients, but only after prolonged etoposide infusions (15 and 49 weeks). Many patients who tolerated prolonged infusions (greater than 28 days) developed moderate leucopenia (WBC 2 to 3×10^9/L), but they tolerated continuation of the infusion without further myelosuppression. Severe myelosuppression was seen during only 4 of a total of 353 weeks on therapy. The leucopenia resolved 2 to 8 days after discontinuation of therapy. Thrombocytopenia was rare (2 patients). Anaemia was seen in 14 patients, and 8 had haematocrits less than 25%. Mild mucositis occurred in 27% (4 patients), and was accompanied by myelosuppression in 2 patients. Alopecia was seen in all patients, but anorexia, nausea, and fatigue were mild.

Five of the 10 patients with NHL responded to long term infusional etoposide (4 partial responses and 1 complete response). Three patients with NHL had prolonged partial remissions (6, 11, and 18.5 months). Each of these patients had received at least one previous chemotherapy regimen (range, 1 to 4), and 2 had previously received intravenous etoposide given as a standard 3- to 5-day schedule. The mean serum etoposide concentration measured was 0.7 ± 0.4 mg/L during the infusion of 25 mg/m^2/day (range, 0.2 to 2.1 mg/L). This dose and schedule were active, as demonstrated by a high response rate in previously treated patients with NHL. The results of this study are consistent with the hypothesis that etoposide concentrations above a critical threshold (near 0.7 mg/L) are cytotoxic against lymphoma and that severe myelosuppression is rare with this schedule. These results support the use of low dose (50 to 100mg) daily etoposide for lymphoma. Although the optimal dose or schedule is not known, data from small cell lung cancer studies coupled with these data from the long term infusional study suggest an oral dose of 50 to 100mg per day for 10 to 14 days. This active dose/schedule will probably avoid severe myelosuppression in most patients. However, patients surviving long term may be at a small risk of secondary leukaemia, a complication now recognised with etoposide.

4. Discussion

The schedule dependency of etoposide is clinically important. The added efficacy of the optimal schedule will most probably be seen in tumours sensitive to the drug, such as lymphomas. Increasing evidence suggests that long term schedules of oral etoposide have increased efficacy when compared with the standard intravenous dose and schedules. Single agent oral etoposide represents an additional option for the treatment of low grade lymphomas. The contribution, if any, of long term oral etoposide-containing combination chemotherapy in patients with lymphomas remains to be firmly established. We are close to identifying a dose and schedule that produce high activity with minimal or no myelosuppression. This dose is near 50 to 100mg orally per day. The 21-day schedule is more toxic than a shorter (10- to 14-day) schedule and does not appear to offer any therapeutic advantage. Long term oral etoposide should be incorporated into study protocols for the treatment of patients with large cell and high grade lymphomas.

Several etoposide-containing regimens that occasionally included oral etoposide have been used for elderly patients with aggressive lymphomas. One of these included oral etoposide for 5 days, mitoxantrone, and prednimustine (VMP), and was inferior to the standard CHOP regimen in good-performance-status patients.[12] CHOP currently represents the standard regimen, but the long term survival rate is no greater than 30%. The appropriate dose and schedule of etoposide used in combination chemotherapy may therefore prove to be superior to CHOP. Further study is necessary, not only in the elderly, but also in patients with aggressive lymphomas.

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Correspondence and reprints: Dr *F. Anthony Greco,* Sarah Cannon Cancer Center, 250 25th Avenue, North Suite 412, Nashville, TN 37203-1632, USA.