Prednisone, Etoposide, Procarbazine, and Cyclophosphamide (PEP-C) Oral Combination Chemotherapy Regimen for Recurring/Refractory Lymphoma: Low-Dose Metronomic, Multidrug Therapy

Morton Coleman, MD
Peter Martin, MD
Jia Ruan, MD
Richard Furman, MD
Ruben Niesvizky, MD
Rebecca Elstrom, MD
Patricia George, MD
Thomas P. Kaufman, MD
John P. Leonard, MD

Center for Lymphoma and Myeloma, Division of Hematology-Oncology, Department of Medicine, Weill Cornell Medical College, and the New York Presbyterian Hospital, New York, New York.

Supported by the Fund for Blood and Cancer Research, a Terry Fox fellowship from the National Cancer Institute of Canada, the Lymphoma Research Foundation, and the Lymphoma Foundation.

Address for reprints: Morton Coleman, Center for Lymphoma and Myeloma, Division of Hematology-Oncology, Department of Medicine, Weill Medical College of Cornell University, and the New York Presbyterian Hospital, 407 East 70th St., New York, NY 10021; Fax: (212) 734-9238; E-mail: mortoncolemanmd@aol.com

Received October 19, 2007; revision received December 14, 2007; accepted December 19, 2007.

BACKGROUND. Many patients with recurrent lymphoma are unable to tolerate intensive therapies, or have disease that is refractory. Metronomic chemotherapy offers a novel, potentially less toxic yet effective treatment strategy.

METHODS. An analysis was performed on 75 lymphoma patients who were treated with the PEP-C regimen at a single institution. The program consisted of oral prednisone 20 mg after breakfast, cyclophosphamide 50 mg after lunch, etoposide 50 mg after dinner, and procarbazine 50 mg at bedtime with an oral antiemetic. All medications were administered daily until the white blood cell count fell to less than 3.0×10^9/L, whereupon treatment was withheld until recovery from the nadir. Therapy was then reinstituted on a daily, alternate day, or fractionated weekly basis (eg, 5 of 7 days), depending on patient tolerance. Doses given per day were held constant.

RESULTS. Eighty percent of patients had previously received 2 or more treatments. Overall, 69% achieved an objective response after PEP-C treatment, with 36% complete responses and 33% partial responses. Subjects with indolent histologies had superior overall responses, complete responses, and time on therapy relative to those with aggressive histologies. The regimen was generally well tolerated.

CONCLUSIONS. Metronomic therapy with low-dose oral agents administered in combination for continuous, prolonged periods with minimal drug-free intervals represents a novel, active, easily tolerated approach to management of patients with recurrent lymphoma, particularly those with indolent histologies. ***Cancer*** **2008;112:2228–32.** © *2008 American Cancer Society.*

KEYWORDS: lymphoma, metronomic therapy, oral chemotherapy, chemotherapy, low-dose chemotherapy, oral combinational chemotherapy.

Although lymphoma therapy has become increasingly more effective with the use of combination regimens, and more recently, the advent of monoclonal antibodies, many patients still face recurrent or refractory disease after initial chemotherapy.[1–6] Depending on the clinical setting, these individuals may ultimately receive alternative approaches, including other combination chemotherapies, continuous intravenous infusions designed to override drug resistance, novel agents, and/or high-dose chemotherapy with stem cell transplantation or pharmacologic rescue.[2,3,7–9] In some situations these techniques may deliver prolonged remissions or cures; however, for many there remains a need for additional treatment. Such strategies, which in 1 form or another may be largely palliative, ide-

DOI 10.1002/cncr.23422
Published online 13 March 2008 in Wiley InterScience (www.interscience.wiley.com).

ally, if not of necessity, should be simple to use, not require intravenous administration, and allow outpatient administration.

With these needs in mind, over the past 16 years the prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) (C3) treatment program was initiated.[10–13] It consists of a combination of chemotherapies, all active in lymphoma, and commercially available in oral formulation. The drugs used as single agents have been associated with response rates from 17% to 60%.[1,14] We report herein a retrospective analysis of our experience with PEP-C, which is an active and well-tolerated treatment option in many settings, with several distinctive possible mechanisms of action.

MATERIALS AND METHODS

Patients

Patients with recurring lymphoma receiving the PEP-C regimen at the Center for Lymphoma and Myeloma, Weill Cornell Medical College were identified through a retrospective chart review. All patients were evaluated and/or had pathology reviewed at the New York Presbyterian Hospital, Weill Cornell Medical Center.

Treatment Schema

Patients were treated with the following oral medications: prednisone 20 mg after breakfast (morning dose); cyclophosphamide 50 mg after lunch (afternoon dose); etoposide 50 mg after dinner (evening dose), and procarbazine 50 mg at bedtime (night dose) with an antiemetic, ondansetron. All medications were administered on a daily basis until the leukocyte count declined to less than 3.0×10^9/L, whereupon treatment was held until recovery from the nadir. The median duration of this 'induction' phase was 3 weeks (range, 2 weeks to 2 months). The subsequent holding of treatment commonly occurred for 2–3 weeks, although these time periods varied among patients based on the blood counts. After the leukocyte count returned to greater than 3.0×10^9/L, patients entered onto a 'maintenance' phase. During the maintenance phase the dosing frequency (ie, the number of days per week) was altered (variably from daily, 5 of 7 days, every other day, twice weekly, or once weekly) as it was titrated to maintain a white blood cell count (WBC) of at least 3.0×10^9/L. Medications and doses given per day were held constant; only the number of days per week was altered.

Response Evaluation

Patient charts were reviewed for predefined clinical information including prior therapies and responses, duration of PEP-C treatment, response to PEP-C, and resulting toxicity. Because some patients were arbitrarily removed from PEP-C for other therapies, and not necessarily for treatment failure or toxicity, data reflect time on therapy (TOT) rather than progression-free, failure-free, or event-free survival. Consistent with standard criteria, all patients labeled herein as complete responders had computed tomography (CT)-confirmed complete resolution of all nodal/tissue masses.[15] Not all complete clinical/radiologic responses, however, were confirmed with bone marrow biopsy. For the purposes of this report, complete radiologic responses were considered complete responses to distinguish them from those patients who achieved only partial response. Toxicity was graded according to the National Cancer Institute CTCAE v. 3.0 criteria.[16] The maximum event occurring during any course of chemotherapy was scored. We defined 'chemosensitive' patients as those who achieved a complete response with their last therapy and 'chemoresistant' patients as those who had less than a complete response with their last therapy.

TABLE 1
Baseline Patient Characteristics

Patient characteristics	No.	%
Total	75	100
Chemosensitive to last therapy	40	53
Chemoresistant to last therapy	35	47
1 prior treatment	11	20
2 prior treatment	19	23
3 or more treatments	45	57
Age, y >60 to ≤60	43/32	57/43

RESULTS

Patients

Ninety-seven patients with lymphoma who had received treatment with the PEP-C (C3) oral combination chemotherapy regimen were identified. Of the 97 patients treated, 22 had mantle cell lymphoma and have been previously reported.[17] The characteristics of the 75 remaining patients reported herein are shown in Table 1. Of these patients, 80% had received 2 or more prior therapies, almost half (47%) were 'chemoresistant' or refractory to last treatment and the majority (57%) were older than 60 years.

Overall Responses

Of the 75 patients treated, 69% achieved an objective response (OR) with 36% complete response (CR) and 33% partial responses (Table 2). Compared with patients with chemoresistant disease, patients with

TABLE 2
Treatment Results by Baseline Clinical Characteristics

Clinical characteristics	Total no. of patients	OR no. of patients	CR no. of patients	PR no. of patients
Overall	75	51	26	25
Chemosensitive to last therapy	40	31	17	14
Chemoresistant to last therapy	35	20	9	11
Age >60 y	43	26	12	14
Age <60 y	32	25	14	11

OR indicates overall response; CR, complete response; PR, partial response.

TABLE 3
Treatment Results by Lymphoma Subtype

Subtype	Total no. of patients	OR no. of patients	CR no. of patients	PR no. of patients
Overall	75	51	26	25
Follicular	26	23	14	9
Marginal zone	14	10	5	5
Small lymphocytic	12	8	2	6
Hodgkin	9	4	2	2
Diffuse large cell	9	3	2	1
T-cell	5	3	1	2

OR indicates overall response; CR, complete response; PR, partial response.

chemosensitive disease had a higher proportion of OR and CR, although neither of these differences achieved statistical significance (OR: 78% vs 57%, $P = .083$; and CR: 45% vs 26%, $P = .150$; 2-sided Fisher exact test with $\alpha = .05$). Patients younger than 60 years of age also tended to respond better than older patients (OR: 78% vs 60%, and CR: 44% vs 28%). There was no difference in OR rate among those who received 1 prior therapy (73%), 2 prior therapies (68%), or 3 or more prior therapies (67%).

Response by Subtype

Response by subtype is shown in Table 3. In general, patients with indolent histologies had superior rates of OR and CR. Patients with follicular lymphoma (FL) had the highest response rate (88% OR, 54% CR) followed by marginal zone lymphoma (MZL) (71% OR, 36% CR), and small lymphocytic lymphoma (SLL/CLL) (67% OR, 17% CR). More aggressive histologies such as Hodgkin lymphoma (HL), large-cell lymphoma (LCL), and T-cell lymphoma (TCL) responded, but often to a lesser degree (HL OR 44%, LCL OR 33%, TCL OR 60%).

TABLE 4
Reason for Discontinuation of Therapy

Reason	No. of patients
Primary resistance	24
Relapse	17
On therapy	8
Alternative therapy	16
Toxicity	10

TABLE 5
Toxicity

Toxicity	Grade 1–2 no. of patients	Grade 3–4 + No. of patients
Infection (including herpes zoster)	7 (4)	8
Gastrointestinal	8	4
Endocrine	8	2
Anemia	18	2
Thrombocytopenia	20	8
Hematuria	2	0

Time on Therapy (TOT)/Discontinuation of Treatment

TOT in responding patients ranged from 3 weeks to 48 months (median, 10 months; mean, 13+ months). Patients with indolent lymphomas and those who achieved a complete remission remained on therapy considerably longer than those with aggressive histologies or those reaching a partial response (indolent lymphoma mean, 16 months; CR mean, 17 months; aggressive histologies mean, 5 months; PR mean, 6 months). This may reflect not only the success of therapy in indolent lymphoma but also the tendency to use alternative strategies earlier and more frequently in patients with aggressive histologies and those faring less well.

Reasons for discontinuation of PEP-C therapy are shown in Table 4. Almost as many patients were removed from therapy because of alternative choices as actually recurring (16 vs 17). Ten patients discontinued PEP-C primarily for toxicity.

Toxicity

Because a reduction in the WBC was considered an 'endpoint' of induction, it was not considered as an adverse reaction per se. Myelosuppression did occur, sometimes for weeks, usually in heavily pretreated patients. Nonetheless, infections requiring hospitalization occurred in only 8 patients (Table 5). There were 4 instances of herpes zoster. Gastrointestinal complaints, usually nausea and vomiting, prompted 4 patients to withdraw from treatment. Anemia and

thrombocytopenia less than 100×10^{12}/L were generally mild and easily managed. Hematuria occurred in 2 patients.

DISCUSSION

Based on our experience with continuous infusions of combination chemotherapy in lymphoma, putatively to override drug resistance mediated by the MDR-1 gene-associated P-glycoprotein pump, the PEP-C program was initiated to deliver continuous combination chemotherapy in a more convenient mode, by daily oral administration.[18,19] Given the vagaries of intestinal absorption, and the half-life of the 4 oral medications, any true overlapping chemotherapeutic effects in the combination would be probably expected to be minimal. More likely, there would be a continuous sequential impact of drugs with different mechanisms of action on cells, both malignant and normal. Stem are reportedly higher in MDR-1 gene expression to protect from toxic assault.[19] Indeed, myelosuppression was encountered with the PEP-C regimen, despite low doses, suggesting that the P-glycoprotein pump protective mechanism may have been abrogated whether expressed in normal or malignant stem cells. Myelosuppression with PEP-C, however, was moderate and reasonably well tolerated considering the heavy pretreatment of most patients, including 10 who had undergone prior autologous stem cell transplantation.

Since we initiated our program over the last 16 years, Kerbel et al.[20] have advanced the concept of low-dose metronomic (LDM) chemotherapy, which is the close, regular administration of low-dose cytotoxic drugs over prolonged periods with minimal or no drug-free breaks. They have shown experimentally that LDM chemotherapy may not only be effective, but may also be less toxic than maximally tolerated cytoxic therapy.[21–23]

A major mechanism of action of LDM therapy may be antiangiogenesis, as shown in experimental models.[24,25] Tumor vasculature, in fact, has emerged as a clinically validated therapeutic target in various malignancies, including lymphoma. In addition to rationally designed molecularly targeted angiogenic drugs, such as anti-vascular endothelial growth factor (anti-VEGF) antibodies, many conventional therapeutic agents, such as in PEP-C, may have angiogenic effects that may be optimized by an LDM approach.[25] Kerbel et al. have shown experimentally that the P-glycoprotein-mediated resistance may be overcome by using LDM single-agent chemotherapy in combination with an anti-VEGF antibody, whereas single-agent chemotherapy alone was not effective. It is not clear, however, whether it was a combination of different modality agents (chemotherapy, antibody) or simply combinations of any effective agents, ie, 2 or more chemotherapies, as in PEP-C, that are necessary.

Therapy with putative antiangiogenic effects has recently been employed in lymphoma. A combination of thalidomide and rituximab has been reported effective in recurring mantle cell lymphoma.[26] Thalidomide is thought to target tumor vasculature, whereas rituximab may have both direct and indirect effects on lymphoma apoptosis. The use of thalidomide here was to impede stromal interaction with lymphoma cells; however, considerable antitumor activity of thalidomide is thought to be mediated by antiangiogenesis.

Buchstein et al.[27] have given LDM chemotherapy (cyclophosphamide 50 mg every other day) with high-dose celecoxib to 35 heavily pretreated aggressive lymphoma patients, the majority with refractory large cell lymphoma. The combination produced a response rate of 37%, with 2 CRs (6%) and 9 PRs (31%). While the patient populations are small, the data are remarkably similar to our data using PEP-C in aggressive histologies, where 9 of 23 patients (39%) responded, with 4 CRs (17%) and 5 PRs (22%). Median overall and progression-free survivals of 14.4 months and 4.7 months are comparable to the TOT with PEP-C. In a similar approach, Shamash et al.[28] employed a low-dose continuous chemotherapy outpatient regimen, consisting of lomustine, chlorambucil, subcutaneous bleomycin, intravenous vincristine, and methotrexate with dexamethasone. This regimen produced 67% responses, with 21% CRs. Significant myelosuppression occurred with hospitalizations in 31% of patients. Regardless of whether this regimen constituted true low-dose therapy, significant responses were achieved, particularly with HL. As in our study, those patients with refractory disease did not fare as well as individuals with chemosensitive recurrence.

Both the oral PEP-C and the LDM therapy advocated by Kerbel et al. and others were remarkable for their tolerability. Not only are they well tolerated with relatively modest toxicity, but they represent an easily administered, effective treatment of lymphoid malignancies, particularly those with slower kinetic growth patterns. Our findings demonstrate that the administration of low-dose oral agents in combination for continuous, prolonged periods with minimal drug-free intervals (metronomic therapy) may represent a novel approach to the treatment of NHL and warrants further exploration.

REFERENCES

1. Pasmantier MW, Coleman M, Silver RT. Chemotherapy of the non-Hodgkins lymphoma. *Med Clin North Am*. 1976;60: 1043–1052.
2. Coleman M, Armitage JO, Gaynor M, et al. The COP-BLAM programs: evolving chemotherapy concepts in large cell lymphoma. *Semin Hematol*. 1988;25:2–10.
3. Yi PI, Coleman M, Saltz N, et al. Chemotherapy for large cell lymphoma: a status update. *Semin Oncol*. 1990;17:60–73.
4. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with 3 intensive chemotherapy regimens for advanced non-Hodgkins lymphoma. *N Engl J Med*. 1998;328:1002–1006.
5. Fisher RI. Overview of non-Hodgkins lymphoma and biology, staging, treatment. *Semin Oncol*. 2003;2(suppl 4):3–9.
6. Sehn LH, Donaldson J, Chanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B cell lymphoma in British Columbia. *J Clin Oncol*. 2005;23:5027–5033.
7. Turman S, Coleman M, Silver RT, Pasmantier M. High dose methotrexate with citrovoram factor in adult resistant lymphoma. *Cancer*. 1977;40:2823–2828.
8. Schuster MW. The refractory patient: new treatment options. *Oncology*. 2003;17:1333–1335.
9. O'Connor OA, Hamlin P. New drugs for the treatment of advanced-stage diffuse large cell lymphoma. *Semin Hematol*. 2006;43:251–256.
10. George P, Coleman M. The C3 regimen for resistant lymphoma: daily oral etoposide, chlorambucil, procarbazine, and prednisone [abstract]. *Proc Am Soc Clin Oncol*. 1993;12. Abstract 1292.
11. Coleman M, Leonard JP, Lee C, et al. The PEP-C (C3) oral combination chemotherapy regimen for refractory/relapsed lymphoma: daily prednisone, etoposide, procarbazine, and cyclophosphamide. *Blood*. 1999;94. Abstract 410-I.
12. Coleman M, Siegel M, Schuster M, et al. Oral combination chemotherapy with PEP-C (C3) for mantle cell lymphoma (MCL): daily prednisone, etoposide, procarbazine and cyclophosphamide. *Proc Am Soc Clin Oncol*. 2003;22. Abstract 2396.
13. Coleman M, Leonard JP, Furman RR, et al. Combination chemotherapy for refractory/relapsed lymphoma with the PEP-C (C3) regimen (daily prednisone, etoposide, procarbazine, cyclophosphamide: low dose continuous metronomic multidrug. *Proc Am Soc Clin Oncol*. 2006;25. Abstract 8064.
14. Hainsworth JD. Chronic administration of etoposide in the treatment of non-Hodgkins lymphoma. *Leuk Lymphoma*. 1993;10(suppl):65–72.
15. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas.NCI Sponsored International Workshop Group. *J Clin Oncol*. 1999;17:1244.
16. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available at: http://ctep.cancer.gov/forms/CTCAEv3.pdf Accessed June 23, 2007.
17. Coleman M, Martin P, Ruan J, et al. Low-dose metronomic, multidrug therapy with the PEP-C oral combination chemotherapy regimen for mantle cell lymphoma. *Leuk Lymphoma*. 2008;49:447–450.
18. Boyd DB, Coleman M, Papish SD, et al. COPBLAM III: infusional combination chemotherapy for diffuse large cell lymphoma. *J Clin Oncol*. 1988;6:425–433.
19. Hollister D, Silver RT, Gordon B, Coleman M. Continuous infusion vincristine and bleomycin with high dose methotrexate for resistant non-Hodgkin's lymphoma. *Cancer*. 1982;50:1690–1694.
20. Kerbel RS, Klement G, Pritchard KI, Kamen B. Continuous low dose anti-angiogenesis/metronomic chemotherapy: from the research laboratory into the oncology clinic. *Ann Oncol*. 2002;13:12–15.
21. Shaked Y, Emmenegger U, Francia G, et al. Low dose metronomic combined with intermittent bolus-dose cyclophosphamide is an effective long-term chemotherapy treatment strategy. *Cancer Res*. 2005;65:7045–7051.
22. Emmenegger U, Man S, Shaked Y, et al. A comparative analysis of low dose metronomic cyclophosphamide reveals absent or low grade toxicity on tissues highly sensitive to the toxic effects of maximum tolerated dose regimen. *Cancer Res*. 2004;64:3994–4000.
23. Man S, Bocce G, Francia G, et al. Antitumor effects in mice of low dose (metronomic) cyclophosphamide administered through the drinking water. *Cancer Res*. 2002;62:2731–2735.
24. Emmenger U, Morton GC, Francia G, et al. Low dose metronomic daily cyclophosphamide and weekly tirpazamine: a well tolerated combination regimen with enhanced efficacy that exploits tumor hypoxia. *Cancer Res*. 2006; 66:1664–1674.
25. Shaked Y, Emmengger U, Man S, et al. Optimal biologic dose of metronomic chemotherapy regimen is associated with maximum antiangiogenic activity. *Blood*. 2005;106: 3058–3061.
26. Kaufman H, Raderer M, Wohrer S, et al. Antitumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma. *Blood*. 2004;104:2269–2271.
27. Buchstein R, Kerbel RS, Shaked Y, et al. High dose celecoxib and metronomic "low dose" cyclophosphamide is an effective and safe therapy in patients with relapsed and refractory aggressive histology non-Hodgkin's lymphoma. *Clin Cancer Res*. 2006;12:5190–5198.
28. Shamash J, Walewski J, Apostolidis J, et al. Low-dose continuous chemotherapy (LBCMVD-56) for refractory and relapsing lymphoma. *Ann Oncol*. 2000;11:857–860.