

Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies

Ian W. Flinn, John C. Byrd, Candis Morrison, Janet Jamison, Louis F. Diehl, Timothy Murphy, Steve Piantadosi, Eric Seifter, Richard F. Ambinder, Georgia Vogelsang, and Michael R. Grever

To evaluate the response rate and potential toxicities, a phase II trial was conducted of fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated low-grade and select intermediate-grade lymphoid malignancies. Symptomatic patients with preserved end organ function received cyclophosphamide 600 mg/m² intravenous (iv) day 1 and fludarabine 20 mg/m² iv days 1 through 5, followed by filgrastim 5 μg/kg subcutaneous starting approximately day 8. Treatment was repeated every 28 days until maximum response or a maximum

of 6 cycles. Sixty patients, median age 53.5 years, were enrolled. Thirty-seven patients with non-Hodgkin lymphoma (NHL) were stage IV and 6 were stage III. Eleven of 17 patients with chronic lymphocytic leukemia (CLL) were Rai intermediate risk and 6 were high risk. The overall complete response (CR) rate was 51% and the partial response (PR) rate was 41%. Of patients with CLL, 47% achieved a CR and the remaining 53% achieved a PR. Of patients with follicular lymphoma, 60% achieved CR and 32% achieved a PR. Although the toxicity of this regimen was

mainly hematologic, significant nonhematologic toxicities, including infections, were seen. Twenty-four patients subsequently received an autologous or allogeneic stem cell transplant. Engraftment was rapid, and there were no noticeable procedure toxicities in the immediate posttransplant period attributable to the fludarabine and cyclophosphamide regimen. Fludarabine, cyclophosphamide, and filgrastim make up a highly active and well-tolerated regimen in CLL and NHL. (*Blood*. 2000;96:71-75)

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Introduction

Although most patients with low-grade lymphomas and chronic lymphocytic leukemia (CLL) are often initially sensitive to chemotherapy, remissions induced by these agents are usually not complete and patients always progress.¹ In addition, there has been no demonstrable improvement in survival for these patients in the last 3 decades.² The lack of improvement in survival may be due in part to the fact that the majority of patients have residual disease detectable after chemotherapy with current regimens. A first step in improvement in survival for these patients is the development of chemotherapeutic regimens that have the potential to produce true complete responses in the majority of patients. The approval of nucleoside analogs such as fludarabine for the treatment of low-grade lymphomas in the early 1990s brought with it a significant increase in complete response rate. Combining a DNA damaging agent, cyclophosphamide, with fludarabine may enhance the activity of the nucleoside analog.³ Several investigators have demonstrated enhancement of the activity of a purine nucleoside analog by combining it with a DNA damaging agent *in vitro*.^{4,5} This hypothesis has also been examined *in vivo*. Several trials have been conducted examining the combination of nucleoside analogs with alkylating agents.⁶⁻⁸ In one phase I/II study in low-grade lymphomas, an 89% complete response (CR) rate and a 100% overall response rate were seen as demonstrating the significant activity of this combination *in vivo*.⁸ A follow-up report indicates that these responses remain durable.⁹ However, another trial using fludarabine in combination with chlorambucil in patients with CLL has raised concern about the toxicities of these regimens, especially the infectious complications.¹⁰ In addition, questions have been raised

about the ability of patients who have received fludarabine-based chemotherapy to undergo subsequent high-dose therapy and stem cell transplant. To further evaluate the efficacy in relation to potential toxicities, we conducted a phase II trial of fludarabine and cyclophosphamide (Flu/Cy) in patients with previously untreated low-grade and select intermediate-grade lymphoproliferative disorders. The objectives of this study were to determine the CR and partial response (PR) rates of this regimen and to determine the associated toxicity. Secondary objectives included determining the effect of prior therapy with this regimen on patients' ability to undergo stem cell transplant. Engraftment, peritransplant infections, and survival were endpoints.

Patients and methods

Eligibility criteria

Patients enrolled in this multicenter study had previously untreated indolent lymphoproliferative disorders, including follicular small, mixed, and large-cell lymphomas, diffuse small lymphocytic lymphoma (SLL) or CLL, marginal zone lymphoma, and mantle cell lymphoma. Patients were required to have progressive disease-related symptoms (including progressive adenopathy, splenomegaly, or cytopenias). CLL patients were required to meet the criteria established by the National Cancer Institute's Working Group on CLL recommendations for starting therapy. Asymptomatic patients could enter the trial if the intention was to prepare for stem cell transplant. Good end organ function (serum creatinine level less than 2 mg/dL, bilirubin level less than 2 mg/dL unless elevated secondary to tumor, left ventricular ejection fraction greater than 45% in patients with a

From Johns Hopkins Oncology Center, Baltimore, MD, and Walter Reed Army Medical Center, Washington, DC.

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Reprints: Ian W. Flinn, Johns Hopkins Oncology Center, Cancer Research

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history of heart failure requiring medications within last 2 years, and forced vital capacity [FVC], DLCO, and FEV1 greater than 50% of predicted) was required. Human immunodeficiency virus (HIV)-positive patients were not eligible. All participants gave written informed consent before they entered the study. The study protocol was approved by the institutional review board of each participating hospital before patients were entered into the study.

Chemotherapy

Patients received cyclophosphamide 600 mg/m² intravenous (iv) day 1 and fludarabine (Berlex, Richmond, CA) 20 mg/m² iv days 1 through 5. Filgrastim (Amgen, Thousand Oaks, CA) 5 µg/kg subcutaneous was given starting approximately day 8 for 10 to 14 days or until postnadir absolute neutrophil count was greater than 10 000/mL. The chemotherapy was repeated every 28 days until maximum response or a maximum of 6 cycles. Patients proceeding to stem cell transplantation received a maximum of 4 cycles of chemotherapy. Patients received *Pneumocystis carinii* prophylaxis (PCP) with trimethoprim/sulfamethoxazole (TMP/SMX) twice daily on Mondays, Wednesdays, and Fridays or equivalent, starting with the initiation of chemotherapy and continuing for at least 6 months after the last dose of chemotherapy. Allopurinol 300 mg/d orally was administered on the first 7 days of the first cycle of chemotherapy.

Toxicity assessment and dose modifications

Toxicity in patients with non-Hodgkin lymphoma (NHL) was graded according to the National Cancer Institute (NCI) Common Toxicity criteria. In patients with CLL, toxicity was graded according to the NCI Working Group for CLL protocols criteria.¹¹ Fludarabine doses were reduced for patients whose creatinine level was 1.5 to 2.0 mg/dL. Reductions were calculated in proportion to the reduction in measured creatinine clearance compared with a normal creatinine clearance. Doses of both fludarabine and cyclophosphamide were reduced in proportion to hematopoietic toxicity. Patients whose pretreatment hemoglobin or platelet count dropped by 25% to 49% received a 25% dose reduction. Doses were reduced by 50% or 75% for patients whose hemoglobin or platelet count dropped 50% to 74% or greater than 75%. All reductions were made assuming a maximum pretreatment hemoglobin of 10.0 g/dL and platelet count of 150 000/mL. In addition, only in patients with NHL, doses of fludarabine and cyclophosphamide were reduced by 25% if the nadir absolute neutrophil count was less than 500/mL and dropped by 75% of pretreatment value. Doses were increased if the 2 subsequent doses were well tolerated.

Staging and response criteria

All patients were carefully staged with physical examination, computed tomographic (CT) scans of the chest, abdomen, and pelvis, and bone marrow biopsy and aspirate with flow cytometry. Patients with NHL were staged according to the Ann Arbor Classification system,¹² whereas patients with CLL were staged according to the Rai staging criteria.¹³ Response was assessed after every 2 cycles of chemotherapy with careful physical examination and CT examinations at sites of prior disease. Patients with prior bone marrow involvement had repeat bone marrow examinations with flow cytometry if there was no other site of disease to follow for response. Responses for patients with CLL were judged according to the NCI Working Group for CLL criteria.¹⁴ Patients with "nodular complete remissions" were considered to have partial remissions. Complete response (CR) for patients with lymphoma was defined as complete disappearance of all clinically detectable malignant disease for at least 4 weeks. Partial response (PR) required greater than or equal to 50% decrease in tumor area for at least 4 weeks without increase in size of any area of known malignant disease. Stable disease was defined as no increase in measurable disease for at least 4 weeks. Response assessment was determined independently by 2 of the investigators (I.W.F. and J.C.B.). Patients had follow-up examinations, including CT examinations of the chest, abdomen, and pelvis, every 3 months for the first year, then every 6 months thereafter.

The Johns Hopkins Oncology Center has a policy to audit all intramural protocols to assure protocol compliance. The records of 30 (50%) patients

on this trial were reviewed by independent auditors who reported to the clinical research office.

Stem cell transplantation

Patients seeking autologous or allogeneic transplant received a maximum of 4 cycles of chemotherapy. These patients received PCP prophylaxis until the time of transplant. Eligible patients received either autologous marrow or peripheral blood stem cell or allogeneic stem cell transplant according to the availability of an HLA-matched donor and institutional protocols. The preparative regimens and posttransplant supportive care, including prophylactic antibiotics and growth factor support, and posttransplant adjuvant therapy also varied according to individual transplant protocols. Patients were followed for engraftment, peritransplant infections, and survival.

Statistics

The study was designed assuming a response rate on standard therapy of 30% to reliably detect a response rate of 50%. Using the optimal 2-stage design, with an alpha of 0.05 and a sample size of 60, the study would have a power of 90%. The primary analysis was based on the number of complete and partial response rates and their 95% exact binomial confidence intervals. Fisher exact test was used to determine differences in response rate. Paired Student *t* test was used to determine differences between immunoglobulin levels and lymphocyte subsets before and after therapy.

Results

Sixty patients (45 male:15 female) were enrolled (Table 1). Forty-three had NHL and 17 had CLL. The median age at time of registration was 53.5 years (range, 30-73 years). Thirty-five patients with NHL were stage IV and 8 were stage III. The median time from diagnosis to treatment was 3 months (range, 0-268 months). Eleven of 17 patients with CLL were Rai intermediate risk and 6 were high risk. All patients with CLL had progressive symptoms requiring chemotherapy. None were entered to the study for the sole purpose of proceeding to stem cell transplantation. Two hundred thirty-two cycles of chemotherapy were delivered to the 60 patients for a median of 4 cycles per patient (range, 1-6 cycles). Two hundred nine cycles were delivered on schedule. Twenty-three cycles (10%) were delayed a median of 1 week (range, 1-3 weeks).

Table 1. Demographics, stage, and baseline hematologic parameters

Demographics	
Male:female	45:15
Age:	53.5 (30-73) y
Performance status	0 (0-2)
Ann Arbor stage for patients with NHL	
Stage IV	37
Stage III	6
Rai stage and baseline hematologic parameters for patients with CLL	
Stage	
IV	3
III	3
II	6
I	5
Median WBC	63.3/mm ³ (11.7-353.0)
Median HGB	13 g/dL (11.1-15.3)
Median HCT	36.6% (20-44.9)
Median PLTS	139,000/mm ³ (81-281)

NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; WBC, white blood cell count; HGB, hemoglobin; HCT, hematocrit; PLTS, platelets.

Table 2. Responses by histology

CLL	8/17 (47%) CR, 9/17 (53%) PR
Follicular CC	12/20 (60%) CR, 6/20 (32%) PR
Mantle cell	4/10 (40%) CR, 4/10 (40%) PR
Other	6/12 (50%) CR, 5/12 (42%) PR

CLL, chronic lymphocytic leukemia; CR, complete response; PR, partial response; Follicular CC, follicular center cell lymphoma.

Cause of treatment delays varied, with only 6 patients being delayed secondary to hematopoietic toxicity.

Response

The overall CR rate was 51% (95% CI 0.37, 0.64) and the PR rate was 42% (95% CI 0.30, 0.56) (Table 2). Of patients with CLL, 47% achieved a CR (95% CI 0.23, 0.72) and the remaining 53% achieved a PR (95% CI 0.28, 0.77). Of patients with follicular lymphoma, 60% achieved CR (95% CI 0.36, 0.81) and 35% achieved a PR (95% CI 0.15, 0.59). Of patients with mantle cell lymphoma, 40% achieved a CR (95% CI 0.12, 0.74) and 40% (95% CI 0.12, 0.74) achieved a PR. Fisher exact tests indicate no statistical differences in response rates by histology for either complete or partial response ($P > .2$). These comparisons were made between CLL and NHL as well as its subtypes. The median follow-up time for CLL and NHL were 246 and 259 days, respectively.

Toxicity

Grades III to V nonhematologic toxicity was seen in 10% of patients within 30 days of last dose of chemotherapy (Table 3). One patient died in the middle of the second cycle of multisystem organ failure and clinical picture of sepsis. No organism was cultured from the blood; however, *P carinii* was reported in the sputum. The treating physician confirmed that the patient had faithfully taken TMP/SMX. One patient developed cryptococcal pneumonia coincident with the second cycle of chemotherapy. This patient had fevers and a cough before receiving the first cycle of chemotherapy but no evidence of pneumonia on CT examination.

Focal seizures developed in 1 patient 1 month after completing chemotherapy. These seizures never recurred. Extensive neurologic evaluation revealed only a very focal and subtle area of demyelination apparent on magnetic resonance imaging. A deep venous thrombosis developed in 1 patient that required intravenous heparin. Pneumonitis rapidly responsive to corticosteroids developed in 2 patients. However, 1 of these patients had progressive disease and, on open lung biopsy, was also found to have an infiltrate consistent with his underlying malignancy. The exact cause of his pulmonary complications is uncertain.

Hematopoietic toxicity was mild with filgrastim support (Table 4). Five patients with NHL experienced grade IV neutropenia in 1 cycle of treatment. Grade III neutropenia was seen in 12 patients for a total of 13 cycles. Grade III anemia was seen in 4 patients in a total of 4 cycles. In patients with CLL, no grade III and IV anemia was seen (Table 5). Two patients had grade III thrombocytopenia in

Table 3. Nonhematopoietic toxicity in all patients

Worst Grade	III	IV	V
Neurologic		1 patient	
DVT	1 patient		
Infection	1 patient		1 patient
Pulmonary	2 patients		

DVT, deep venous thrombosis.

Table 4. Hematopoietic toxicity in NHL patients

Worst Grade	III	IV
Anemia	4 patients 4 cycles	0 patients 0 cycles
Thrombocytopenia	1 patient 1 cycle	0 patients 0 cycles
Neutropenia	12 patients 13 cycles	5 patients 5 cycles

NHL, non-Hodgkin lymphoma.

a total of 2 cycles and 1 patient had 1 cycle of grade IV thrombocytopenia.

Several infections have been seen subsequent to chemotherapy. In 3 patients herpes zoster developed, 1 patient had a reactivation of chronic hepatitis B develop, 1 patient had a lower extremity cellulitis develop, and 1 patient had sinusitis develop. Other infectious toxicity included confirmed PCP in 1 patient who had been taking prednisone for immune-mediated thrombocytopenia and had stopped his TMP/SMX.

Immunologic effects

CD4 counts dropped significantly with Flu/Cy. The mean pretreatment absolute CD4 count was 799 cells/ μ L (range, 18-2450 cell/ μ L). This value was significantly reduced ($P < .001$) to 139 cells/ μ L (range, 9-376 cells/ μ L) after treatment. Quantitative assessment of immunoglobulins before and after chemotherapy revealed a significant decrease in serum levels of IgG and IgA ($P = .015$ and $P = .001$, respectively) and a trend toward lower values ($P = .085$) in serum IgM levels. The mean values before and after chemotherapy were 1109.7 and 906.5 mg/dL for IgG, 129.4 and 99.2 mg/dL for IgA, and 327 and 172.8 mg/dL for IgM, respectively. However, the postchemotherapy values were still within normal range for adults.

Stem cell transplantation

This study also sought to determine whether Flu/Cy is detrimental to patients seeking stem cell transplantation, both in terms of eligibility and transplant outcome. Pulmonary function was assessed before after completing chemotherapy because of the known pulmonary toxicity of fludarabine. There was no significant change in pulmonary function before and after chemotherapy. The median value for each test is FEV1 97.7% predicted (59.4-144.5) before, 98.7% predicted (67-123.4) after; FVC 99.1% predicted (50-156.1) before, 100% predicted (72-130.3) after; DLCO 98% predicted (55-129) before, 98.4% predicted (52-122) after. In 1 patient grade IV interstitial pneumonitis did develop, which would have prohibited proceeding with peripheral blood stem cell transplantation (PBSCT). No cardiac or renal toxicity from the regimen eliminated the option of stem cell transplantation for any patient on this study.

Twenty-four patients received high-dose therapy and stem cell

Table 5. Hematopoietic toxicity in CLL patients

Worst Grade	III	IV
Anemia	0 patients 0 cycles	0 patients 0 cycles
Thrombocytopenia	2 patients 2 cycles	1 patients 1 cycle

CLL, chronic lymphocytic leukemia.

*Toxicity graded according to the National Cancer Institute Working Group for CLL protocols.¹¹

transplant. An autologous graft suitable for transplant was obtained in all patients seeking autologous transplant. The choice of stem cell source varied according to institutional protocols and the date of transplant. The characteristics of the preparative regimen and graft composition are listed in Table 6.

Harvest of autologous stem cells varied by institution, time, and protocol, and content was not prospectively assessed. However, engraftment, defined as absolute neutrophil count greater than 500/mL and unsupported platelets greater than 20 000/mL days for 7 days occurred at a median of day 17.5 (range, 14-25) after transplant in patients receiving autologous peripheral blood stem cells (PBSC). Four of the transplant recipients, 2 allogeneic and 1 autologous marrow, and 1 autologous PBSC, died. Cause of death in the 2 allogeneic recipients was interstitial pneumonitis. Cause of death in the autologous marrow recipient was *Pseudomonas* sepsis and multisystem organ failure after graft failure occurred in the recipient of autologous PBSC.

Discussion

Despite the introduction of multiple chemotherapeutic regimens for the treatment of low-grade lymphoid malignancies over the last 3 decades, there has been no improvement in survival demonstrated for these patients.² However, although the majority of patients initially respond to chemotherapy, only a minority achieve a complete remission.^{2,15} Experience with other hematologic malignancies suggest that overall survival does not improve until the majority of patients achieve a complete remission.¹⁶ Although this may be readily apparent in more aggressive diseases such as acute leukemia or aggressive lymphomas, it is also true of hairy cell leukemia, another low-grade lymphoid malignancy. The introduction of purine nucleoside analogs into the treatment of this disease brought with it not only a high complete remission rate but also improvement in overall survival^{17,18} relative to historical controls.

Our data demonstrate that the combination of fludarabine and cyclophosphamide is a highly active regimen that was well tolerated by most patients, requiring dose modifications in only 10% of patients. The complete response rate in follicular lymphomas is less than that seen in a phase I/II study reported preliminarily by the Eastern Cooperative Oncology Group in which a variety of doses of cyclophosphamide were used. This difference may be real or may be a function of the relatively small number of patients with follicular lymphoma in the 2 studies. This regimen compares favorably with the fludarabine and mitoxantrone regimen in which a 43% CR and 91% overall response rate has been reported.¹⁹ Comparison with the fludarabine, mitoxantrone, and dexametha-

sone regimen is difficult as publications to date have largely been in patients with relapsed disease.²⁰

The results of this regimen in patients with CLL are quite encouraging. To our knowledge, complete and overall response rates of this magnitude are previously unreported in CLL with fludarabine and alkylating agent combinations. Prior studies of fludarabine and alkylating agents in CLL have been complicated by excessive toxicity, predominantly hematopoietic and infectious. The arm containing the combination of fludarabine and chlorambucil in the intergroup randomized phase III trial comparing single agents fludarabine, chlorambucil, and the combination fludarabine and chlorambucil was closed early because of excessive toxicity.²¹ Differences in doses may explain this difference or there may in fact be poorly understood but real differences between chlorambucil and cyclophosphamide. In addition, because of information gained from the intergroup study and other studies using combination regimens with nucleoside analogs, significant attention was made to supportive care, including hematopoietic support with growth factors and the use of PCP prophylaxis. However, significant nonhematopoietic toxicity was seen with this regimen and these toxicities should be considered when evaluating a patient for this therapy. The response rates in CLL compare favorably with other small series of concomitant or sequential fludarabine and cyclophosphamide in previously untreated patients with CLL. In 14 previously untreated patients, a response was noted in 13 patients.²² The CR rate was not reported. Using a sequential design of fludarabine followed by cyclophosphamide, 8 of 21 patients achieved a CR and 11 of 21 achieved a PR.²³

The use of high-dose therapy and stem cell transplantation is increasingly common in patients with low-grade lymphoproliferative disorders. Unfortunately, the morbidity and mortality appears to be higher in this group than that seen in some other patient populations.²⁴ One concern that has been raised is the use of fludarabine in these patients. Fludarabine is clearly immunosuppressive, which may increase the risk of infectious complications with a transplant. Furthermore, there is preliminary data to suggest that it is more difficult to obtain a viable autologous stem cell graft from patients who have had prior therapy with fludarabine.²⁵ Our results indicate that fludarabine and cyclophosphamide treatment does not prevent patients from receiving high-dose therapy with stem cell transplantation. We were able to harvest a graft in all patients seeking an autologous transplant. However, it is important to note that we limited the number of cycles of chemotherapy in those patients seeking stem cell transplantation. The results may be different if more cycles are given. In addition, there was no significant pulmonary or other toxicity that would render a patient ineligible for transplant. As this regimen achieved a high complete response rate in patients with CLL, it may have rendered more patients eligible for transplant than would be expected with single agent fludarabine or other regimens.

The combination of fludarabine and cyclophosphamide is clearly immunosuppressive. CD4 counts drop significantly after this therapy. Prior combination therapy with fludarabine has been limited by concomitant increases in infectious toxicity. Infections in this study may have been minimized by the use of prophylactic TMP/SMX and filgrastim; however, they were not eliminated. Although no infections with varicella-zoster virus were seen during the chemotherapy, depression of CD4 counts can be expected for at least 6 months or longer, during which time patients are at risk for varicella-zoster virus and other opportunistic infections. An increase in these infections has been noted in patients with CLL

Table 6. Transplant characteristics and graft types

Transplant characteristics		
Preparative regimen		
Cy/TBI		18
BCNU/Cy/VP16		6
Graft type		
Allogeneic elutriated		4
Autologous PBSC		15
Autologous marrow		5

Cy/TBI, cyclophosphamide and total body irradiation; BCNU/Cy/VP16, carmustine/cyclophosphamide/etoposide; PBSC, peripheral blood stem cell.

receiving fludarabine-based regimens.^{10,26} Patient teaching, close surveillance, and the early institution of antibiotics is warranted. An alternative solution is to decrease the immunosuppression associated with nucleoside analog-based chemotherapy. Our group is pursuing this strategy using interleukin-2 during chemotherapy in a randomized, blinded, placebo-controlled study to prevent CD4 depression.

The long-term toxicities of this regimen are unknown. Myelodysplasia has been seen in patients treated with purine analogs.²⁷ A recent report suggests there may be an increase in myelodysplastic syndromes with the combination of chlorambucil and fludarabine in patients with CLL.²⁸ Although we did not note this in our patients, follow-up remains short, and we will continue to monitor these patients.

It is clear from our experience with other hematologic malignancies that we are unlikely to change the natural history of a disease until we can achieve a complete remission in the majority of patients. The ultimate value of the combination of fludarabine and cyclophosphamide in CLL and low-grade lymphomas remains to be proven. The Eastern Cooperative Oncology Group is currently evaluating this regimen in comparison with single agent fludarabine in a randomized study in patients with previously untreated CLL. A similar regimen is being evaluated in Eastern Cooperative Oncology Group in low-grade lymphoma patients. However, ultimately to improve the outcome for patients with low-grade lymphoid malignancies, regimens like Flu/Cy that produce complete responses in the majority of patients will be needed.

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