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Treatment of refractory chronic lymphocytic leukemia with prednimustine: A phase II study using strict response criteria*, **

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Summary. Twenty-one patients with refractory chronic lymphocytic leukemia (CLL) were entered into this Northern California Oncology Group (NCOG) study of prednimustine, an ester of chlorambucil and prednisolone. All patients had active disease and were refractory to standard alkylating agent chemotherapy. Treatment consisted of prednimustine 100 mg/m^2/day orally for 3 consecutive days every 2 weeks. By strict response criteria used in this study there was one complete remission (CR), no partial remissions (PR), and three cases of clinical improvement (CI) in 18 evaluable patients, for a total response rate of 22%. The median duration of response is 20+ months, with two patients continuing to respond. Toxicity of this intermittent prednimustine regimen consisted primarily of mild to moderate thrombocytopenia and neutropenia. No episodes of treatment-associated infection or hemorrhage occurred, and nonhematologic toxicity was minor. Using strict response criteria, this study fails to confirm previous reports of high response rates for prednimustine in patients with CLL refractory to standard therapy. The significance of the response category of clinical improvement in CLL is demonstrated by the substantial improvement in objective parameters and the long duration of response. This study also emphasizes the need for standardization of response criteria for this disease.

Introduction

Chronic lymphocytic leukemic (CLL) is characterized by a presistent, usually progressive, accumulation of morphologically well-differentiated B-lymphocytes. The clinical course of this disorder may be extremely variable [1]. The recently developed clinical staging system of Rai et al. [2] has shown progressively shortened survival in patients with lymphadenopathy, hepatosplenomegaly, and anemia or thrombocytopenia. Traditionally, CLL has been treated with chlorambucil, with or without prednisone. Despite initial responsiveness, many patients eventually become refractory to standard alkylating agent therapy and enter a phase in which secondary types of treatment are either less effective or not possible because of disease-related cytopenias. Therefore, new and alternative therapeutic agents are needed for patients with refractory CLL.

Prednimustine, a prednisolone ester of chlorambucil, has been shown to be active in a wide spectrum of animal tumor systems [3]. A favorable therapeutic index for prednimustine compared with chlorambucil has recently been attributed to prolonged low-level bioavailability [4]. Clinical studies have reported activity of prednimustine, both as primary and secondary therapy, in CLL, non-Hodgkin's lymphoma, and breast cancer, and have confirmed a low degree of toxicity [5–10].

Treatment of refractory advanced-stage CLL with intensive chemotherapy is often complicated by severe myelosuppression, requiring significant dose reduction and resulting in an inadequate course of therapy. If active, an agent with mild myelotoxicity, such as prednimustine, would be of value in patients with refractory disease. The present report describes the results of a Northern California Oncology Group (NCOG) study of prednimustine in patients with CLL refractory to standard alkylating agent therapy. Results are analyzed by strict response criteria as reported by Silver et al. [11].

Materials and methods

Patient selection. This NCOG protocol (9L-80-3) uses criteria for diagnosis and staging of CLL as previously defined [2, 11]. The condition for eligibility is active CLL refractory to standard alkylating agent chemotherapy. Refractory disease is defined as primary treatment failure or lack of response to retreatment. Patients merely relapsing after prior treatment were not considered refractory and were ineligible for study entry. Active CLL is defined as meeting at least one of the following criteria:

1. Anemia (males: hemoglobin <12 g%; females: hemoglobin <11 g%
2. Thrombocytopenia (platelet count $\leq 100000/mm^3$)
3. Neutropenia (absolute granulocyte count $\leq 2000/mm^3$)

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4. Progressive enlargement of lymph nodes, liver, or spleen within previous 8 weeks, or involvement of other areas, such as skin

5. Nonprogressive organomegaly producing symptoms of organ dysfunction

Treatment schedule. Prednimustine 100 mg/m^2/day orally for 3 consecutive days every 2 weeks. Therapy is repeated in 2-week cycles until complete response or progression of disease. Patients with stable disease following six cycles (12 weeks) of therapy are considered treatment failures and removed from the study.

Definition of response criteria. This study employs strict response criteria as previously defined:

Complete response (CR): Complete disappearance of all objective and subjective evidence of disease. Normal bone marrow with $<20\%$ lymphocytes; peripheral neutrophil count $>2500/mm^3$, lymphocytes $<4000/mm^3$, platelets $>150000/mm^3$, hemoglobin >13 g%; normal-size liver, spleen, and lymph nodes.

Partial response (PR): Hemoglobin >11 g% in women and >12 g% in men, platelet count $>100000/mm^3$, lymphocyte count $<15000/mm^3$, neutrophil count $>2000/mm^3$; reduction in lymph node, liver, and spleen size and decrease in marrow lymphocytes by 50% of pretreatment values.

Clinical improvement (CI): Decrease in peripheral blood lymphocytes to $<20000/mm^3$; increase in neutrophils to $>1500/mm^3$, platelets $>75000/mm^3$, hemoglobin >9 g% without transfusions; reduction in lymph nodes, liver, and spleen to less than 50% of pretreatment size; absence of significant infection or bleeding.

Results

Patient characteristics. Twenty-one patients from member institutions of NCOG were registered in this study. Patient characteristics at the time of study entry are summarized in Table 1. The mean patient age is 63 years. There are 15 males and six females. By the Rai staging system for CLL, 67% of patients are stage III or stage IV. All patients are refractory to standard alkylating agent chemotherapy. In addition, 57% of patients have been treated with extensive prior combination chemotherapy, with a median number of two prior regimens, and 24% have received prior radiation therapy. The majority of patients (86%) have received previous corticosteroid therapy.

Table 1. Patient characteristics

Total number of patients registered		21
Karnofsky performance status	50–70	6 (29%)
	80–100	15 (71%)
Rai classification	I–II	7 (33%)
	III–IV	14 (67%)
Previous chemotherapy		21 (100%)
Extensive prior chemotherapy (CVP, CHOP)		12 (57%)
Previous radiotherapy		5 (24%)
Previous corticosteroid therapy		18 (86%)

CVP, cyclophosphamide + vincristine + prednisone; CHOP, cyclophosphamide + hydroxydaunorubicin + vincristine + prednisone

Table 2. Response in 18 evaluable patients

Response categories	Patients (%)
Complete response	1 (6%)
Partial response	0 (0%)
Clinical improvement	3 (16%)
Total	4 (22%)
No response	14 (78%)

Response data. Of 21 patients entered, 18 are fully evaluable and form the basis of this report. Following NCOG pathology review, two patients are inevaluable because of histologic misclassification. In one patient, inevaluability is due to early death. Response data are summarized in Table 2. All evaluable patients received an adequate trial of therapy, defined as a minimum of two courses. Using the response criteria of Silver et al. [11], the response rate in 18 evaluable patients is 22% (1/18 CR, 0/18 PR, 3/18 CI). Time to response ranged between 2 and 6 months. Of 14 patients classified as nonresponders, nine had stable disease and five showed disease progression during the period of study. The median survival time from study entry for all evaluable patients is 24.4 months. The median survival for the four responding patients is 34+ months with a median duration of response of 20+ months. Two patients continue to respond at 23+ and 38+ months following initiation of therapy. Characteristics of responding patients are shown in Table 3. Two responders each have stage I and stage III disease. Prior therapy consists of chlorambucil and prednisone in all four responders, radiation therapy in three of four patients, and extensive prior combination chemotherapy in one patient.

Toxicity. All 21 patients are evaluable for toxicity analysis. Intermittent pulse prednimustine as administered in this study was relatively well tolerated, even in these pretreated patients. In patients with normal granulocyte and platelet counts at study entry, grade III–IV neutropenia ($<1000/mm^3$) occurred in five of 16 patients and grade III–IV thrombocytopenia ($<50000/mm^3$) occurred in two of eight patients. In those patients with cytopenias at study entry, significant worsening of neutropenia during treatment developed in one of five and worsening of thrombocytopenia in four of 13 patients. No correlation between hematologic toxicity and response to therapy was evident. There were no episodes of treatment-associated infection or hemorrhage. Mild elevation in blood glucose (>200 mg/dl) was observed in five patients, but no other nonhematologic toxicity was seen.

Discussion

A direct comparison of therapeutic trials in CLL is difficult because of the clinical heterogeneity of the disease, differences in staging methods, inclusion of previously treated patients, and variability in response criteria among studies. The clinical heterogeneity of CLL has long been recognized as a complicating factor in comparing the results of therapy. Even in early reports, an indolent or "benign" form of the disease was recognized and contrasted with a more aggressive or "active" subgroup of patients [12].

Table 3. Characteristics of four responding patients

Patient number	Stage	Prior therapy	Hematologic toxicity	Response category
3	III	CL-P, RT, CVP, CHOP	Grade III neutropenia	CI
5	I	CL-P, RT	Grade III thrompocytopenia	CI
6	III	CL-P, RT	None	CI
14	I	CL-P	None	CR

CL-P, chlorambucil + prednisone; CVP, cyclophosphamide + vincristine + prednisone; RT, radiotherapy; CHOP, cyclophosphamide + hydroxydaunorubicin + vincristine + prednisone

Recent attempts to stratify CLL into clinical stages, such as the classification of Rai et al. [2], have acknowledged the importance of anemia (stage III) and thrombocytopenia (stage IV) as indicators of a poor prognosis. In studies which include all stages of disease, a direct correlation between response rate and stage has been observed, those patients with advanced-stage disease having a much lower response rate [12, 13].

Another important factor in analyzing clinical trials in CLL is the impact of prior therapy. In most series, the response rate to secondary therapy is markedly reduced, with a virtual absence of CR. Thus, studies consisting only of patients without prior therapy cannot be directly compared with those containing an admixture of patients undergoing primary and secondary treatment.

The last factor, equally important in analyzing reports of therapy in CLL, is the set of response criteria used. Prior studies in CLL have used a variety of criteria. Some required only a reduction in peripheral lymphocyte count or improvement in symptoms. Others, such as the Guideline Criteria of the CALGB reported by Silver et al., had strict requirements for response, including reduction in bone marrow lymphocytic infiltration.

European studies in CLL have reported high response rates of 50%–90% using prednimustine as primary and secondary therapy [5, 8]. In an early study, Brandt et al. [8] described responses in 14 of 15 patients with CLL. In Idestrom et al.'s series [5] a 53% response rate was achieved in previously untreated patients. There were no significant differences in efficacy or toxicity between continuous and intermittent prednimustine regimens (20 mg twice daily vs 100 mg twice daily for 3 days, repeated every 2nd week) compared with a control arm receiving chlorambucil and prednisolone. Responses to prednimustine after failure with standard alkylating agents have suggested a relative lack of cross-resistance [9, 10]. In a study of secondary therapy, Pedersen-Bjergaard obtained a 43% response rate in 14 patients [9]. Since some studies predate the Rai clinical staging system, and prior therapy and response criteria are not well defined in others, the exact value of prednimustine in CLL has remained unclear.

The present study describes the results of therapy with the investigational agent prednimustine in a group of heavily pretreated patients with predominantly advanced disease. The response criteria used in this study describe three categories of response: CR, PR, and CI. As defined by these criteria, the response rate in this study is 22%. In our study, all three patients achieving CI status appeared to benefit clinically, including objective improvement in disease-related cytopenia, reduction in adenopathy, and improvement in performance status, thus substantiating the validity of this response category.

The specific reasons for a lower response rate in this study in comparison with previous trials are unclear. All patients in our study were clearly refractory to prior alkylating agents and corticosteroids, and stage of disease was well defined. All evaluable patients received an adequate course of therapy, defined as two cycles of drug treatment. The dose schedule selected for this study is comparable with that of prior trials of prednimustine [5]. Dose escalation was not part of the study design, because of concern regarding severe myelosuppression in these heavily pretreated patients and cytopenia at study entry in the majority of patients. Since myelosuppression proved to be tolerable, a study design incorporating dose escalation should be considered in future trials using this agent.

In conclusion, this study does not confirm previous reports of high response rates for prednimustine in patients with advanced CLL refractory to standard therapy. Our results do, however, substantiate the low degree of toxicity previously reported and suggest the potential for a study design incorporating dose escalation in future studies. The results of this study, analyzed by strict response criteria, emphasize the need for standardization in order better to compare the results of current therapeutic trials in CLL.

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