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A Phase II Study of Prednimustine in Acute Non-Lymphocytic Leukemia, Smouldering Leukemia, and Refractory Anemia with Excess Blasts

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Summary. *Prednimustine, an ester of chlorambucil and prednisolone, was evaluated for efficacy and toxicity in a selected group of leukemia patients with a poor prognosis. Disease subsets consisted of patients with acute non-lymphocytic leukemia (ANLL) over age 60; ANLL refractory to standard therapy; smouldering leukemia; and refractory anemia with excess blasts (RAEB). In agreement with previous studies, toxicity from Prednimustine was relatively mild, consisting primarily of infrequent myelosuppression, gastrointestinal side-effects, and mild hyperglycemia. This study did not, however, confirm previously reported remission rates in ANLL: in 41 evaluable patients only two complete remissions were achieved. Both occurred in the subset of patients with smouldering leukemia. We conclude that Prednimustine has limited activity in this patient population.*

Introduction

Significant progress has been made in the overall treatment of acute non-lymphocytic leukemia (ANLL) in recent years, with complete remission rates of 60%–85% reported following intensive induction chemotherapy [8, 18, 19]. In previous studies, poor prognostic factors have included advanced age, presence of infection, morphologic subtype, initial blast count, and evolution from an underlying myelodysplastic or preleukemic syndrome. With improved induction regimens and advances in supportive care, recent studies suggest that many of these variables may no longer be significant [9, 20]. Despite these advances, patients with RAEB or smouldering leukemia continue to present difficult management problems [7, 12]. Although in the majority the disease may evolve into acute leukemia, a significant number of patients will die from infections or hemorrhagic complications before this transformation occurs. Intensive chemotherapy, used either as an early intervention or at the time of evolution to acute leukemia, has largely been ineffective in these patients [5, 16].

Prednimustine, an ester combination of the corticosteroid prednisolone and the alkylating agent chlorambucil, has been shown to be active in a wide spectrum of animal tumor systems [6, 13]. A favorable therapeutic index has been demonstrated for Prednimustine compared with chlorambucil, primarily attributed to lower myelotoxicity. Clinical studies have reported activity in chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and breast carcinoma, and have confirmed a low degree of toxicity with this agent [4, 14, 15]. Responses to Prednimustine after failure with standard alkylating agents have suggested a relative lack of cross resistance [11, 15, 17].

In a pilot study in ANLL, five of eleven patients obtained complete remission, all without a preceding drug-induced pancytopenic phase. In this report, two of seven patients over the age of 60 achieved a complete remission [2].

In elderly patients with ANLL or smouldering leukemia, intensive chemotherapy with its obligatory aplastic phase is frequently associated with significant morbidity and mortality. If active, an agent with mild myelotoxicity such as Prednimustine would be of potential value in these patients.

In this paper we report the results of the Northern California Oncology Group (NCOG) study of Prednimustine in patients with poor-risk leukemia: ANLL over 60 years of age, refractory ANLL, smouldering leukemia and refractory anemia with excess blasts (RAEB).

Materials and Methods

Study Design. Fifty-eight patients from member institutions of the Northern California Oncology Group entered this study from 1 March 1980 to 30 June 1981. Leukemia subtypes eligible for study were: previously untreated ANLL > 60 years of age; ANLL refractory to standard therapy; smouldering leukemia; and RAEB. The diagnosis of *ANLL* was based on histochemical staining and morphologic examination of the peripheral blood and bone marrow. In this category, only patients over the age of 60 or those refractory to standard therapy were eligible. *Smouldering leukemia* was defined by a bone marrow showing 31%–80% blasts plus promyelocytes, absence of leukemic infiltration interfering with organ function, and an indolent clinical course (a minimum observation period of 1 month without significant increase in bone marrow leukemic infiltrate or worsening of peripheral blood cytopenias. A doubling of the percentage of blasts was considered a significant increase in marrow infiltrate. A 50% decrease in peripheral blood granulocyte count or platelet count was considered a significant worsening of cytopenia). *RAEB* was defined by refractory anemia (hemoglobin less than 11 g%), bone marrow blast forms of 10%–30%, bone marrow cellularity of greater than 50%, and an observation period of at least 1 month without evolution to acute leukemia. Almost all patients also had peripheral blood granulocytopenia or thrombocytopenia.

Corticosteroid receptor assays were not performed in this study.

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Patient Characteristics. The characteristics of patients at the time of study entry are summarized in Table 1. There were approximately equal numbers of males and females. The mean age of all patients was 64.2 years, and was relatively uniform within each subgroup except ANLL > 60, in which the mean age was 75. In the majority of patients, initial Karnofsky performance scores were ≥ 80. Of the 58 patients, 21 developed leukemia from a pre-existing myelodysplastic or myeloproliferative syndrome.

Treatment Schedule. Induction therapy consisted of Prednimustine, 40 mg/m^2/day PO for 3 weeks, administered as a single daily dose. Therapy was repeated in 3-week cycles until remission, progression of disease, or a maximum of four courses (12 weeks). For complete responders (M-1), maintenance therapy consisting of Prednimustine, 12.5 mg/m^2 daily was given until relapse or until treatment had continued for 2 years. Patients with stable disease at 21 days continued to receive Prednimustine therapy to a maximum of four courses (12 weeks). If no improvement had occurred at this point, patients were considered induction failures and were removed from study. Patients with an increasing peripheral blast count during the first 10 days of treatment received a dose escalation to 40 mg/m^2 twice daily for the remainder of the initial 3-week course. Drug administration was delayed for myelosuppression (granulocyte count < 2,000/mm^3 or platelet count < 100,000/mm^3) with demonstrated bone marrow hypocellularity (< 25%).

Table 1. Patient characteristics at study entry

	Treatment group				
	ANLL age > 60	Refractory ANLL	RAEB	Smouldering leukemia	Total
Number	16	13	7	22	58
Sex					
Male	8	7	5	12	32
Female	8	6	2	10	26
Age					
Mean	75	55.7	60.5	65.8	64.2
	63–92	25–79	22–81	44–90	22–92
Performance status					
30– 50	5	3	0	0	8
60– 70	9	2	3	4	18
80–100	2	8	4	18	21

Table 2. Response rate for remission induction

	Number of patients responding			
	ANLL, age > 60	Refractory ANLL	RAEB	Smouldering leukemia
Complete response	0	0	0	2
Partial response	0	0	0	1
No response	10	9	6	13

Results

Response Data

Forty-one patients were fully evaluable and form the basis for this report. Evaluability for response required a minimum of 4 weeks of therapy. Inevaluability resulted from: diagnostic misclassification, 1 (non-Hodgkin's lymphoma); pre-evaluability death, 7; treatment refusal, 1; abbreviated trial secondary to toxicity, 5; and major protocol violations, 3.

Response data are summarized in Table 2. Two complete and one partial remission occurred in the subgroup of patients with smouldering leukemia, so that there was a complete response rate of 13% within this category. Although clearing of the peripheral blood blasts and improvement in disease-related cytopenias were observed in an additional five patients, there were no significant bone marrow responses in patients with ANLL > 60, refractory ANLL, or RAEB. All pre-evaluability deaths occurred in the subgroups with ANLL > 60 and refractory ANLL; none appeared to be related to drug toxicity.

The median survival for all patients is 93 days. The median survival periods by subgroup are: refractory ANLL, 34 days; ANLL > 60, 82 days; smouldering leukemia, 151 days. The two complete responders remain in remission at 17+ and 13+ months.

Toxicity

Prednimustine therapy as administered in this study resulted in infrequent myelosuppression. Five patients (8.6%) developed grade 4 WBC toxicity (granulocyte count < 500/mm^3). In two of these this occurred during the dose escalation phase. Thrombocytopenia (platelet count < 50,000/mm^3) occurred in seven patients (12%). No episodes of serious hemorrhage were observed. Non-hematologic toxicity, in general, was mild and reversible upon discontinuation of treatment. Three patients, however, were removed from study due to gastrointestinal side-effects of nausea, vomiting, or epigastric discomfort. Mild to moderate elevation of blood glucose occurred in 11 patients, 5 of whom had pre-existing diabetes mellitus. There were no episodes of ketoacidosis or hyperosmolar syndrome.

Discussion

Despite advances in the overall treatment of ANLL, certain categories of patients continue to have a poor prognosis for even short-term benefit. Although recent reports indicate that elderly patients with ANLL may benefit from treatment, many are not good candidates for aggressive chemotherapy because of the severity of underlying medical conditions, such as ischemic heart disease [2]. In addition, delayed bone marrow recovery may occur in these elderly patients, requiring intensive supportive care for prolonged periods.

Another category of patients with a poor prognosis is that of RAEB and smouldering leukemia. These entities appear to share certain clinical features. Common findings include the presence of anemia or other peripheral blood cytopenias, hypercellular bone marrow with increased blast forms, and, in the majority of cases, an indolent course before eventual evolution to acute leukemia [12, 16]. Since these disorders characteristically respond poorly to cytotoxic therapy, some authors have recommended that no treatment be given other than supportive care [5].

Prednimustine has reported activity in elderly patients with ANLL. Brandt and Konyves reported remission rates in 17% of 23 patients with ANLL over the age of 64. In younger

patients, 43% achieved complete remission when treated with Prednimustine plus vincristine [3]. In a more recent study, however, only 1 complete remission occurred in 7 previously untreated patients, and no responses were seen in 11 patients refractory to standard therapy [10]. In each of these studies, the dose schedule of Prednimustine was 60–80 mg/day, comparable to that in the present study.

To define the activity of Prednimustine, four subsets of non-lymphocytic leukemia with a poor prognosis were selected for treatment. The median age for the subgroup with ANLL > 60 was 75 years, and many patients were not candidates for aggressive chemotherapy due to the severe underlying medical conditions. Eligibility criteria for smouldering leukemia and RAEB were based on previously described clinical and laboratory features [1].

Our study confirms the low degree of myelosuppression noted in previous reports. With a daily dose of 40 mg/m^2, drug-induced granulocytopenia below 500/mm^3 was seen in only three patients (5%). Thrombocytopenia below 50,000/mm^3 occurred in 12%. Gastrointestinal side-effects, although uncommon, were severe enough in three patients to result in early removal from study.

This study does not confirm significant activity for Prednimustine in ANLL in the elderly. Only two complete remissions occurred, both in patients with smouldering leukemia. We conclude that Prednimustine appears to have limited activity in this study population.

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