Short Communication

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Philadelphia Chromosome (Ph¹-Positive Acute Lymphoblastic Leukemia (ALL) Is Resistant to Effective Therapy for Ph¹ Negative ALL

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Key Words

Lymphoblastic leukemia

Philadelphia chromosome-positive

Resistance

Abstract

Amsacrine with high-dose cytarabine is effective therapy for Philadelphia chromosome (Ph¹-negative acute lymphoblastic leukemia (ALL). We examined the effectiveness of this regimen in 19 patients with Ph¹-positive lymphoblastic leukemia. Four had an antecedent chronic phase of chronic myelogenous leukemia and 15 presented with ALL. There were no complete responders in either group. All 14 patients whose bone marrow could be assessed after completion of therapy showed persistent leukemia. We conclude that patients with Ph¹-positive lymphoblastic leukemia have a disease that is resistant to treatment that is highly effective in patients with Ph¹-negative ALL.

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Although Ph¹-positive ALL frequently responds to standard therapy of ALL, long-term survival is rare [1,2]. After achieving remission, patients must receive supralethal therapy followed by allogeneic bone marrow transplantation, otherwise relapse is virtually universal [1, 2]. We have recently reported that Ph¹-negative lymphoblastic leukemia is highly responsive to an amsacrine-based regimen [3]. In that report, patients with lymphoblastic leukemia in relapse had a complete remission rate (CR) of 75% (CRs in 25 of 36 patients) and 50% (CRs in 2 of 4 patients) in patients with primary refractory disease. Since patients with Ph¹-positive ALL who are not candidates for a bone marrow transplant require additional effective sublethal therapy, we examined our most effective amsacrine-based regimen in patients with this disease.

required. In all patients cytogenetic evaluation confirmed the presence of the Philadelphia chromosome. Prior treatment with vincristine-prednisone combinations was permitted and all patients required normal liver and renal function as documented by a serum bilirubin less than 2 mg/dl and creatinine less than 2 mg/dl.

Since amsacrine does not affect cardiac function, an adequate left ventricular ejection fraction as measured by gated multinuclide scan was not required.

Treatment

All patients received amsacrine 200 mg/m² over 30 min daily for 3 days together with cytarabine 3 g/m² over 3 h once daily for 5 days. To assure safety, they also received potassium chloride, 10 mEq/h for 10 h prior to receiving amsacrine and only received the drug if the serum potassium exceeded 4.0 mEq/l within 4 h prior to drug administration. All patients had a bone marrow aspiration done at 7–10 days after treatment and if persistent disease was demonstrated a second course of therapy was given. This treatment consisted of 2 days of amsacrine and 3 days of cytarabine given at the doses administered during the first cycle.

Materials and Methods

In order to be eligible for treatment, patients must have had a diagnosis of ALL or blastic transformation of chronic myelogenous leukemia documented by a bone marrow aspiration. In the latter group, unequivocal lymphoid morphology or a positive result in a standard terminal deoxynucleotidyl transferase assay was

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Results

Patient Characteristics

A total of 19 patients were treated (the median age was 33 years, range 16–53). Of the 19 patients treated, 4 patients had an antecedent chronic phase of chronic myelogenous leukemia and 15 patients presented with ALL. Their characteristics are shown in table 1.

218

Arlin/Feldman/Ahmed/Liebowitz/Shapiro/Wilms

19

16–53

33

4 15

0.5–202.0 48.3

7–874 90

8.2–13.5 10.2

Table 1. Patient characteristics

Total patients treated Age, years

Range

Median

Diagnosis

B1CML

ALL

Pretreatment blood values WBC($\times 10^6$ /l)

Range

Median

Platelets($\times 10^9$ /l) Range Median

Hemoglobin, g/dl Range Median

B1CML = Blastic phase of chronic myelogenous leukemia.

Treatment Outcome

Of the 19 patients treated, there was only 1 partial response in a patient who presented with Ph⁺-positive ALL. When he responded, morphologic evaluation of the bone marrow showed

reduction to 10% blasts. This one patient underwent an allogeneic bone marrow transplant and remained disease-free for 8 months. Of the remaining 18 patients, 5 patients died prior to assessment of the effectiveness of therapy, but 13 failed to respond because of persistent leukemia after one or two courses of therapy. Toxicity encountered was not different from that reported previously and included hepatic dysfunction in one third of patients. There was no evidence of central nervous system dysfunction, conjunctivitis or cutaneous toxicity.

Discussion

The therapy used in these patients has proved to be the most effective we have tried for relapsed Ph⁺-negative lymphoblastic leukemia. Other therapies which include (1) sequential methotrexate-asparaginase [4], (2) reinduction with vincristine, prednisone and adriamycin, and (3) mitoxantrone, alone or in combination [5] have previously proven effective in Ph⁺-negative disease and some responses have also been seen in Ph⁺-positive ALL [1, 5]. The results reported here show that this regimen is ineffective in patients with Ph⁺-positive lymphoblastic leukemia. Unusual or excessive toxicity was not observed and thus the poor response rate seen was due to the ineffectiveness of the regimen against the disease being treated. All the 14 patients in whom bone marrow was evaluable for response after treatment showed persistent leukemia. This same resistance was evident in only 6 cases of the 36 treated with Ph⁺-negative ALL in relapse [3]. The fact that Ph⁺-positive lymphoblastic leukemia responds poorly to therapy that is so effective in Ph⁺-negative disease may help explain why relapse is so common in this group. The same resistance seen with these drugs may also exist for other drugs. Although in acute Ph⁺-negative disease this regimen offers hope for increasing the cure rate, the failure seen here further lends support to the use of bone marrow transplantation in this disease. A good alternative for patients without a bone marrow donor is currently not at hand. Progress in the chemotherapy of this disease will come with a greater understanding of the reasons for resistance and the development of methods of circumventing them.

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