Immunotherapy for Chronic Myelogenous Leukemia: Survival Not Affected by Treatment in the Stable Phase¹


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ABSTRACT

Thirty-one consecutive patients with chronic myelogenous leukemia were treated in the chronic phase with immunotherapy in addition to chemotherapy. Immunotherapy consisted of Bacillus Calmette-Guérin and allogeneic myeloblasts given by vaccination, and chemotherapy comprised busulfan p.o. in most patients. No randomly allocated control group was designated, but patient characteristics appear to be typical of those of other published groups. Twenty-eight of 31 patients were followed from diagnosis to death, and the remaining patients were followed for over 5 years.

The median survival of the patients in our group was 37 months. There was a constant rate of decline in survival with time, with a mean annual death rate of 30% per year. Twenty-five of the 31 patients terminated in blast crisis. One of 21 patients achieved complete remission in blast crisis of myeloid or indeterminate type, and three of four patients achieved complete remission for blast crisis of lymphoid type. The median survival, the rate of decline in survival, and the remission rate in blast crisis do not appear to differ from those of comparable groups of patients treated with chemotherapy alone.

INTRODUCTION

CML⁴ is characterized by an initial phase that is easily controlled by medication, followed by an accelerated phase that is generally difficult to control and is ultimately fatal (6). Although the initial phase may be stable for long periods in individual patients, analysis of patient survival in large series has shown a steady annual death rate from leukemia despite chemotherapy (10). The median survival of CML patients has shown little variation from study to study and is generally in the range of 36 ± 4 months or greater (1, 3, 5, 6, 10, 14).

Immunotherapy with BCG and cell vaccine given in addition to chemotherapy has been studied in CML and reported to produce increased survival when compared to historical controls (11–13). We have reported previously that patients with CML receiving immunotherapy may produce antibodies against myeloblast antigens particularly during a favorable disease course (8). In the current study, we have given immunotherapy with BCG and leukemic myeloblasts to 31 consecutive patients with CML. All patients were followed to their death (28 patients) or for over 5 years (3 patients) to determine the median survival and the rate of decline of survival in the patient group.

MATERIALS AND METHODS

Patient Selection and Clinical Follow-up. Adult patients with CML were diagnosed by hyperleukocytosis, bone marrow myeloid hyperplasia, and low leukocyte alkaline phosphatase scores. All patients from whom technically adequate samples could be obtained (27 patients) were studied for the presence of the Philadelphia chromosome by karyotypic analysis. Patients were treated with intermittent chemotherapy for control of blood counts and symptoms at the discretion of the attending hematologist. Thirty of 31 patients received busulfan in intermittent high doses, and some patients (7 of 31) received intermittent hydroxyurea in addition (1). Patients who developed an acute blast crisis were treated initially with vincristine and prednisone and subsequently with 1-ß-D-arabinofuranosylcytosine and daunorubicin.

Immunotherapy with BCG and Allogeneic Leukemia Cells. Informed consent for immunotherapy was obtained from all patients. Human acute leukemic myeloblasts were obtained from peripheral blood of untreated hepatitis B surface antigen-negative patients. The WBC-rich supematant was collected after sedimentation, frozen at a controlled rate in 10% dimethyl sulfoxide, and stored in 2-ml aliquots in screw-capped polyethylene tubes in liquid nitrogen at −196°. When required, the cells were thawed by gentle agitation in a 37° water bath and resuspended in nutrient medium at a concentration of 10⁶ or 10⁷ cells/ml.

BCG organisms were obtained from the Connaught Research Laboratories, Toronto, Ontario, Canada. The preparations contained 5 to 15 × 10⁵ organisms/ml when reconstituted as directed with distilled water. The immunotherapy regimen consisted of 10⁷ irradiated allogeneic acute leukemic myeloblasts injected at 4 or 5 closely spaced i.d. sites. This procedure was followed by 0.2 ml of BCG vaccine administered i.m. at the same site by the multiple-puncture technique using a disposable metal disc (Research Foundation, Chicago, Ill.). This initial regimen was repeated weekly for 4 weeks at a different site each week. Thereafter, BCG vaccine and 10⁷ leukemic cells were given in a similar manner but at monthly intervals.

RESULTS

Thirty-one consecutive patients with CML received immunotherapy with BCG and allogeneic cells in addition to chemotherapy. The clinical characteristics of the patient population are summarized in Table 1. There were 18 males and 13 females.

¹ Supported by the National Cancer Institute of Canada and National Cancer Institute (U. S. A.) Grants CA 31761-03 and CA 31762-03.
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⁴ The abbreviations used are: CML, chronic myelogenous leukemia; BCG, Bacillus Calmette-Guérin; i.d., intradermal; i.c., intracutaneous.

Received June 20, 1983; accepted September 29, 1983.
The mean age was 41.9 ± 15.4 (S.D.) years with a range of 17 to 68. The Philadelphia chromosome was present in 24 of 27 tested. The mean WBC count (× 10⁹/liter) at presentation was 94.8 ± 88.2 with a range of 22-373.0. Splenomegaly was present in 24 of 27 patients. Chemotherapy in the chronic phase consisted of busulfan in 30 patients, hydroxyurea alone in one patient, and hydroxyurea in addition to busulfan in 6 patients. One patient received therapy with cyclophosphamide in addition to busulfan. Twenty-five patients terminated in blast crisis of which 16 appeared to be of the myeloid type, 4 were of the lymphoid type, and 5 were of indeterminate type. The incidence of remission in blast crisis was one of 16 for those of myeloid type, and 3 of 4 for those of lymphoid type.

All patients developed local reaction to immunotherapy vaccination with redness, itching, and eventual minimal scarring. Some patients would not wear bathing suits because of unsightly marks. The dose of BCG was reduced in 10 patients, and vaccination with cells was stopped in one patient because of severe local reaction to vaccination. No systemic reactions were documented. Only one patient (age 68) was purified tubercle bacillus protein derivative positive at diagnosis. All purified tubercle bacillus protein derivative-negative patients converted to positive during the course of immunotherapy.

The median survival of all patients was 37 months. The rate of decline of survival (death rate per year) for the first 6 years of follow-up was 19% in the first year, 16% in the second year, 28% in the third year, 40% in the fourth year, 55% in the fifth year, and 25% in the sixth year. The survival distribution estimated by the method of Kaplan and Meier (7) from this sample of patients is given in Chart 1.

**DISCUSSION**

Immunotherapy for CML given in the chronic phase has been reported to significantly prolong the median duration of survival in good-risk patients up to a year compared to historical controls (11-13). In one published study, the historical control group showed a median survival of 43 months, while the group immunized with BCG and s.c.-injected cultured lymphoblastoid cells showed a median survival of 55 months (13). The mean annual death rate of immunized patients was 22% compared to 25% per year in controls (13). Previous studies by ourselves (8) and others (11, 12) have demonstrated stimulation of immune reactivity in CML patients to leukemia-related and other antigens after immunization with antigenically related cell vaccines. The 31 patients treated in this group received both immunotherapy and chemotherapy so that no randomly allocated control group is available for comparison. Since 28 of 31 patients have been followed from diagnosis to death, and the 3 remaining patients have been followed for over 5 years, actual and not projected survival can be documented. The 31 patients treated in this group demonstrate a median survival of 37 months. Although this number cannot be statistically compared to survival numbers published elsewhere, the patient characteristics appear to be comparable to those of other published groups (1, 3, 5, 6, 10, 14). The median survival of the patients in our group does not appear to be different from survival numbers published previously for treatment with chemotherapy alone (1, 3, 5, 6, 10, 14). In addition, the constant rate of decline in survival with time, a mean death rate of 30% per year, seems comparable to that of groups receiving chemotherapy alone (10). Survival over 70 months from diagnosis as seen in 3 of our patients is not unusual in other series (6, 10), and there is no reason to attribute this to the use of immunotherapy. We had no greater success with treatment of the blast crisis phase than was seen in series using chemotherapy alone (2, 4, 9).

We conclude that patients with CML in this study receiving immunotherapy with BCG and allogeneic myeloblasts in addition to chemotherapy continue to have a steady decline in survival with time as reported previously with chemotherapy alone (10). Neither the rate of decline in survival nor the median survival...
appears to differ from that of comparable groups of chemotherapy-treated patients reported previously (1, 3, 5, 6, 10, 14).

REFERENCES

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