CONCISE REPORT

Long-Term Disease-Free Survival in Acute Nonlymphocytic Leukemia

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Twenty-six of 45 adults (58%) with acute nonlymphocytic leukemia who were treated with intensive induction chemotherapy over 5 yr ago entered complete remission. All patients entering remission were placed on weekly maintenance chemotherapy consisting of cytosine arabinoside and 6-thioguanine. The median duration of complete remission was 17 mo and 7 patients (27%) remained in their initial remission for 62 to 102 mo. All

but one of the patients in complete remission over 5 yr have had treatment discontinued. Only 1 of 7 patients in remission for more than 5 yr has relapsed. Median survival is 26.5 mo, and 8 patients (31%) currently remain alive without evidence of leukemia 63–105 mo from diagnosis. It is possible to achieve long-term disease-free survival with chemotherapy alone in acute nonlymphocytic leukemia.

THE ADMINISTRATION of intensive chemotherapy to adults with acute nonlymphocytic leukemia in the context of modern supportive care has resulted in significant improvements in the complete remission rate and, consequently, in survival. With the newer combination regimens, remissions are regularly obtained in over 50% of patients participating in clinical trials conducted by the large cooperative groups. Complete remission rates of more than 80% have been reported from several single institutions. Because of this success with induction chemotherapy, relapse of the leukemia has now emerged as the preeminent problem in clinical management.

A variety of maintenance and consolidation chemotherapy programs have been formulated in efforts directed toward prolonging remissions and ultimately preventing recurrent leukemia. Although it has recently been stated that there is little or no suggestion that patients receiving only chemotherapy have been cured, preliminary reports have recognized the existence of such long-term survivors. Other approaches have also been successful. A promising alternative is the transplantation of allogeneic bone marrow cells following maximal chemotherapy and irradiation. Based on early results, this approach has been recommended by some authors as the preferred procedure to ensure prolonged survival in adults with acute leukemia. We previously described a simple outpatient maintenance regimen that seemed effective in prolonging remissions. This report details our long-term results in a consecutive series of 26 adults with acute nonlymphocytic leukemia who achieved complete remission over 5 yr ago.

MATERIALS AND METHODS

Between November 1971 and December 1975, 45 adults with acute nonlymphocytic leukemia were treated at the University of Minnesota Masonic Cancer Center. Twenty-six patients, or 58%, achieved complete remission following intensive induction treatment. These 26 patients ranged in age from 17 to 72 (median 48) yr; 6 patients were over 60 yr and 1 was over 70 yr of age. Fifteen were male and 11 were female. Each patient’s leukemia was subclassified according to cytologic and cytochemical criteria that have been previously described. Fourteen patients had acute myelogenous leukemia, 6 acute myelomonocytic leukemia, 5 acute promyelocytic leukemia, and 1 patient had acute monoblastic leukemia.

Each patient was treated with one of three combination chemotherapy regimens for the induction of remission. Five patients achieved complete remission with daunorubicin plus prednisone, 9 patients with 6-thioguanine plus cytosine arabinoside, and 12 patients achieved complete remission with daunorubicin plus cytosine arabinoside. Upon achieving complete remission, all 26 patients were placed on an outpatient weekly maintenance regimen consisting of 6-thioguanine, 2 mg/kg on each of 4 successive days, followed on the fifth day by cytosine arabinoside, 1.5 mg/kg intramuscularly. None of the patients received immunotherapy or consolidation chemotherapy. All patients were monitored in the outpatient clinic by monthly physical examination, blood counts, and periodic liver function tests. Bone marrow examinations, including aspiration and trephine biopsy, were routinely repeated at least every 3 mo and at any time a suspicion of relapse arose.

Remission status was assessed using the criteria of the Cancer and Leukemia Group B. The duration of remission was measured from the date complete remission was documented to the first demonstration of hematologic relapse. A relapse of leukemia was diagnosed when either the marrow myeloblast count rose above 5% or leukemic myeloblasts were detected in the blood or bone marrow. Survival was calculated from the date of diagnosis.

RESULTS

Remission Duration

The median duration of complete remission was 17 mo and remission duration for all 26 patients ranged...
from 3 to 102+ mo (Fig. 1). Eleven of the patients (42%) remained continuously free of leukemia for more than 2 yr, 9 patients (35%) for more than 3 yr, and 7 patients (27%) for more than 4 yr. Currently, 6 patients (23%) are still in their initial complete remission from more than 5 (62 mo) to 8.5 yr (102 mo) from the initial documentation of complete remission. Previously, we reported that patients with shorter remissions had higher initial leukocyte counts. No other factors that correlated significantly with either duration of remission or long-term survival were found in this present study.

Eighteen of the patients (69%) have had relapses of their leukemia. Two of these patients independently discontinued their maintenance chemotherapy and relapsed within a short interval of time. The duration of initial complete remission in these patients was 10 and 25 mo, respectively. Both subsequently obtained second complete remissions with intensive reinduction chemotherapy and were once again placed on maintenance chemotherapy with cytosine arabinoside and 6-thioguanine. One of these two patients eventually relapsed again at 11 mo. However, the other patient remains in her second complete remission more than 57 mo following the completion of reinduction chemotherapy. Two of the patients died while still in remission at 16 and 39 mo. Among the 18 patients who have relapsed, 12 (67%) relapsed within 1 yr of achieving remission. Only one of the seven patients at risk for more than 3.5 yr has relapsed. This late relapse occurred at 83 mo and consisted of the observation of occasional cells with Auer rods in a bone marrow with 2% myeloblasts. These were not detected on subsequent bone marrow examinations following the reinstitution of maintenance chemotherapy.

Maintenance chemotherapy has been discontinued in all who have been in continuous complete remission for more than 5 yr with the exception of one patient. He was continued on therapy after expressing reluctance to terminate it. The others have been off of maintenance chemotherapy from 2 to 50 (median 25) mo. The patient who relapsed at 83 mo had been off of maintenance chemotherapy for 12 mo at the time of her relapse.

**Toxicity**

The maintenance program consisting of 6-thioguanine and cytosine arabinoside was well tolerated. However, 21 of the patients (81%) experienced nausea and vomiting following the intramuscular injection of cytosine arabinoside. This discomfort generally lasted only a few hours and was never cause for discontinuing or altering the dose of the medication. Leukopenia defined as a leukocyte count less than 2500/μl and thrombocytopenia defined as less than 100,000 platelets/μl occurred transiently in 14 and 10 patients, respectively. No patient had a significant infection that was associated with leukopenia during complete remission, and there was only one minor episode of bleeding associated with thrombocytopenia.

Fourteen patients exhibited abnormalities in their hepatic enzymes or bilirubin while in complete remission. The most common abnormalities detected were slight elevations of alkaline phosphatase and SGOT. Although the changes in hepatic enzymes were detected more frequently in patients with longer remissions, the temporal appearance of the abnormalities was variable and did not appear to be related to the duration of treatment. Three of 12 patients (25%) with remissions shorter than 12 mo displayed abnormal liver function tests compared to 12 (86%) of 14 patients with longer remissions ($p < 0.01$). Two patients died while in complete remission at 16 and 39 mo with evidence of hepatic decompensation. In one, portal cirrhosis and fatty infiltration of the liver consistent with alcoholic liver disease were found. An autopsy was not obtained in the second patient. It is possible that the chemotherapy contributed to the deaths of both patients.

**Survival**

The survival of all 26 patients from diagnosis is presented in Fig. 2. The median survival is 26.5 mo. Eight patients (31%) remain alive 63–105 mo from diagnosis. Six patients are currently in their initial complete remissions and two are in second remissions. With the exception of two patients who died while in complete remission, all deaths were related to recurrent leukemia.
Continuously free of leukemia for more than 5 yr or longer.8 Our results are similar in that 7 of 26 patients, or 27%, remained continuously free of leukemia for more than 5 yr from the end of induction chemotherapy despite receiving only simple outpatient maintenance treatment.

A previous survey of long-term survivors in a large number of adults with acute nonlymphocytic leukemia found evidence that less than 1% of all patients survived for more than 5 yr.20 Our patients and those in the other series reporting long-term survivors with acute nonlymphocytic leukemia were treated at a time when remission rates ranged from 25% to 60%.8,10 Thus, overall 5-yr disease-free survival, including nonresponders as well as the responders, ranges from 5% to 16%. From an analysis of the data of two large studies, it is apparent that the overall percentage of long-term survivors has increased as the complete remission rate has improved with modern intensive therapy.6,9 Whether the number of 5-yr survivors will be increased further with the highly efficient induction regimens currently in use remains to be seen.6,6 The role of maintenance chemotherapy in prolonging the survival of adults with acute nonlymphocytic leukemia or its contribution to actually effecting cures is uncertain. However, patients who receive maintenance therapy in some form have complete remissions which are, in general, longer than those observed in unmaintained series.14,21

Despite reports of long-term survival, the question of which patients with acute nonlymphocytic leukemia, regardless of postinduction management, are actually cured remains unsettled. Allogeneic bone marrow transplantation following ablative therapy has been suggested as an alternative to chemotherapy in patients with acute nonlymphocytic leukemia in first remission.7,12,13 Further experience is necessary before definitive conclusions regarding the role of this approach in producing a significant proportion of long-term survivors can be reached. Following maintenance chemotherapy, it has been suggested that a 7-yr interval of continuous disease-free survival approximates cure.8 Certainly, the majority of relapses in our study occurred within the first 2.5 yr of remission, but one patient relapsed after 7 yr in complete remission. Many of the other long-term disease-free survivors who are off of therapy have probably been cured of their leukemia. However, because of the occasional late relapse, caution must be exercised in declaring an individual patient cured.

DISCUSSION

It is becoming increasingly evident that chemotherapy alone can result in long-term disease-free survivors among adults with acute nonlymphocytic leukemia. Preliminary reports from cooperative groups and from single institutions have recently appeared documenting that 16%–25% of all patients achieving complete remission after 1970 may remain in continuous remission for 5 yr or longer.8,10 Our results are similar in that 7 of 26 patients, or 27%, remained continuously free of leukemia for more than 5 yr from the end of induction chemotherapy despite receiving only simple outpatient maintenance treatment.

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