Intensive Chemotherapy is the Treatment of Choice for Elderly Patients With Acute Myelogenous Leukemia

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One-hundred and seven patients with acute myelogenous leukemia (AML) ranging in age from 15 to 82 yr who were previously untreated, received a 7-day high-dose remission induction regimen consisting of daunorubicin, cytarabine, and thioguanine (TAD). Identical complete remission rates of 76% were observed for 33 patients 60 yr of age and older and for 74 patients age 15-59 yr. Median remission duration and survival were 14 mo and 22 mo for patients 60 yr and older, and 16 mo and 22 mo for patients 15-59 yr. These differences are not significant. These data indicate that older patients respond to intensive chemotherapy in a similar manner to younger patients with this disease.

The prognosis for elderly patients with acute myelogenous leukemia (AML) is generally regarded as poor.1-4 Although recent studies using intensive induction chemotherapy report complete remission rates of greater than 60% for patients with AML,5-8 there is controversy as to whether elderly patients should receive these intensive chemotherapy regimens.

In 1975, we began a prospective single institution trial of the treatment of AML. One-hundred and seven patients ranging in age from 15 to 82 yr were treated with TAD, a high-dose sequential chemotherapy regimen given over 7 days, which includes cytarabine, 6-thioguanine, and daunorubicin. The study was open to patients of all ages, and there were no exclusions once therapy was initiated. In this report we review response rates and survival of patients 60 yr and older. These data are compared to results in younger patients.

MATERIALS AND METHODS

Patients

One-hundred and seven previously untreated patients with AML entered the study. None of the patients included in this study developed AML following treatment for a prior malignancy.

Induction Chemotherapy

Induction chemotherapy consisted of 1-3 cycles of cytarabine at 100 mg/sq m intravenously every 12 hr for 7 days and 6-thioguanine, 100 mg/sq m orally every 12 hr for 7 days. Daunorubicin, 60 mg/sq m intravenous, was given 4 hr following the morning cytarabine injection on days 5, 6, and 7 of each induction cycle.9

Consolidation and Maintenance

Patients who achieved a complete bone marrow remission as defined by criteria of Cancer and Leukemia Group B9 received consolidation therapy. The first 68 patients who entered this study received two consolidation cycles of a modified TAD consisting of cytarabine and 6-thioguanine for 5 days and a single dose of daunorubicin on day 6. Drug doses were identical to those used in the induction regimen. During the consolidation phase, patients also received central nervous system (CNS) prophylaxis consisting of cranial irradiation (24 Gy) and 5 intrathecal injections of cytarabine, 100 mg/sq m over 2-3 wk. Patients who remained in remission following completion of consolidation chemotherapy were randomized to receive maintenance chemotherapy with or without immunotherapy. Immunotherapy consisted of monthly intravenous injections of Corynebacterium parvum and subcutaneous injections of allogeneic, irradiated leukemia cells. Maintenance chemotherapy consisted of 2 monthly cycles of cytarabine, 100 mg/sq m intravenous, and 6-thioguanine, 100 mg/sq m orally, every 12 hr for 5 days. The third cycle consisted of a single dose of daunorubicin (60 mg/sq m) on day 1. Cytarabine and thioguanine were substituted for daunorubicin when the cumulative daunorubicin dose reached 500 mg/sq m. Maintenance chemotherapy was given in the outpatient clinic. Details of this protocol have been described.9

In 1978, the second chemotherapy regimen was developed for the treatment of AML (TAD-2). Induction chemotherapy was identical. Consolidation therapy was modified and maintenance omitted. Patients achieving a complete remission received two cycles of consolidation chemotherapy consisting of a 5-day course of 5-azacytidine (150 mg/sq m/day) with doxorubicin (45 mg/sq m) given on days 4 and 5. This was followed in 3 wk by a 5-day course of TAD. Once consolidation was completed, patients received no further chemotherapy. Central nervous system prophylaxis was also omitted. The distribution of patients by age treated in the TAD-1 protocol was 48 in the 15-59 yr group and 17 in the >59 yr group, and in TAD-2, it was 26 and 16, respectively.

Supportive Therapy

Transfusions of blood and platelets were given when required. Human leukocyte antigen (HLA) matched platelets were given to patients unresponsive to random platelet transfusions. Patients were maintained in conventional hospital isolation rooms and received oral nonabsorbable antibiotics. Infectious complications were treated with carbencillin and an aminoglycoside antibiotic. Some

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patients with documented infections unresponsive to antibiotics received granulocyte transfusions from related donors. Patients were discharged when their neutrophil count exceeded 10⁹/liter and their general condition was considered satisfactory.

Data Analysis
All patients with AML were included in the analysis. Remission duration was calculated from the date of complete hematologic remission to the date of relapse. Survival was computed from the date of study entry to death. Actuarial remission and survival analysis was performed by the product-limit method (Kaplan-Meier) and analyzed using program BMDPIL (+) of the UCLA Health Science Computing Facility. Remission and survival curves were compared by the Breslow (Gehan) and generalized Wilcoxon tests. Treatment cohorts were compared by chi-square analysis with Yates correction or paired Student's t test as appropriate.

RESULTS
Remission Induction
Complete remissions were obtained in 25 of 33 patients (76%) 60 yr and older, and in 56 of 74 patients (76%) 15-59 yr of age. Response rates were independent of sex, pretreatment blood counts, presence of organomegaly, infection, fever, or hemorrhage.

Remission Duration and Survival
Median remission duration and survival for patients achieving a complete remission was 14 mo and 22 mo, respectively, for patients 60 yr and older and 16 and 22 mo for patients 15-59 yr of age (Fig. 1 A and B). The projected 3-yr survival for patients 60 yr and older is 38% (95% confidence intervals, 10%-66%) and for patients 15-59 yr is 38% (95% confidence intervals, 18%-58%). Median survival for nonresponders was 82 days for the 60 yr and older group, and 70 days for those patients 15-59 yr of age.

Toxicity
Severe reductions in granulocytes and platelets occurred in all patients within 7 days of completing induction chemotherapy. Greater than 90% of induction cycles were associated with fevers ≥38.5°C on ≥2 occasions. FEVERS in patients with granulocytes ≤0.5 x 10⁹/liter were assumed to be related to infections and were treated with systemic antibiotics. Rarely, patients developed perirectal abscesses or urinary tract infections. Infections occurred less frequently following consolidation chemotherapy and were rare during maintenance chemotherapy. Less than 5% of maintenance cycles were complicated by severe reductions in granulocytes or platelets. Patients who received prophylactic granulocyte transfusions had fewer episodes of sepsis but more pneumonias. Remission rate, remission duration, and survival were comparable for patients receiving or not receiving granulocyte transfusions. These data are analyzed in detail elsewhere.¹¹

All patients developed platelet counts ≤20 x 10⁹/liter following induction chemotherapy and most had clinical evidence of bleeding on at least one occasion. Platelet transfusions were given to all patients. Bleeding occurred less frequently in patients receiving consolidation chemotherapy and were rare during maintenance chemotherapy.

DISCUSSION
Several recent studies have reported high remission rates and improved survival in patients with AML who receive intensive induction chemotherapy. Although most investigators agree that intensive therapy is
optimal in young patients, there is no consensus as to how elderly patients should be treated. Several recent studies have reported comparably high response rates in elderly patients receiving intensive chemotherapy.12-14 Most earlier studies of chemotherapy of AML in elderly patients have been limited by small numbers of patients, nonuniformity in the induction therapy used, or employment of induction regimens not intensive enough to cause adequate tumor cytoreduction.

We treated 107 patients with a single intensive induction chemotherapy regimen. Patients 60 yr and older had the same remission rate as the younger patients. Furthermore, median remission duration, median survival, and projected long-term survival were comparable between the two age groups.

Leukemia cells from patients were classified according to the French-American-British (FAB) criteria.15,16 Most patients (60%) were classified as having undifferentiated myeloid leukemia (M1), myelogenous leukemia (M2), or myelomonocytic leukemia (M4). These three subtypes were equally represented within the two age groups. Less than 10% of patients were classified as progranulocytic leukemia (M3), monocytic leukemia (M5), or erythroleukemia (M6). Cells from 20% of patients could not be classified using the FAB scheme. Remission rate and duration of remission and survival did not correlate with FAB classifications. This is consistent with previously reported data.17,18

After 1978 we changed the consolidation portion of the protocol and discontinued maintenance chemotherapy. Azacytidine was added to the consolidation regimen. Azacytidine is reported to be active in resistant AML;19 it was added in an attempt to further reduce the tumor cell burden and prevent development of drug resistance. Central nervous system prophylaxis was not included in the TAD-2 trial. We and others have failed to demonstrate a biologically important role for it in prolonging remissions in AML.9 Finally, maintenance therapy was eliminated because of its questionable value in prolonging remissions in AML.20 To date, median remission duration and survival of patients treated with TAD-2 are comparable to those who received TAD-1. The median remission duration for patients 60 yr and older for TAD-1 and TAD-2 combined is 14 mo and for TAD-1 alone is 13 mo.

Based on our data, we conclude that age is not a contraindication to the use of intensive induction chemotherapy in patients with AML. Treatment of elderly patients with AML with intensive chemotherapy results in a high proportion of remission and improves survival.

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