Long-Term Outcome of High-Dose Cytarabine-Based Consolidation Chemotherapy for Adults With Acute Myelogenous Leukemia

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Modern induction chemotherapy produces 60% to 80% complete remissions in adults with newly diagnosed acute myelogenous leukemia. A major challenge is to eradicate subclinical disease in remission and prevent leukemic relapse. We analyzed the long-term results of high-dose cytarabine-anthracycline consolidation chemotherapy without maintenance treatment and examined the effect of major prognostic factors, including age, sex, history of preleukemia, and cytogenetics. Two hundred twenty-seven patients with newly diagnosed acute leukemia were enrolled on two sequential anthracycline consolidation chemotherapy without maintenance treatment and examined the effect of major prognostic factors, including age, sex, history of preleukemia, and cytogenetics. Two hundred twenty-seven patients with newly diagnosed acute leukemia were enrolled on two sequential studies conducted from 1982 to 1991. One hundred fifty-one patients (67%) achieved a complete remission. One hundred twenty-three patients were eligible for high-dose cytarabine-based consolidation administered in two to three courses. After a median follow-up of 4.8 years, 40 patients remain alive, with 28 in continued remission. Median remission duration for all eligible patients is 12.8 months, and actuarial leukemia-free survival (LFS) at 5 years is 26% ± 8%. Advanced age and male sex were negative prognostic indicators for LFS. For patients <45 years of age, 5-year LFS was 35% ± 13%, as compared with 18% ± 11% for patients greater than age 45 (P = 0.03). Toxicity of consolidation chemotherapy included treatment-related death in nine patients and serious neurotoxicity in five. Our results show an improved LFS for younger patients treated with high-dose cytarabine-based consolidation. There was no apparent benefit for older patients compared with reported data with less intensive regimens.

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W I T H M O D E R N induction chemotherapy, 60% to 80% of adults with acute myelogenous leukemia achieve complete remission (CR).1-4 Despite consolidation and/or maintenance chemotherapy, most patients relapse. A major challenge is to eradicate subclinical disease in remission. The median duration of remission is 12 to 18 months, and only 20% to 30% survive free of recurrence at 5 years.5-6 The presumed mechanism of relapse is proliferation of leukemia cells surviving induction chemotherapy. A variety of postremission treatment regimens have been evaluated. High-dose cytarabine-based consolidation chemotherapy has resulted in encouraging results in a number of studies.7-13 These studies generally have had limited numbers of patients with relatively brief follow-up. To evaluate the long-term effects of high-dose cytarabine consolidation, we analyzed the results of 123 consecutive patients receiving high-dose cytarabine-anthracycline consolidation chemotherapy without maintenance therapy on one of two clinical trials conducted from 1982 to 1991, and examined the effect of major prognostic factors, including age, sex, history of preleukemia, and cytogenetics.

MATERIALS AND METHODS

Two hundred twenty-seven adult patients with newly diagnosed acute myeloid leukemia (AML) were enrolled on two sequential studies, ALP3 and ALP4, conducted by the UCLA School of Medicine from 1982 to 1991. Data were analyzed as of March 27, 1992. Median follow-up from the time of remission induction for the surviving patients eligible for consolidation is 57.6 months (range, 8.4 to 109.2 + months). The study designs were approved by the UCLA Human Subject Protection Committee and all patients provided informed consent to participate.

The diagnosis of AML was made according to French-American-British (FAB) criteria.14 De novo AML was defined if no documented hematologic abnormality was identified more than 2 months before the diagnosis of AML. Preleukemia was defined as ineffective hematopoiesis documented more than 2 months before the diagnosis of AML by either an abnormal bone marrow (BM) evaluation or an otherwise unexplained peripheral blood cytopenia (leukocytes, < 4.0 x 10^9/L; granulocytes, < 2.0 x 10^9/L; hemoglobin, < 10 g/dL; or platelets, < 120 x 10^9/L). Morphologic subtypes of preleukemia were analyzed according to the FAB classification for myelodysplasia.14 Patients with leukemia secondary to treatment for another malignancy were not eligible. Karyotype was classified as follows: (1) normal, ie, diploid; (2) abnormal but favorable, ie, t(8;21), t(15;17), or abnormalities of 16q; (3) abnormal and unfavorable, ie, trisomy 8, abnormalities of chromosomes 5 and/or 7, abnormalities of chromosome 11, multiple or complex translocations; (4) abnormal, all others.7 Two hundred twenty-six patients received induction chemotherapy consisting of daunorubicin 60 mg/m^2 by intravenous (IV) bolus for 3 days in combination with cytarabine in one of several schedules. One hundred seventy-six patients received cytarabine 200 mg/m^2 by continuous infusion for 7 days. Fifty patients received cytarabine at a dose of 500 mg/m^2 by IV infusion over 2 hours every 12 hours for 12 doses. One hundred twenty-five patients receiving continuous infusion cytarabine also received 6-thioguanine 100 mg/m^2 orally every 12 hours for 7 days. One patient received single-agent cytarabine to achieve remission because of a history of severe cardiac insufficiency; his results are included for analysis. Patients received a second course of their original induction regimen on or after day 21 if residual acute leukemia was found in blood or BM. Complete hematologic remission was defined by the criteria of Ellison et al.15 One hundred fifty-one patients achieved CR. Twenty-eight patients ≤ 45 years of age who had an available histocompatible-matched sibling donor were assigned to allogeneic BM transplantation (BMT); their results are not included for analysis of duration of remission or survival. The remaining 123 patients were eligible for high-dose cytarabine-based consolidation, which was administered in two to three courses, began a median of 1 month after achieving complete remission. From 1982 to 1987, on the ALP3 study,3 61 patients were assigned to receive consolidation chemother-
therapy consisting of a first course using high-dose cytarabine 3 g/m² administered as a 2-hour IV infusion every 12 hours for 4 days and daunorubicin 45 mg/m² by continuous IV infusion for 7 days with daunorubicin 45 mg/m² IV bolus/d for 3 days. The second course of consolidation consisted of cytarabine 200 mg/m² by continuous IV infusion for 7 days with daunorubicin 45 mg/m² by IV bolus/d for 3 days. A second course of consolidation consisted of etoposide 200 mg/m² over 1 hour IV infusion/d for 5 days and mitoxantrone 10 mg/m² by IV bolus/d for 3 days. A third cycle of consolidation consisted of cytarabine 2 g/m² administered as a 2-hour IV infusion every 12 hours for 4 days and daunorubicin 45 mg/m² by IV bolus/d for 3 consecutive days. Nine elderly patients (age, >60 years) entered into the study after 1988 received dose-reduced consolidation chemotherapy due to concerns about regimen-related toxicity in the elderly as follows: high-dose cytarabine was reduced to 500 mg/m² every 12 hours for 4 days, daunorubicin to 30 mg/m²/d for 3 days, and mitoxantrone to 8 mg/m²/d for 3 days for all cycles of consolidation. After the completion of consolidation therapy, no maintenance therapy or other antileukemic therapy was administered until relapse. Toxicity was scored according to standard criteria.

Supportive care. Supportive care for granulocytopenic patients consisted of reverse isolation in single rooms and treatment with oral nonabsorbable antibiotics including vancomycin at 100 mg every 8 hours, polymyxin B at 100 mg every 8 hours, and nystatin at 10⁶ U every 4 hours. Laminar air flow rooms were not used routinely. Febrile granulocytopenic patients were empirically treated with broad spectrum antibacterial antibiotics consisting of a semisynthetic penicillin and a third generation cephalosporin or imipenem. Patients with documented or suspected fungal infection were treated with amphotericin B. Random or single donor platelet transfusions were administered to maintain a platelet count ≥10⁵ × 10⁹/L. Erythrocytes were transfused to maintain a hematocrit ≥27%. Leukocyte transfusions were not used.

Statistical analysis. The date of diagnosis of AML and the date of remission were defined by the date the diagnostic BM studies were performed. Patients were analyzed for overall survival as well as leukemia-free survival (LFS) from the time of remission by the product limit method of Kaplan and Meier. Univariate comparisons of patients undergoing induction and consolidation chemotherapy were performed using the Fisher’s exact test and the Wilcoxon rank-sum test. Summary estimates included survival fractions ± 2 × SE for 95% confidence intervals for median survival time. Survival curves were compared using the log-rank test. Prognostic factors for entering remission were analyzed using logistic regression. Prognostic factors for survival and LFS were evaluated using the Cox regression analysis. Analyses were performed using the BMDP statistical package. P values were two-sided throughout.

RESULTS

Two hundred twenty-seven patients with newly diagnosed AML aged 16 to 84 years (median, 48 years) were entered into study. Median duration of follow-up for surviving patients from the time of complete remission was 57.6 months (range, 8.4 to 109.2+ months). Fifty-six patients (25%) had a preleukemic syndrome before the diagnosis of AML and 171 (75%) had de novo AML. Patient characteristics at the time of induction and consolidation chemotherapy are described in Table 1.

One hundred fifty-one patients (67%) achieved CR, 104 with the first course of chemotherapy. Seventy-seven patients failed to achieve remission because of persistent leukemia in 45 and early death, which occurred in 32 patients. Age less than 60 years and the absence of a preceding preleukemia were significant prognostic factors for achieving remission (P < .0001 and P = .0002, respectively). Abnormal karyotype was also a significant prognostic factor associated with a lesser likelihood of entering remission (P = .007); however, no statistically significant cytogenetic risk group could be identified. Twenty-eight patients aged ≤45 years with a histocompatible-matched sibling donor went on to receive allogeneic BMT at first CR; these patients are not considered further in this report.

One hundred twenty-three patients were eligible to receive consolidation chemotherapy (Fig 1). One hundred eight patients received at least one cycle of consolidation and 15 patients received no further therapy after induction due to infection (5 patients), excessive toxicity related to induction (4 patients), patient refusal (3 patients), and early relapse (3 patients). All patients who went on to receive consolidation were assigned to receive at least two cycles of treatment; however, 29 did not receive cycle 2 for reasons of infection (4 patients), excessive toxicity related to the first consolidation course (10 patients), patient refusal (7 patients), or relapse (8 patients). Thirty-one patients were eligible to receive a third cycle of consolidation under protocol ALP4, but only 23 actually received a third course. Patients aged more than 60 years were less likely to receive the prescribed course of therapy; only 13 of 37 patients aged more than 60 years completed two to three consolidation cycles compared with 56 of 86 patients aged less than 60 years (P < .01).

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>All Patients</th>
<th>Patients Eligible for Consolidation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>119/106</td>
<td>70/53</td>
</tr>
<tr>
<td>Median WBC (×10⁹/L) (range)</td>
<td>7.6 (0.3-308)</td>
<td>4.6 (0.3-308)</td>
</tr>
<tr>
<td>Antecedent hematologic disorder (%)</td>
<td>56 (25)</td>
<td>24 (20)</td>
</tr>
<tr>
<td>Chromosomal abnormality (yes/no/un-known)</td>
<td>75/76/76</td>
<td>39/42/42</td>
</tr>
<tr>
<td>Karyotypet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>Abnormal (favorable)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal (unfavorable)</td>
<td>41</td>
<td>24</td>
</tr>
<tr>
<td>Abnormal (other)</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Unknown</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>Achieved remission (%)</td>
<td>161 (67)</td>
<td></td>
</tr>
<tr>
<td>No. of patients age (% CR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45 yr</td>
<td>103 (80)</td>
<td>54</td>
</tr>
<tr>
<td>46-60 yr</td>
<td>45 (69)</td>
<td>32</td>
</tr>
<tr>
<td>&gt;60 yr</td>
<td>79 (47)</td>
<td>37</td>
</tr>
<tr>
<td>BMT in first remission</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>BMT after relapse</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: WBC, white blood cell count.

*Includes all patients achieving remission who did not receive allogeneic BMT in first CR.
†Classifications described in Materials and Methods.
Toxicity of consolidation chemotherapy course one included serious neurotoxicity due to high-dose cytarabine in 5 of the 108 patients and treatment-related death in 9. There was no difference in consolidation-related deaths in the different age groups. There was no difference in the incidence of neurotoxicity as a function of cytarabine dose in consolidation cycle one. Two of 79 patients receiving the second consolidation course and 2 of 23 patients receiving a third course of consolidation died as a result of treatment-related complications. One late death due to cardiomyopathy occurred 2 years after completing consolidation chemotherapy.

**Disease-free survival (DFS) and survival.** DFS and survival from remission are indicated in Figs 2 and 3. Forty of the original 123 patients eligible for consolidation (33%) remain alive, with 28 in continued remission from 12 to 110+ months. Median remission duration for all patients eligible for consolidation is 12.8 months (range, 1.3 to 110+ months) and actuarial DFS at 5 years is 26% ± 8%. Median survival from remission is 24 months (range, 1.3 to 110+ months), and actuarial survival from remission is 33% ± 10% at 5 years. Seventy-five (61%) of those eligible for consolidation have relapsed with an actuarial risk of relapse of 69% ± 10% at 5 years. Forty-nine received further intensive chemotherapy and 31 achieved a second remission. Nine underwent BMT and two received retinoic acid.

Median survival after relapse was 6 months (range, 1 day to 90+ months).

Age was a significant predictor of both DFS and overall survival from remission. The actuarial DFS 5 years from complete remission for patients over age 45 is 18% ± 11% as opposed to 35% ± 13% for patients ≤45 years of age (P = .03). Actuarial survival for patients greater than 45 years of age achieving CR was 17% ± 11% (median, 16 months) as opposed to 49% ± 15% (median, 38.4 months) for those aged less than 45 years (P < .001) (Figs 4 and 5). The actuarial risk of relapse for patients greater than age 45 is 78% at 5 years compared with 62% for the group of patients aged ≤45 years (P = .07).

DFS was significantly better for women than men (P = .0054) (Fig 6) (regardless of age). Analysis of pretreatment characteristics showed that advanced age and male sex were negative prognostic indicators for LFS. The presence of a chromosome abnormality, AML subtype, lactate dehydrogenase (LDH), marrow cellularity and pretreatment peripheral blood counts were not significant.
prognostic factors. A history of an antecedent hematologic disorder also did not affect LFS (Fig 7).

An important unresolved issue is the optimal number of consolidation chemotherapy courses. A beneficial effect of more than one consolidation treatment on LFS could not be demonstrated from these data. Although patients receiving only one course of consolidation chemotherapy had a significantly poorer LFS than patients who received two to three courses ($P = .03$), the group receiving only one course was biased by eight patients who relapsed before a second cycle could be administered. When patients who relapsed before receiving a second cycle of consolidation chemotherapy are excluded from analysis, there remain 21 patients who received only one course of consolidation chemotherapy for reasons of toxicity or patient refusal. The 5-year actuarial LFS for this group is $38\% \pm 21\%$. The 5-year actuarial LFS for patients who received two to three consolidation courses (excluding 2 patients for early relapse) is $27\% \pm 11\%$; the difference is not statistically significant ($P = .42$).

**DISCUSSION**

Postremission therapy is necessary to prevent or delay leukemia relapse, but the optimal form of treatment is uncertain. Moderate dose maintenance chemotherapy significantly prolonged remission duration in randomized studies. Use of one to several courses of intensive consolidation chemotherapy may obviate the need for prolonged maintenance therapy and there is controversy whether both consolidation and maintenance are required. Encouraging data have been reported using high-dose cytarabine consolidation therapy.

The objective of this analysis was to determine the long-term LFS and overall survival of adult patients receiving high-dose cytarabine-based intensive consolidation and to analyze the toxicity associated with this regimen. Of 123 eligible patients, 108 received at least one course of consolidation treatment. Although all patients were designated to receive at least two cycles of dose-intensive consolidation chemotherapy, nearly one-third of those patients completing one course were unable or unwilling to proceed with a second course. Thus, repeated courses of dose-intensive therapy are difficult to administer, particularly to older patients. Similarly, only $74\%$ of patients assigned to a third course received the intended therapy. Although this study was not designed to assess the efficacy of additional cycles of consolidation chemotherapy, no advantage in DFS could be demonstrated for patients receiving multiple consolidation cycles versus a single
course when patients not receiving the second consolidation course because of early relapse are excluded.

Our results showed an improved LFS for younger patients treated with high-dose cytarabine-based consolidation as compared with older patients. Because adverse events related to consolidation were unequally distributed and occurred primarily in the older age group and older patients had a greater risk of relapse, there was no apparent benefit of high-dose cytarabine, particularly for patients aged more than 60 years compared with reported data with less intensive regimens.

We analyzed results in patients aged from 18 to 45 years because they might otherwise be candidates for BMT; median remission duration was 21.6 months and DFS at 5 years was 35% ± 13%. Median follow-up for all patients was 57.6 months. There have been no relapses occurring after 4 years, suggesting that the results are unlikely to substantially change with further follow-up. Overall survival after remission was 50% ± 15%. These results compare favorably to many marrow transplant studies in adults23-25 and are consistent with other reports of high-dose cytarabine consolidation in young patients.7,10,26 Less intensive postremission therapy generally produces a remission duration of 12 to 20 months, with approximately 25% of patients in remission at 36 months.5,7,26-29

Intensive consolidation therapy is associated with greater risk in older patients. In the present study, high-dose cytarabine-based consolidation produced serious toxicity in 27% of patients over age 60. Also, those older patients who were able to receive high-dose cytarabine-based consolidation did not enjoy improved long-term LFS because of a higher risk of relapse. Thus, these data do not support the use of high-dose cytarabine-based consolidation therapy in the elderly.

High-dose cytarabine-based consolidation chemotherapy produced an LFS of 27% ± 9% for all patients and 35% ± 13% for patients under age 45. Regimen-related toxicity and infection had a significant impact on the ability to complete the prescribed course of treatment, suggesting that further dose intensification, or an increase in the number of consolidation cycles, is unlikely to produce further improvement in LFS in older adult patients.

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REFERENCES


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