Frequency of Prolonged Remission Duration after High-Dose Cytarabine Intensification in Acute Myeloid Leukemia Varies by Cytogenetic Subtype


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ABSTRACT

Advances in the treatment of acute myeloid leukemia (AML) have occurred with the introduction of new therapies including high-dose cytarabine and the identification of powerful prognostic factors such as cytogenetics that predict for long-term outcome. To date, the prognostic impact of cytarabine dose escalation within various cytogenetic groups of AML has not been assessed. We describe 285 newly diagnosed patients with primary AML who had adequate karyotypes and were enrolled on a prospective Cancer and Leukemia Group B cytogenetic study. All patients were randomly assigned to postremission treatment with standard-, intermediate-, or high-dose cytarabine intensification. Patients were categorized into one of three cytogenetic groups: (a) core binding factor type ([CBF]; i.e., t(8;21) inv(16), t(16;16), and del(16)); (b) normal; and (c) other abnormal karyotype. An evaluation of these patients after a median follow-up time of over 7 years was performed to determine the relationship of intensification to outcome by cytogenetic group. Patients included 57 patients with CBF AML, 140 patients with normal karyotype AML, and 88 patients with other cytogenetic abnormalities. The treatment outcome of CBF AML patients was superior, with an estimated 50% still in complete remission (CR) after 5 years as compared with 32 and 15% for patients with normal karyotype AML and other abnormal AML, respectively (P < 0.001). Univariate analysis showed the following nonkaryotype factors to predict a prolonged CR duration: (a) younger age (P < 0.008); (b) lower leukocyte count (P = 0.01); (c) the presence of Auer rods (P = 0.004); (d) a lower percentage of bone marrow blasts (P = 0.001) at the time of diagnosis, (e) and a higher postremission cytarabine dose (P < 0.001). The impact of cytarabine dose on long-term remission was most marked (P < 0.001) in the CBF AML group (after 5 years, 78% of those with a dose of 3 g/m2 were still in CR, 57% of those with a dose of 400 mg/m2 were still in CR, and 16% of those with a dose of 100 mg/m2 were still in CR) followed by normal karyotype AML (P = 0.01; after 5 years, 40% of those with a dose of 3 g/m2 were still in CR, 37% of those with a dose of 400 mg/m2 were still in CR, and 20% of those with a dose of 100 mg/m2 were still in CR). In contrast, cytarabine at all doses produced only a 21% or less chance of long-term continuous CR after 5 years as compared with 32 and 15% for patients with normal karyotype AML and other abnormal AML, respectively (P < 0.001). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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The introduction of postremission strategies such as high-dose cytarabine and allogeneic and autologous stem cell transplantation has contributed to an improved outcome for adult patients with AML. For high-dose cytarabine, the steep in vitro dose-response curve observed with this agent (10), combined with initial small studies (11, 12), prompted large randomized studies (13-16) that established high-dose cytarabine intensification therapy as a commonly accepted treatment for young patients with AML. Allogeneic and autologous stem cell
transplantation have similarly been demonstrated to have efficacy in the initial management of AML but have higher treatment-related mortality rates (17–19). Randomized studies comparing these therapies with high-dose cytarabine have failed to demonstrate any survival benefit (17–19). Thus, debate persists as to the optimal therapy for young patients with AML. Utilization of pretreatment cytogenetics to stratify patients to particular treatments has been advocated, but the relationship of cytogenetic subtype and the dose intensity of cytarabine as it relates to the long-term remission of patients with AML has not been reported. Herein, we describe such an analysis of outcome of cytogenetically defined groups of patients who were assigned to receive varying doses of postremission cytarabine therapy.

PATIENTS AND METHODS

Patients. Patients included in this analysis were 16 years or older with primary AML as defined by the FAB classification system (20) and were participants in a previously reported randomized trial conducted by the CALGB (13). Patients with a prior history of myelodysplasia, other antecedent hematological malignancies, prior nonsteroidal cytotoxic chemotherapy or radiation therapy, preexisting liver disease as defined previously (13), or uncontrolled infection were excluded. Central review of the pathological diagnosis was performed. Due to the recently recognized unique biology of patients with acute promyelocytic leukemia, such patients have been excluded from this analysis of postremission therapy.

Cytogenetics. Chromosomal analysis of bone marrow was performed in institutional CALGB cytogenetics laboratories, and karyotypes were centrally reviewed biannually by an expert panel of CALGB cancer cytogeneticists. Specimens were obtained at diagnosis from all patients. Specimens were processed using direct methods and unstimulated short-term (24, 48, and 72 h) cultures. G-banding was usually done, although Q-banding was acceptable for inclusion in this series. A minimum of 20 bone marrow metaphase cells was analyzed in each patient designated as having a normal karyotype. The criteria used to describe a cytogenetic clone and the description of karyotype followed the recommendations of the International System for Human Cytogenetic Nomenclature (21).

Treatment. The therapy administered to patients included in this study has been described previously (13). Briefly, the patients received induction therapy consisting of 7 days of a continuous infusion of cytarabine (200 mg/m²/day) and 3 days of bolus daunorubicin (45 mg/m²/day for patients ≥ 60 years and 30 mg/m²/day for patients > 60 years). Patients not attaining a CR received a second course of induction therapy consisting of 5 days of cytarabine and 2 days of daunorubicin at doses identical to those administered initially. Patients in CR were stratified according to the number of induction courses (one or two) and their age (less than 40 years, 40–60 years, and more than 60 years) and randomly assigned by the CALGB statistical center to receive four courses of single-agent cytarabine in one of three regimens: (a) 100 mg/m²/day for 5 days as a continuous infusion; (b) 400 mg/m²/day for 5 days as a continuous infusion; and (c) 3 g/m² bolus over 3 h every 12 h on days 1, 3, and 5 for a total of six doses. These courses were administered approximately every 28 days, unless recovery from toxicity had not occurred. After cytarabine, patients received four monthly treatments with 100 mg/m² cytarabine every 12 h by s.c. injection for 5 days (total of 10 doses) and 45 mg/m² daunorubicin by rapid infusion on day 1.

Evaluation. During treatment, patients underwent a bone marrow aspiration after the completion of each cytarabine intensification and maintenance therapy. Thereafter, patients were followed with bone marrow testing every 3 months for 1 year, every 6 months for 2 years, and then every year for 2 additional years. Patients were followed yearly after 5 years of remission with bone marrow examinations being performed only if the blood counts suggested a relapse of AML.

Criteria for Response and Definition of Relapse. A CR was defined as the presence of a morphologically normal bone marrow and at least 1,500 granulocytes/µl and 100,000 platelets/µl in the blood. Relapse was defined as greater than 5% leukemic cells in bone marrow aspirates or new extramedullary leukemia in patients with a previously documented CR using the previously published National Cancer Institute guidelines (22).

Statistical Analysis. The level of significance was evaluated with two-sided tests. Uncensored continuous variables and percentages were compared among groups using the Kruskal-Wallis test. Nominal (discrete) variables were compared among groups with Pearson’s χ² test. The Kaplan-Meier method was used to estimate the distribution of survival and CR duration. Censored data were compared among groups using the log-rank test, Cox’s proportional hazards model, or the Tarone-Ware trend test (23). Pairwise comparisons were performed as appropriate.

An intent-to-treat analysis was performed based on randomization to one of the three intensification arms after CR. Survival end points, measured from the date of randomization to that of intensification, were death (failure) and alive at last follow-up (censored). For CR duration, as measured from the date of randomization, the end point was the first occurrence of relapse (failure), death (in CR (censored), bone marrow transplant while in CR (censored), or continuous CR at last follow-up (censored). The three cytogenetic groups of interest were: (a) group CBF [CBF karyotypes i.e., t(8;21)(q22;q22), inv(16)(p13q22), t(16;16)(p13q22), and del(16)]; (b) group NL (normal karyotype); and (c) group other (other karyotypes). The median follow-up time was 92 months for the 96 patients censored for survival and 86 months for the 88 censored patients for CR duration. Of the latter 88 censored patients, 12 died during the first CR, and 4 were transplanted while in the first CR. Because substantial censoring occurred for CR duration beyond 48 months, an analysis of the Kaplan-Meier plateau for cure was performed with the test of Maller and Zhou (24). In this regard, 37 cases had CR durations longer than the last relapse at 91.4 months. Follow-up was lengthy enough on this plateau (P < 0.001) to indicate that a cure in the statistical sense (P < 0.001) had occurred, and a cure rate model would be applicable (25). At a median follow-up of over 7 years for 88 censored cases, there is strong evidence that modeling for cure is justified. There were only five relapses beyond 5 years and two relapses beyond 7 years of follow-up, respectively.

For multivariable analysis of CR duration, the Farewell cure rate model, a parametric mixture model, was selected (26, 27). A Weibull function approximated the relapse process, and the other term described the cure. The Weibull parametric regression model includes covariates only in the scale (not in shape or term) and therefore has the proportional hazard property (28). A logistic parametric mixture model includes covariates only in the scale (not in shape or term) and therefore has the proportional hazard property (28). A logistic model with covariates determined the proportion labeled as cured. An initial screening of variables was made with either the log-rank test or the proportional hazards model at a P of 0.1 (29). Using the 264 cases complete for all candidate variables, location in the model at either the logistic or Weibull component was checked separately for each variable (P = 0.1 level, likelihood ratio test) for continued testing during the model building. Indicator variables were used for discrete variables. All covariates were centered. Variables were entered with forward selection into the model using a likelihood ratio test until no variable entered at the P = 0.01 level. The interaction of cytogenetics with intensification arm was examined and did not enter the model. Fit was evaluated graphically.

RESULTS

Validation of Using Cytogenetically Defined Patients on the CALGB Treatment Study. Because this report includes only the subset of patients enrolled on the CALGB therapeutic trial who had adequate, pretreatment, centrally reviewed cytogenetics, a comparison of outcome between this subset and the remaining patients was performed. A total of 1104 patients with AML were enrolled on the protocol between October 31, 1985 and October 1, 1990, of whom 1088 were eligible. Of these 1088 patients, 826 were enrolled on the prospective cytogenetic study. Inadequate or incomplete cytogenetics (n = 216) were documented on the central karyotype review, leaving 610 patients with adequate pretreatment cytogenetics. Of the 610 patients having adequate cytogenetics, 19 myelodysplasia cases (based on central morphological review) and 66 acute promyelocytic leukemia cases were excluded. Of the remaining 525 patients, 321 (61%) attained a CR, with 285 (89%) subsequently being randomized to postremission cytarabine. Thus, 285 patients were evaluable for assessment of the dual impact of cytogenetics and cytarabine dose.
intensity on prolonging the CR duration of AML. To assure that patients with adequate cytogenetic studies were representative of the entire cohort of AML patients, an analysis of outcome among these three groups of patients was performed [i.e., patients who were enrolled on the cytogenetic study with adequate cytogenetics (known cytogenetic subtype), patients who were enrolled on the cytogenetic study without adequate cytogenetics (unknown cytogenetic subtype), and patients who were not enrolled on the cytogenetic study (unknown cytogenetic subtype)]. The CR rate, CR duration, and overall survival as defined by CALGB conventions (30) demonstrated no significant differences among the groups (data not shown), thereby justifying the cytogenetic group of patients with adequate karyotype data as being representative of all patients enrolled on the treatment study.

Preintensification Patient Features. Of the 285 randomized patients, 57 patients were classified as group CBF [CBF karyotypes, i.e., t(8;21)(q22;q22), inv(16)(p13q22), t(16;16)(p13q22), and del(16)(q22)], 140 patients were classified as group NL (normal karyotype), and 88 patients were classified as group other (other karyotypes). Group CBF included patients with two biologically similar (i.e., t(8;21) and rearrangements of 16q22) chromosomal abnormalities that had statistically similar outcomes in terms of CR rate, CR duration, and overall survival. Group other included a wide variety of abnormalities including isolated trisomy 8 (n = 10), 11q23 abnormalities (n = 13), other isolated trisomies (n = 9), 5q deletions (n = 4), other single structural abnormalities (n = 38), other dual abnormalities (n = 8), and complex karyotypes (n = 6). The frequency of CR patients randomized to intensification therapy in group CBF (93%), group NL (89%), and group other (86%) was similar (P = 0.37). Similarly, there was no difference in the distribution of the three cytarabine dose schedules among the three cytogenetic groups (P = 1.0). The pretreatment clinical features of patients in cytogenetic groups CBF, NL, and other randomized to receive intensification are summarized in Table 1. Patients with group CBF karyotypes were younger and had a lower percentage of bone marrow blasts as compared with group NL and group other karyotypes (P < 0.001). Of note, only three patients with normal cytogenetics and one with another abnormality were classified with a M4Eo FAB histological subtype of AML.

Clinical Outcome by Cytogenetic Group. An overall difference in CR duration (Fig. 1) and survival (Fig. 2) was noted among
karyotype groups CBF, NL, and other (P < 0.001). The estimated percentage of patients remaining in CR at 5 years was 50% for group CBF, 32% for group NL, and 15% for group other, respectively (Table 2). Compared with group other patients, paired comparisons of CR duration demonstrated a difference for group CBF (P < 0.001) and group NL (P = 0.001) patients. Because this analysis used an intent-to-treat design, completion of all four intensification therapies by each cytogenetic group could partially explain these results. Therefore, we examined the frequency of completion of intensification within the three cytogenetic groups. The frequency of completing each dose of cytarabine therapy was statistically similar among each of the cytogenetic groups. Furthermore, the great majority (93%) of patients completing intensification therapy in this treatment study went on to receive the assigned maintenance therapy, making this an unlikely source for explaining the difference in CR duration among the different cytogenetic groups. Similarly, the difference in outcome of different cytogenetic groups was not significantly altered by the small percentage (6%) of patients who were censored for death in the first CR, with a similar representation in group CBF (7%), group NL (6%), and group other (3%).

Patients in group CBF also had a prolonged survival. The estimated percentage of patients surviving at 5 years was 64% for group CBF as compared with 35 and 27% in group NL and group other, respectively. Paired comparisons demonstrated a difference in survival between group CBF patients as compared with both group NL (P = 0.002) and group other (P < 0.001) patients. However, survival was not different between group NL and group other patients (P = 0.10).

Univariate Analysis of Factors Affecting CR Duration. In an attempt to define factors other than the cytogenetic subtype of AML that might impact on CR duration, a univariate analysis of a number of pretreatment features along with assignment of cytarabine intensification dose was performed and is summarized in Table 2. In addition to cytogenetic subtype, age ≤ 60 years, a lower leukocyte count at the time of diagnosis, the presence of Auer rods in the myeloblasts, a lower percentage of bone marrow blasts, and a higher postremission cytarabine dose were each associated with a longer CR duration. As has been reported previously (13), CR duration for all patients was related to the cytarabine dose (Fig. 3). The estimated proportion of patients remaining in CR at 5 years by treatment group was 42% for the high-dose cytarabine group, 33% for the intermediate-dose cytarabine treatment group, and 17% for the standard-dose cytarabine treatment group, respectively (P < 0.001). Only 16 patients (6%) were censored for death during the first CR, with the frequency being similar among the high-dose (6%), intermediate-dose (6%), and low-dose (5%) cytarabine arm. Paired comparisons demonstrated a marked difference in CR duration between patients receiving either high-dose (P < 0.001) or intermediate-dose (P = 0.003) cytarabine as compared with those receiving standard-dose cytarabine. However, CR duration was not different among patients receiving high-dose cytarabine as compared with those receiving intermediate-dose cytarabine (P = 0.63).

Assessment of the response duration to various intensification therapies by cytogenetic subtype of AML is summarized in Table 3. A trend test of intensification level stratified by cytogenetic groups revealed an overall difference (P < 0.001). In particular, with subset analysis, it is notable that the remission duration of patients with the CBF karyotype increases (P < 0.001) with an increasing dose of cytarabine intensification (Fig 4a). Patients with CBF karyotypes receiving 100 mg/m² cytarabine intensification had only a 16% chance of remaining in CR at 5 years as compared with a 78% frequency in those receiving 3 g/m² cytarabine. The benefit of cytarabine intensification was less obvious in patients with normal karyotypes (P = 0.01) and was absent in patients with other cytogenetic abnormalities (P = 0.10; Fig. 4, b and c, respectively).

Multivariate Analysis to Assess Characteristics Impacting on the Cure of AML. Because the median follow-up after attaining CR in this cohort of patients is in excess of 7 years with a prolonged plateau, the use of a multivariate analysis that addresses the impact of different variables on both potential cure and treatment failure was deemed to be statistically appropriate. Candidate pretreatment clinical features including cytogenetic types of AML, age (60 years or less and 61 years or greater), the percentage of both blood and bone marrow blasts at the time of diagnosis, the log of the leukocyte count, histo-

Table 3 CR duration by cytogenetic group according to cytarabine dose randomization

<table>
<thead>
<tr>
<th>Cytogenetic group</th>
<th>Cytarabine dose</th>
<th>No. of patients</th>
<th>Median time of CR (mo)</th>
<th>% 5-yr CR estimate (95% CI)</th>
<th>% cure estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group CBF</td>
<td>3 g/m²</td>
<td>18</td>
<td>NR⁵</td>
<td>78 (59-97)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>400 mg/m²</td>
<td>20</td>
<td>NR⁵</td>
<td>57 (34-80)</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>100 mg/m²</td>
<td>19</td>
<td>14.3</td>
<td>16 (0-32)</td>
<td>23</td>
</tr>
<tr>
<td>Group NL</td>
<td>3 g/m²</td>
<td>45</td>
<td>18.2</td>
<td>40 (25-54)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>400 mg/m²</td>
<td>48</td>
<td>21.4</td>
<td>37 (13-51)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>100 mg/m²</td>
<td>47</td>
<td>12.5</td>
<td>20 (8-32)</td>
<td>12</td>
</tr>
<tr>
<td>Group other</td>
<td>3 g/m²</td>
<td>27</td>
<td>13.3</td>
<td>21 (5-37)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>400 mg/m²</td>
<td>31</td>
<td>10.6</td>
<td>13 (1-25)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>100 mg/m²</td>
<td>30</td>
<td>9.6</td>
<td>13 (0-26)</td>
<td>3</td>
</tr>
</tbody>
</table>

⁵ See the text for definitions of the different cytogenetic groups.
⁶ Kaplan-Meier estimates. CI, confidence interval.
⁷ Estimates were obtained using Farewell mixture model.
⁸ NR, not reached.
remission duration after high-dose cytarabine in AML

A

B

C

Fig. 4. CR duration of patients within specific groups by cytarabine dose intensification. A, group CBF; B, group NL; C, group other.

DISCUSSION

Our data demonstrate that both pretreatment karyotype and high-dose cytarabine intensification independently impact the chance of attaining long-term remission and apparent cure of adult AML. Randomized treatment studies (13-15) examining high-dose cytarabine dose intensification, a therapy currently considered standard for younger patients with AML, have not included an assessment of the competing impact of both cytarabine dose and cytogenetics on the potential cure of AML. Other factors such as age, the absence of Auer rods, and extramedullary leukemia, which have been identified as prognostic factors in earlier AML studies, were also examined in this study and were found not to independently contribute to the likelihood of AML cure. Indeed, it is well documented that adverse risk factors such as older age and the absence of Auer rods occur more frequently in poor-risk cytogenetic groups (1-5, 31-33). These adverse risk features are underrepresented in most series with CBF AML (34-37). The coassociation of poor-risk clinical features with an adverse cytogenetic aberration or of a better-risk clinical feature with CBF AML renders the interpretation of outcome impossible unless the relationship of all variables is considered. Our multivariate analysis assessing independent variables that predict for statistical cure demonstrated that only the cytogenetic type of AML and the cytarabine postremission dose seem to be major prognostic factors for long-term remission and apparent cure of adult patients with AML. Importantly, unlike most AML treatment studies that have relied on models to project long-term estimates of disease-free outcome beyond 5 years, our study has a >7-year median patient follow-up of censored cases. This long-term follow-up lends credence to the model for cure used in this study.

An equally important finding of this study is that increasing the intensity of cytarabine is not of significant benefit to all cytogenetic groups. Dose escalation of cytarabine in patients with CBF karyotypes and, to a lesser extent, in patients normal karyotypes significantly increases the duration of prolonged remission and likely cure. Such a

Table 4. Multivariate analysis of factors impacting potential cure of AML

<table>
<thead>
<tr>
<th>Factor</th>
<th>Regression coefficient</th>
<th>SE of the mean</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td>0.00001</td>
</tr>
<tr>
<td>Group CBF</td>
<td>0.823</td>
<td>0.366</td>
<td></td>
</tr>
<tr>
<td>Group NL</td>
<td>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group other</td>
<td>-1.457</td>
<td>0.456</td>
<td></td>
</tr>
<tr>
<td>Cytarabine intensification</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>3 g/m²</td>
<td>1.874</td>
<td>0.434</td>
<td></td>
</tr>
<tr>
<td>400 mg/m²</td>
<td>1.269</td>
<td>0.437</td>
<td></td>
</tr>
<tr>
<td>100 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a See the text for definitions of the cytogenetic groups.

b Positive regression coefficient indicates an improved cure rate for CBF as compared with the normal (NL) cytogenetic AML group; negative regression coefficient indicates a lower cure in group other as compared with the NL AML cytogenetic group.

c Increasing regression coefficient indicates a higher cure rate with dose escalation of cytarabine intensification relative to the 100 mg/m² group. FAB classification and the log of the leukocyte count also entered the model in the relapse portion.
cytogenetically specific dose escalation finding has not been identified previously in any randomized adult AML trial. However, other nonrandomized studies have reported favorable results of high-dose cytarabine in patients with CBF karyotypes as compared with other cytogenetic groups, thus supporting these findings (38). The reasons for this differential response are uncertain but likely include molecular aberrations that render cells with CBF karyotypes more sensitive to high-dose cytarabine. Additional laboratory studies investigating the biological basis for CBF AML cell sensitivity to high-dose cytarabine are needed.

One limitation of this study is the narrow eligibility criteria that only allowed AML patients without antecedent hematological disorders or cytopenias to be enrolled on the treatment study. These exclusion criteria limit the generalizability of our results to a larger proportion of patients with AML seen in the community who would have been ineligible for this study. Patients with refractory anemia with excess blasts or refractory anemia with excess blasts in transformation were also ineligible for the treatment study. Consequently, individuals later identified as having these findings on central review were excluded in the current study. This later group was excluded in the current study to maintain a homogeneous group of patients, although the frequency of myelodysplastic syndrome patients excluded on central review among the different cytogenetic groups was similar. The exclusion of this small number of patients did not alter the conclusions of the study.

The ramifications of our study, as it relates to the current management of adult AML patients, are substantial. In the setting of cytogenetic risk stratification for postremission intensification, our data strongly support the use of high-dose cytarabine as the best treatment option for postremission therapy in patients with CBF AML. For the highly heterogeneous group of AML patients with a normal karyotype, the choice of postremission therapy is less certain and will require the identification of cytogenetically undetectable molecular aberrations, such as the ALL-1 duplication, that predict for poor outcome (39). Randomized studies comparing the efficacy of high-dose cytarabine with new novel intensification therapies in such poor-risk patients with normal karyotypes seem warranted. Although there may be certain other karyotypic abnormalities that benefit from high-dose cytarabine, the current data suggest that these patients should be treated with novel therapeutic approaches with either new therapeutic agents alone or possibly in concert with allogeneic transplant. Based on the data presented, CALGB currently is enrolling on a cytogenetically stratified treatment approach to adult patients with AML.

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