Treatment of Newly Diagnosed Acute Myelogenous Leukemia With Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Before and During Continuous-Infusion High-Dose ara-C + Daunorubicin: Comparison to Patients Treated Without GM-CSF

By Elihu Estey, Peter F. Thall, Hagop Kantarjian, Susan O'Brien, Charles A. Koller, Miloslav Beran, Jordan Gutterman, Albert Deisseroth, and Michael Keating

We gave 56 patients with newly diagnosed acute myelogenous leukemia (AML) granulocyte-macrophage colony-stimulating factor (GM-CSF) 20 or 125 μg/m² once daily subcutaneously before (for up to 8 days or until GM-CSF-related complications developed) and during, or only during (patients presenting with blast counts >50,000 or other leukemia-related complications) ara-C (1.5 g/m² daily × 4 by continuous infusion) and daunorubicin (45 mg/m² daily × 3) chemotherapy. Because results seemed independent of GM-CSF schedule, we compared results in these 56 patients with results in 176 newly diagnosed AML patients given the same dose and schedule of ara-C without GM-CSF (110 patients ara-C alone, 66 patients ara-C + amsacrine or mitoxantrone). Comparison involved fitting a logistic regression model predicting probability of complete remission (CR) and a Cox regression model to predict survival (most patients in all three studies were dead) with treatment included as a covariate in both analyses. After adjusting for other prognostically significant covariates [presence of an antecedent hematologic disorder, an Inv(16), t(8;21), or abnormalities of chromosomes 5 and/or 7, performance status, age, bilirubin], treatment with ara-C + daunorubicin + GM-CSF was predictive of both a lower CR rate and a lower survival probability. There were no treatment-covariate interactions, suggesting that the negative effect of this GM-CSF treatment regime was not an artifact of some imbalance in patient characteristics. The unadjusted Kaplan-Meier hazard rate of the ara-C + daunorubicin + GM-CSF group was not uniquely high during the initial 4 weeks after start of therapy, but was highest among the three treatment groups throughout weeks 5 to 16, suggesting that the negative effect of this treatment was not caused by acute toxicity. Patients who did not enter CR with this treatment tended to have persistent leukemia rather than prolonged marrow aplasia, suggesting that this treatment and, in particular, GM-CSF may increase resistance of myeloid leukemia cells to chemotherapy. To date, relapse rates are similar in all three groups (P = .43) as are survival rates once patients are in CR but much of the remission duration data is heavily censored, unlike the survival data. Our results suggest caution in the use of GM-CSF to sensitize myeloid leukemia cells to daunorubicin + ara-C chemotherapy.

© 1992 by The American Society of Hematology.

We gave 56 newly diagnosed AML patients GM-CSF before and during or, if at diagnosis the circulating blast count was high or other complications of leukemia were present, only during, daunorubicin + cytosine arabinoside (ara-C) chemotherapy. This is the largest clinical trial reported to date with this therapy. We compare CR rates and survival in these patients with results in 176 previous patients with newly diagnosed AML given the same dose and schedule of ara-C without GM-CSF. We focus on CR and survival because these endpoints are, along with remission duration, the ones of greatest clinical importance and because most of the survival data (unlike the remission duration data) are no longer censored. In addition to standard chi-square and logrank tests, the main statistical methods used here for comparative analyses are logistic and Cox regressions in which the treatment administered (eg, GM-CSF or no GM-CSF) is considered as a potential predictive covariate for patient outcome along with pretreatment patient characteristics such as cytogenetic abnormalities, performance status, age, etc. While recognizing that more time will be needed for a complete picture to emerge because remission duration data are still heavily censored (of 147 patients attaining CR, 62 currently are still in remission), we believe the comparative results focusing on CR and survival are of sufficient interest to report now.

PATIENTS AND METHODS

GM-CSF studies (DM 89-124 and 90-062). Patients received GM-CSF on two protocols, the first (DM 89-124) operative between January 1, 1990 and August 31, 1990 and the second (DM 90-062) operative between August 24, 1990 and November 1, 1990. The intent of both protocols was to determine if GM-CSF...
administered before daunorubicin and ara-C would improve remission rate, remission duration, and/or survival in newly diagnosed AML. Criteria for AML were greater than 30% myeloblasts in the bone marrow or either a circulating blast count greater than 10,000/μL or greater than 30%. In DM 89-124 all newly diagnosed adults were eligible if they were under age 60 and did not have acute promyelocytic leukemia (French-American-British [FAB] subtype M3). In DM 90-062 all newly diagnosed adults were eligible, again provided that they did not have APL. Sixty-four patients were eligible for these studies and 56 (88%) were treated on them. The other eight patients did not receive GM-CSF because of physician choice (seven cases) or patient choice (one case). Of those eight patients, three had the prognostically favorable cytogenetic abnormalities Inv(16) (16) or t(8;21) and these three entered CR with chemotherapy without GM-CSF, whereas five had prognostically unfavorable cytogenetic abnormalities: of these five patients, two entered CR with chemotherapy without GM-CSF, two did not, and one refused treatment. In DM 89-124, patients received GM-CSF 125 μg/m² once daily subcutaneously (SC) for 7 days before starting chemotherapy unless GM-CSF–related complications (circulating blast count ≥ 50,000/μL or grade 3 to 4 extramedullary toxicity) developed, in which case chemotherapy began immediately. In DM 90-062, patients age 60 and over received GM-CSF 20 μg/m² once daily SC for 4 days, and if this was well tolerated then received 125 μg/m² once daily SC for 4 days before chemotherapy. A starting dose of 20 μg/m² was chosen for older patients because it had produced hematologic effects in patients with myelodysplastic syndromes and appeared to be better tolerated than higher doses. Patients under age 60 received 125 μg/m² for 4 days before chemotherapy. As in DM 89-124, patients in whom GM-CSF–related complications developed began chemotherapy before completing the planned number of days of GM-CSF. In both studies patients presenting with circulating blast counts > 50,000/μL, DIC, or a Zubrod performance status of ≥ 2 began GM-CSF 125 μg/m² once daily SC simultaneously with chemotherapy. In both studies chemotherapy consisted of daunorubicin 45 mg/m² by bolus injection daily for 3 days and ara-C 1.5 g/m² daily × 4 days by continuous intravenous (IV) infusion (CHDAC), and in both GM-CSF–recombinant, Escherichia coli-derived; supplied by the Schering-Plough Corp, Kenilworth, NJ) continued until chemotherapy was completed. A marrow aspirate and biopsy were evaluated 2 weeks after chemotherapy began (day 14) and were evaluated weekly thereafter until response to the first course was clear. Patients who had persistent leukemia (> 20% blasts, in a marrow that was ≥ 20% cellular) on days 14 and 21 without evidence of improvement between the two dates received a second round of therapy beginning on day 21. The same criteria for blasts and cellularity (in two consecutive marrows) were used for starting the second course in patients whose marrow became hypocellular with decreased blasts on day 14 or day 21 and then regrew leukemia. Patients not in CR (a morphologically normal marrow with < 5% blasts, together with granulocyte and platelet counts of > 1,000, and > 100,000/μL, respectively, no circulating blasts, and a Zubrod performance status < 2) after 2 courses of therapy were declared “resistant” and offered other therapies. Once in CR patients received 2 courses of GM-CSF 125 μg/m² SC daily for 2 days followed by daunorubicin + CHDAC as described above with GM-CSF again continuing until completion of chemotherapy. Thereafter, patients were generally observed off therapy but 22% of the patients entering CR were entered on an interleukin-2 (IL-2) postremission protocol.

Comparative studies (DM86-00 and DM 87-080). Results in GM-CSF–treated patients were compared with those in two previous studies in which patients with newly diagnosed AML received ara-C in the dose and schedule described above (CHDAC) but without GM-CSF: (1) Between 1985 and 1988 (DM 86-00)10 110 patients (excluding patients with promyelocytic leukemia who, as mentioned previously, were ineligible for the GM-CSF study) received CHDAC for induction followed sequentially in remission by course of conventional-dose ara-C (100 mg/m²/d for 5 days), 1 of CHDAC, 3 of daunorubicin/6 mercaptopurine/methotrexate/vincristine + prednisone, 2 of CHDAC, and finally 3 of conventional-dose ara-C + 6 thioguanine. (2) Between 1988 and 1990 (DM 87-080) 66 patients (again excluding patients with promyelocytic leukemia) received CHDAC plus either amsacrine (75 mg/m² daily × 4 days; 54 patients) or mitoxantrone (7.5 mg/m² daily × 4 days; 12 patients) for induction followed sequentially in remission by 1 course of amsacrine (or mitoxantrone, whichever was received for induction) + CHDAC, 1 of amsacrine (or mitoxantrone) + ara-C 0.5 g/m² over 2 hours every 12 hours for nine doses, and 1 of amsacrine (or mitoxantrone) alone with the sequence then repeated once. Because remission rates, remission duration, and survival were not significantly different in the amsacrine + CHDAC and mitoxantrone + CHDAC studies, patients receiving either were considered as one group. Eligibility criteria for DM 86-00 (CHDAC, no GM-CSF) were similar to those for DM 89-124 (GM-CSF followed by CHDAC + daunorubicin) in that initially only patients considered to have a relatively high survival probability (as assessed by a Cox model in which age was a dominant factor) were eligible, with subsequent eligibility extended to all patients. Eligibility for DM 87-080 (CHDAC + amsacrine or mitoxantrone, no GM-CSF) remained restricted throughout to patients with a relatively high probability of surviving the initial 28 days after the start of induction chemotherapy as assessed by a fitted logistic regression model.11 Of the patients eligible for DM 86-00 and DM 87-080, 88% and 87% received these therapies, respectively. As with the GM-CSF studies, physician choice was the principal reason that patients who were eligible for DM 86-00 and DM 87-080 received other treatments. With both DM 86-00 and DM 87-080 the criteria for the diagnosis of AML, the timing of postchemotherapy marrows, and criteria for starting a second course were as described for the GM-CSF studies. With all studies patients not in CR (as defined above) after two courses of induction therapy were considered resistant and administered salvage therapies.

Statistical methods. Unadjusted CR rates were compared using a standard chi-square test of homogeneity. Unadjusted survival and remission duration rates were compared via Fleming-Harrington12 and log-rank tests13 and Kaplan-Meier14 plots. Logistic regression was used to assess the ability of various patient characteristics and treatment group indicators to predict the probability of achieving CR [prob(CR)], and the Cox proportional hazards model15 was used to assess their ability to predict survival. Individual associations first were sought between each endpoint, CR (1 = Yes/0 = No) or survival time, and each of the following variables: pretreatment cytogenetic group [Inv(16) (16) or (8;21) v 7, 7q+, 7q−, v 5, or v 5– v other abnormalities or insufficient metaphases for analysis v normal karyotype], pretreatment Zubrod performance status (0 to 2 = High v 3,4 = Low), age, presence/absence of antecedent hematologic disorder (AHD: a documented abnormality in blood count for ≥1 month before diagnosis as AML at our hospital), pretreatment hemoglobin, neutrophil count, albumin, fibrinogen, BUN, creatinine, bilirubin, and treatment group (CHDAC alone v CHDAC + amsacrine or mitoxantrone = CHDAC + A/M v CHDAC + daunorubicin + GM-CSF = CHDAC + D + GM-CSF). Pretreatment variables were selected based on previous associations with survival time or prob(CR) in AML patients.9 The functional relationship of each quantitative covariate X with prob(CR) was assessed initially via a smoothed plot of CR on X; death rate was assessed initially by a
plot of the martingale residuals from the “no covariate” Cox model on X. Separate logistic regressions of CR and Cox regressions of survival on individual covariates were also performed. For each type of regression, a final predictive model was obtained via the following variable selection algorithm, with test level .05 used throughout: (1) a standard stepdown procedure beginning with all variables was first performed; (2) all treatment-covariate interaction terms generated by variables still in the model were then introduced, and a second stepdown procedure was performed on these terms; (3) the additional contribution of each variable not in the model at this stage was tested to determine whether it could be re-entered; and (4) each treatment or cytogenetic subgroup combination obtained as a consequence of dropping terms in step (1) was tested to determine whether it remained valid in the final model. Goodness-of-fit for the final logistic model was assessed by deviance, Pearson, and likelihood ratio statistics; residual analysis consisted of standardized and deviance residual plots on age; behavior of age in the linear term was assessed by a partial residual plot; and influence diagnostics consisted of leverage and generalized Cook’s statistic plots.17,18 Goodness-of-fit for the final Cox model was assessed by likelihood and score statistics; residual analysis consisted of martingale and deviance residual plots on age and bilirubin; the behaviors of age and bilirubin in the linear term were assessed by added variable plots; and a plot of score residuals on death times was used to identify high leverage cases.19 All computations were performed in Splus20 on a SUN SPARC Station 2. All residual, partial residual, and added variable plots were smoothed using the Splus scatter plot smoother lowess.21 Hazard rates were calculated from the unadjusted Kaplan-Meier survival curves and smoothed according to the method of Simes and Zelen.22

### RESULTS

**Response and survival.** Table 1 illustrates the response rate by number of days of GM-CSF received before chemotherapy, the reasons for abbreviation of the planned number of days of GM-CSF, and the status of the marrow after therapy. Thirteen (23%) patients received GM-CSF simultaneously with chemotherapy, 28 patients received GM-CSF for 4, 7, or 8 days before chemotherapy (the maximum allowed per protocol), while in 15 patients (ie, 35% of the patients administered GM-CSF before chemotherapy) GM-CSF was abbreviated because of GM-CSF-related complications (high blast count 9, splenic pain 1, pericarditis 1, fluid retention 1, hypotension 1, fever 1, rash 1). Although relatively few patients thus received GM-CSF for any given number of days, there was no indication or trend suggesting that any one schedule produced better results than any other, thus providing a rationale for linking all 56 patients in one group for comparative purposes. The CR rate of 48% (27 of 56; 95% confidence interval 36% to 61%) in the CHDAC + D + GM-CSF group compares with a CR rate of 65% (71 of 110; 95% confidence interval 55% to 73%) in the CHDAC alone group and a CR rate of 74% (49 of 66; 95% confidence interval 63% to 83%) in the CHDAC + A/M group. The difference between these three unadjusted CR rates was significant ($P$ = .011, chi-square test of homogeneity). Similarly, differences in survival between the three groups (Fig 1) were significant ($P$ = .052, Fleming-Harrington test, $P$ = .035, log-rank test)

<table>
<thead>
<tr>
<th>Days of GM-CSF Before Chemotherapy*</th>
<th>Patients</th>
<th>CR</th>
<th>After 1 Course Chemotherapy</th>
<th>After 2 Courses</th>
<th>Persistent Hypoplasia</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1†</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>3‡</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>1**</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>7§</td>
<td>3</td>
<td>3 (7,27,36)</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>7</td>
<td>1 (16)</td>
<td>1</td>
<td>1††</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>1†</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1‡‡</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>3†</td>
<td>2</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>6</td>
<td>2 (60,200)</td>
<td>1</td>
<td>1 (26)</td>
<td>1§§</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2</td>
<td>1 (15)</td>
<td>1</td>
<td>2 (14,20)</td>
<td>1</td>
</tr>
<tr>
<td>O (ie, simultaneously with chemotherapy)</td>
<td>13‡</td>
<td>6</td>
<td>4 (15,16,31,42)</td>
<td>—</td>
<td>3 (20,21,28)</td>
<td>—</td>
</tr>
<tr>
<td>0–8</td>
<td>56</td>
<td>27</td>
<td>11</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Numbers in parenthesis refer to the number of days after the start of a course of chemotherapy at which persistent leukemia or hypoplasia was last documented.

*All patients received the full course of GM-CSF during chemotherapy.

†High fever, 1 patient.

‡High blasts, 1 patient; hypotension, 1 patient; fluid retention, 1 patient.

§High blasts, 6 patients; rash, 1 patient.

¶Spleenic pain, 1 patient.

#High blasts, 2 patients; pericarditis, 1 patient.

||High blasts, 11 patients; DIC, 1 patient; poor performance status, 1 patient.

**Marrow hypercellular without blasts, but patient died day 43, course 1.

††Marrow normocellular without blasts or megakaryocytes; patient died day 29, course 1.

§§Patient died day 2, course 1; no marrow obtained.

||Patient died day 8, course 1; no marrow obtained.
with the CHDAC + D + GM-CSF patients exhibiting the lowest survival rate. It should be noted that most of the patients on each study have died so that these curves are relatively insensitive to further change, unlike the remission duration plots discussed below.

Table 2 presents pretreatment patient characteristics that individually were predictive of achievement of CR or longer survival (\(P \leq .05\)) in all 232 patients. These were: high performance status (predictive of both), younger age (predictive of both), absence of an AHD (predictive of both), high serum albumin (predictive of both), serum fibrinogen (predictive of both), low serum bilirubin (predictive of longer survival), BUN (predictive of higher CR probability), presence of an Inv(16) or t(8;21) (predictive of both), and absence of abnormalities of chromosomes 5 or 7 (predictive of both). Other cytogenetic abnormalities, a normal karyotype, pretreatment neutrophil count, hemoglobin, and creatinine were not significantly predictive of either CR or survival.

Table 3 presents the distribution of each significant pretreatment patient characteristic within each of the three treatment groups. The 66 patients administered CHDAC + A/M had a slightly higher incidence of the favorable chromosomal abnormalities Inv(16) or t(8;21) (23% vs 15% for the CHDAC alone group and 12% for the CHDAC + D + GM-CSF group, \(P = .243\), chi-square test of homogeneity), a slightly lower incidence of the unfavorable chromosome 5 or 7 abnormalities (8% vs 14% and 16%, \(P = .282\)), and a somewhat higher proportion of high performance status (97% vs 86% and 91%, \(P = .066\)), probably reflecting the limiting of the CHDAC + A/M study throughout to patients relatively likely to survive the initial 28 days after initiation of chemotherapy. As described above this determination was made using a fitted logistic regression model\(^11\) in which performance status was the dominant variable, while both the CHDAC alone and the CHDAC + D + GM-CSF studies were open in their later stages to all patients. Patients administered CHDAC + D + GM-CSF had a significantly higher incidence of AHD than patients not administered GM-CSF (41% vs 28% and 27% for each of the other two groups, \(P = .05\)), probably reflecting a higher incidence of prior myelodysplasia in these patients, although this is impossible to document because many of our patients have not had bone marrow examination until they come to our hospital. The GM-CSF group also had lower values for serum albumin (\(P < .001\), Kruskal-Wallis test) but were similarly aged (\(P = .94\), Kruskal-Wallis test) and had similar (\(P = .13\), Kruskal-Wallis test) BUN levels as patients in the other two groups. Patients in the CHDAC + A/M group had lower bilirubin levels than patients in the other two groups (\(P < .001\), Kruskal-Wallis test) whereas patients in the GM-CSF group had higher fibrinogen levels than patients in the CHDAC alone or CHDAC + A/M groups (\(P = .003\) Kruskal-Wallis test).

We next examined whether the lower CR rate and shorter survival probability in the CHDAC + D + GM-CSF group reflected (1) the higher proportion of these patients who had an AHD or low serum albumin (Table 3) or (2) an interaction between this treatment and one or more prognostically important covariate(s), in particular cytogenetic group. Table 4 presents the final fitted logistic regression model, with covariates predictive of CR arranged in predictive order (a "+" sign before a parameter estimate indicates the variable has a favorable impact on achievement of CR, a "−" sign indicates the converse). Although presence of an AHD was the leading predictor of failure to achieve CR, administration of CHDAC + D + GM-CSF was also strongly associated with failure to achieve CR (\(P = .017\)) even after accounting for AHD status, performance status, age, presence of an Inv(16) or t(8;21), or abnormality of chromosomes 5 or 7, the other significant predictors in the final logistic regression model. No individual covariates not in the final model were able to re-enter. Moreover, addition of individual terms constructed from each variable in the final model multiplied by the CHDAC + D + GM-CSF treatment group indicator showed completely insignificant treatment-covariate interactions, the most significant of these being the AHD interaction term with \(P = .278\). These results strongly suggest that the negative effect of this
Table 3. Distributions of Categorical and Continuous Prognostic Variables Within Treatment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHDAC Alone (N = 110)</th>
<th>CHDAC + Amsacrine or Mitoxantrone (N = 66)</th>
<th>CHDAC + Daunorubicin + GM-CSF (N = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Categorical prognostic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lnv(16) or t(8;21) (N = 38)</td>
<td>15%*</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>5–7 (N = 29)</td>
<td>(15)</td>
<td>(15)</td>
<td>(7)</td>
</tr>
<tr>
<td>Other nondiploid chromosome abnormality (N = 75)</td>
<td>33%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>No cytogenetic abnormality (N = 89)</td>
<td>38%</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>High performance status (Zubrod 0-2) (N = 210)</td>
<td>86%</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>Antecedent hematologic disorder (N = 71)</td>
<td>27%</td>
<td>27%</td>
<td>41%</td>
</tr>
<tr>
<td>B. Continuous prognostic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (47±) (336, 62)</td>
<td>50</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (.5) (4.8)</td>
<td>.4</td>
<td>.5</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (350) (250, 450)</td>
<td>320</td>
<td>415</td>
<td></td>
</tr>
<tr>
<td>Albumin (3.7) (3.2, 4.1)</td>
<td>3.6</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (9.4) (8.3, 10.3)</td>
<td>9.4</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>BUN (11) (9, 15)</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*ie, 15% of CHDAC patients had an lnv(16) or t(8;21).
†ie, 16 CHDAC patients had an lnv(16) or t(8;21).
*Median.
§25th percentile.
∥75th percentile.

The final model combines the CHDAC alone and CHDAC + A/M treatment groups. However, when the two indicators for these groups were added separately to the model (thus replacing the term for CHDAC + D + GM-CSF) each was a significant positive predictor of achievement of CR (P = .044 and .024, respectively), ie, the significant negative impact of CHDAC + D + GM-CSF was not simply a consequence of lumping the two other treatments together. Furthermore, the coefficients of these two non-GM-CSF treatments, .79 and 1.00, were not significantly different (P = .655), strongly supporting the

Table 4. Summary of Logistic Regression Model for Predicting CR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>SE</th>
<th>P Value</th>
<th>Deviance</th>
<th>DF</th>
<th>Change in Deviance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.7467</td>
<td>.7967</td>
<td></td>
<td>304.8</td>
<td>231</td>
<td></td>
</tr>
<tr>
<td>AHD</td>
<td>-1.092</td>
<td>.3490</td>
<td>.002</td>
<td>282.9</td>
<td></td>
<td>21.9</td>
</tr>
<tr>
<td>High performance status</td>
<td>1.653</td>
<td>.6110</td>
<td>.007</td>
<td>256.6</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>5–7</td>
<td>-1.331</td>
<td>.4916</td>
<td>.007</td>
<td>250.9</td>
<td></td>
<td>11.8</td>
</tr>
<tr>
<td>GM-CSF group</td>
<td>-0.8700</td>
<td>.3648</td>
<td>.017</td>
<td>245.4</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>lnv(16)/t(8;21)</td>
<td>1.246</td>
<td>.5870</td>
<td>.034</td>
<td>238.0</td>
<td>225</td>
<td>7.4</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0221</td>
<td>.0105</td>
<td>.035</td>
<td>238.0</td>
<td>225</td>
<td></td>
</tr>
</tbody>
</table>

Predictive equation: log(\( \hat{P} / (1 - \hat{P}) \)) = -0.746 - 1.092 (AHD) + 1.653 (high performance status) - 1.331 (5–7) - 0.8700 (GM-CSF Group) + 1.246 (lnv(16) or t(8;21)), -0.0221 Age. \( \hat{P} \), estimated probability of CR; characteristics in parentheses, 1 if present, 0 if absent.
Table 5. Summary of Cox Proportional Hazards Model for Predicting Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>SE</th>
<th>P Value</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.0236</td>
<td>0.0053</td>
<td>&lt;.001</td>
<td>20.4</td>
</tr>
<tr>
<td>inv(16) or t(8;21)</td>
<td>1.013</td>
<td>0.2870</td>
<td>&lt;.001</td>
<td>15.9</td>
</tr>
<tr>
<td>High performance status</td>
<td>0.8452</td>
<td>0.2534</td>
<td>&lt;.001</td>
<td>9.2</td>
</tr>
<tr>
<td>GM-CSF group</td>
<td>-0.6673</td>
<td>0.2228</td>
<td>.003</td>
<td>8.2</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>-0.4158</td>
<td>0.1461</td>
<td>.004</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Predictive equation: Log \( \hat{\lambda}(t;\mathbf{x})/\hat{\lambda}_0(t) \) = -0.0236 Age + 1.013 inv(16) or t(8;21) + 0.8452 (high performance status) - 0.6673 (GM-CSF group) - 0.4158 bilirubin. \( \hat{\lambda}(t;\mathbf{x}) \), estimated death rate for a patient with covariate vector \( \mathbf{x} \); \( \hat{\lambda}_0(t) \), estimated baseline hazard rate; characteristics in parentheses, 1 if present, 0 if absent.

hypothesis that they had an equally positive effect on achieving CR, compared with the GM-CSF group.

Table 5 presents the final Cox model for survival, again with variables arranged in order of predictive strength. Treatment with CHDAC + D + GM-CSF was predictive of shorter survival probability even after the influence of other prognostically significant covariates [older age, cytogenetics other than Inv(16) or t(8;21), low performance status, high bilirubin] had been accounted for. As might be expected, achievement of CR was itself a powerful predictor of survival when included as a covariate, and in this case only age, Inv(16) or t(8;21), and bilirubin were significant additional covariates in a Cox model. This essentially underscores the validity of achievement of CR as a reasonable surrogate endpoint for survival, rather than invalidating the prognostic value of nonresponse variables.

The final logistic model fit the data quite well, with a deviance of 238.0 and a Pearson statistic of 243.7 on 225 df. All residual plots showed random scatter, and the partial residual plot on age showed a clearly linear trend. Refits with probit and complementary (c-) log-log links in place of the logit each gave slightly worse fits. The final Cox model also gave a good fit with a likelihood ratio of 70.7 on 5 df. The residual plots on age and bilirubin showed random scatter. Added variable plots for age and bilirubin both showed linear trends.

The fit of the logistic model can also be appreciated by comparing the predicted probabilities of CR with the corresponding observed results in different patient subgroups. In Table 6 the logistic model of Table 4 is applied to compute predicted CR probabilities in 12 different pairs of patient groups, with each pair differing only according to whether or not CHDAC + D + GM-CSF was received. The observed results closely match the predicted values in groups with a reasonably large number of patients, with lower predicted rates in all CHDAC + D + GM-CSF subgroups. The negative effect of this treatment is further illustrated in Figs 2 and 3, which illustrate the difference between the CHDAC + D + GM-CSF group and the other two groups combined in terms of predicted probability of CR (Fig 2) and survival (Fig 3). To construct these figures,

Table 6. Predicted Versus Observed Probabilities of CR in Different Groups

<table>
<thead>
<tr>
<th>AHD</th>
<th>Performance Status</th>
<th>GM-CSF + D + CHDAC</th>
<th>-5, -7</th>
<th>t(8;21) or Inv(16)</th>
<th>Predicted CR</th>
<th>Observed CR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0 t</td>
<td>0.125</td>
<td>1/3 = 0.333</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.254</td>
<td>0/4 = 0.000</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.027</td>
<td>0/2 = 0.000</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.061</td>
<td>0/2 = 0.000</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.298</td>
<td>1/3 = 0.333</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.503</td>
<td>6/11 = 0.546</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.075</td>
<td>0/1 = 0.000</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.162</td>
<td>0/3 = 0.000</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.652</td>
<td>3/3 = 1.000</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.817</td>
<td>4/5 = 0.800</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.264</td>
<td>0/0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.461</td>
<td>0/0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.848</td>
<td>3/4 = 0.750</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.930</td>
<td>23/25 = 0.920</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.517</td>
<td>0/0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.718</td>
<td>1/1 = 1.000</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.350</td>
<td>4/13 = 0.308</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.563</td>
<td>15/33 = 0.465</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.094</td>
<td>0/2 = 0.000</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.198</td>
<td>2/4 = 0.500</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.018</td>
<td>15/25 = 0.600</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.793</td>
<td>67/81 = 0.827</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.235</td>
<td>0/0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.423</td>
<td>2/7 = 0.286</td>
</tr>
</tbody>
</table>

For each group assume the average age of the population.

*The number "1" indicates the following in the various columns: AHD present; Performance status high (Zubrod 0, 1, 2); CHDAC + D + GM-CSF given; abnormality of chromosomes 5 or 7 (-5, 5Q-, -7, 7Q-); t(8;21) or Inv(16) present.

†The number "0" indicates: AHD absent; Performance status low (Zubrod 3, 4); CHDAC + D + GM-CSF not given; abnormality of chromosomes 5 or 7 absent; t(8;21) or Inv(16) absent.
was evaluated at a vector of typical patient characteristics. With a normal karyotype, no AHD, and a favorable perfor-

ance status, no inv(l6) or t(8;21), the mean age for all patients (47.7 years), and the mean pretreatment bilirubin value for all patients (0.61 mg/mL) depending on whether they received CHDAC + D + GM-CSF or rather CHDAC with or without A/M. Patients with these characteristics for performance status, AHD status, and cytogenetics were the most common group treated. Each vertical hash mark represents a patient so that the total number of hash marks is 232 (176 for the CHDAC alone group and 56 for the CHDAC + D + GM-CSF group) reflecting the derivation of the logistic regression model from the entire data set.

Each predictive model (derived from the entire data set) was evaluated at a vector of typical patient characteristics. Figure 2 illustrates that while the predicted probability of CR decreases with increasing age, this is even more marked in the CHDAC + D + GM-CSF subgroup among patients with a normal karyotype, no AHD, and a favorable performance status. Similarly, for the typical patient subgroup with karyotypes other than INV(16) or t(8;21), a high performance status and the observed mean values for age and bilirubin, Fig 3 illustrates that predicted survival probability is uniformly lower for patients administered CHDAC + D + GM-CSF compared with the other two treatments combined (similar curves could be generated for other groups sharing all prognostically relevant covariates except treatment).

Causes of failure in the CHDAC + D + GM-CSF group. The apparent negative impact of CHDAC + D + GM-CSF could have resulted either if the treatment were too toxic or if it increased resistance of leukemic cells. To examine these questions we first computed treatment-specific hazard rates in intervals of 4 weeks beginning from the start of therapy. As can be seen in Table 7, the hazard rate (ie, the risk of death per 4-week unit of time) remained high in the CHDAC + D + GM-CSF group past the first 4 weeks, while it decreased after this time in the CHDAC alone group and was low from the start in the CHDAC + A/M group. This suggests that the negative effect on CR rate and survival in the CHDAC + D + GM-CSF group was not mediated through acute toxicity (eg, in the first 4 weeks) but through either prolonged marrow hypoplasia or persistent leukemia, each of which could contribute to failure to enter CR and death.

Table 1 examines the issue of persistent leukemia versus prolonged hypoplasia in GM-CSF-treated patients not entering CR. Eighteen of 29 such patients had persistent leukemia, 11 after one course of chemotherapy (thus necessitating a second course) and 7 after two courses, while only six patients died with hypoplastic marrows after the first course and in none of these did hypoplasia last 28 days beyond the start of chemotherapy. This suggested that persistence of leukemia, rather than prolonged aplasia, was the primary cause of failure to enter CR, to thus remain myelosuppressed, and eventually to die of complications of myelosuppression. The overall incidence of persistent leukemia in the CHDAC + D + GM-CSF group was 10 of 56 (18%) compared with incidences of 15 of 110 (14%) in the CHDAC alone group and 9 of 66 (14%) in the CHDAC + A/M group. The duration of neutropenia (<1,000/μL) in patients who entered CR was slightly longer in the CHDAC + A/M group than the other two groups, and consistent with the suggestion that persistence of AML rather than prolonged aplasia was the principal cause of failure of CHDAC + D + GM-CSF-treated patients to enter CR was shorter in the CHDAC + D + GM-CSF group than in the CHDAC alone or CHDAC + A/M groups, although the differences were only marginally significant (Table 8). The duration of thrombopenia

![Fig 2. Predicted probability of CR as a function of age for patients with high performance status (Zubrod 0, 1, 2), no AHD, and no INV(16), t(8;21), or chromosome 5, or 7 abnormalities depending on whether they received CHDAC + D + GM-CSF or rather CHDAC with or without A/M. Patients with these characteristics for performance status, AHD status, and cytogenetics were the most common group treated. Each vertical hash mark represents a patient so that the total number of hash marks is 232 (176 for the CHDAC ± A/M groups and 56 for the CHDAC + D + GM-CSF group) reflecting the derivation of the logistic regression model from the entire data set.](image)

![Fig 3. Predicted probability of survival for patients with a high performance status, no inv(16) or t(8;21), the mean age for all patients (47.7 years), and the mean pretreatment bilirubin value for all patients (0.61 mg/mL) depending on whether the received CHDAC + D + GM-CSF or rather CHDAC with or without A/M. Medians are 19.5 weeks for the former and 39.5 for the latter. Each vertical hash mark represents a patient so that the total number of hash marks is 232 (176 for the CHDAC ± A/M groups and 56 for the CHDAC + D + GM-CSF group) reflecting the derivation of the Cox model from the entire data set.](image)

### Table 7. Hazard Functions for Successive Four-Week Intervals

<table>
<thead>
<tr>
<th>Weeks</th>
<th>CHDAC Alone</th>
<th>CHDAC + A/M</th>
<th>CHDAC + D + GM-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>25.6*</td>
<td>9.5</td>
<td>24.8</td>
</tr>
<tr>
<td>5-8</td>
<td>7.3</td>
<td>5.4</td>
<td>14.1</td>
</tr>
<tr>
<td>9-12</td>
<td>4.0</td>
<td>5.4</td>
<td>14.0</td>
</tr>
<tr>
<td>13-16</td>
<td>4.0</td>
<td>5.4</td>
<td>10.9</td>
</tr>
</tbody>
</table>

*Deaths per 100 persons per 4 weeks.
GM-CSF BEFORE AND DURING AML CHEMOTHERAPY 2253

A/M and 5 have relapsed and corresponding rates are 29
with CHDAC alone, CHDAC
log-rank test). Of the 71 patients entering CR with CHDAC alone, 50
are no significant differences between the three groups
done because the assumption of independent censoring
patients who die myelosuppressed before entering CR.

GM-CSF studies, 62 are currently in remission, 21 of these
instrumental to the Kaplan–Meier test cannot be applied to
remission duration data in the CHDAC group is heavily censored and most of the censored observa-
tions are relatively early. Similarly, the probabilities of
death once in CR (including deaths in CR and deaths after
relapse) do not differ among the three treatment groups
(P = .18, log-rank test). Thus, as formally indicated by the
intimate relationship between achievement of CR and
survival (see above), the shorter survival for patients
achieved CR with this
Group is impossible to exclude, we believe it is relatively unlikely
because numerous variables were identified in the data set
that were of clear prognostic significance (variables such as
cytogenetics, presence of an AHD, etc, whose relevance we
cannot ascertain retrospectively. Hence, it is possible that our
results are confounded by differences that cannot be
adjusted out by regression; eg, if an unknown, unobserved
but powerful prognostic factor were unequally distributed
between the three treatment groups. While this possibility
is impossible to exclude, we believe it is relatively unlikely
because numerous variables were identified in the data set
that were of clear prognostic significance (variables such as
cytogenetics, presence of an AHD, etc, whose relevance we
and others16,24,25 using other data sets have identified
before) and particularly because the models presented in
Tables 4 and 5 fit the actual data well. In this context it
should also be noted that the two treatments that included
neither GM-CSF nor daunorubicin did give equivalent
results after adjusting for prognostically important covari-
ates, consistent with results of Curtis et al26 that high-dose
ara-C therapy of newly diagnosed AML may, on average,
make therapy with topoisoiserase II drugs less important.

A second issue is that follow-up in the CHDAC + D +
GM-CSF–treated patients is relatively short; in particular,
most of the patients who have achieved CR with this
therapy have yet to relapse. Clearly if all of the patients
currently in CR remained alive in CR results in this

leukemia) rather than death after relapse or death while in
CR.

DISCUSSION

Our results indicate that therapy of newly diagnosed
AML with CHDAC + D + GM-CSF may decrease
remission rates relative to therapy with CHDAC alone or
CHDAC + A/M. The results also indicate that CHDAC +
D + GM-CSF may shorten survival relative to these other
therapies. No treatment-covariate interactions were found,
suggesting that statistically the effect of CHDAC + D +
GM-CSF on CR and survival was negative in all patients
(patients with APL were not administered GM-CSF and
hence were not included in this analysis). However, several
facts must be borne in mind when interpreting these results.
First, the three studies were not arms of a single randomized
trial, but rather were performed separately in se-
quenCe over 5 years. There were differences in eligibility
criteria and possibly in assignment practice, with any
possible differences in the latter practically impossible to
ascertain retroactively. Hence, it is possible that our
results are confounded by differences that cannot be
adjusted out by regression; eg, if an unknown, unobserved
but powerful prognostic factor were unequally distributed
between the three treatment groups. While this possibility
is impossible to exclude, we believe it is relatively unlikely
because numerous variables were identified in the data set
that were of clear prognostic significance (variables such as
cytogenetics, presence of an AHD, etc, whose relevance we
and others16,24,25 using other data sets have identified
before) and particularly because the models presented in
Tables 4 and 5 fit the actual data well. In this context it
should also be noted that the two treatments that included
neither GM-CSF nor daunorubicin did give equivalent
results after adjusting for prognostically important covari-
ates, consistent with results of Curtis et al26 that high-dose
ara-C therapy of newly diagnosed AML may, on average,
make therapy with topoisoiserase II drugs less important.

A second issue is that follow-up in the CHDAC + D +
GM-CSF–treated patients is relatively short; in particular,
most of the patients who have achieved CR with this
therapy have yet to relapse. Clearly if all of the patients
currently in CR remained alive in CR results in this

Table 8. Duration of Neutropenia or Thrombopenia in Patients Entering CR

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of CR</th>
<th>Minimum No. of Days</th>
<th>25th Percentile</th>
<th>Median</th>
<th>75th Percentile</th>
<th>Maximum No. of Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHDAC</td>
<td>71</td>
<td>17</td>
<td>21</td>
<td>26</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>CHDAC + A/M</td>
<td>49</td>
<td>18</td>
<td>22</td>
<td>27</td>
<td>34</td>
<td>46</td>
</tr>
<tr>
<td>CHDAC + D + GM-CSF</td>
<td>27</td>
<td>16</td>
<td>20</td>
<td>24</td>
<td>27</td>
<td>61</td>
</tr>
<tr>
<td>CHDAC t</td>
<td>71</td>
<td>18</td>
<td>21</td>
<td>23</td>
<td>29</td>
<td>86</td>
</tr>
<tr>
<td>CHDAC + A/Mt</td>
<td>49</td>
<td>17</td>
<td>21</td>
<td>24</td>
<td>28</td>
<td>54</td>
</tr>
<tr>
<td>CHDAC + D + GM-CSFt</td>
<td>27</td>
<td>16</td>
<td>21</td>
<td>22</td>
<td>25</td>
<td>109</td>
</tr>
<tr>
<td>*P = 0.06, Kruskal-Wallis test for differences among groups.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fP = 0.18, Kruskal-Wallis test for differences among groups.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(< 100,000/μL) in patients entering CR was the same in all
three groups. Similar comparisons for all patients cannot be
done because the assumption of independent censoring
fundamental to the Kaplan–Meier test cannot be applied to
patients who die myelosuppressed before entering CR.

Remission duration. Of the 147 patients achieving CR
on the CHDAC alone, CHDAC + A/M or CHDAC + D +
GM-CSF studies, 62 are currently in remission, 21 of these
on the CHDAC + D + GM-CSF study, which is the most
recent of the three studies. To date relapse rates are similar
in all three groups (Fig 4), but unlike the survival data the
remission duration data in the CHDAC + D + GM-CSF
group is heavily censored and most of the censored observa-
tions are relatively early. Similarly, the probabilities of
death once in CR (including deaths in CR and deaths after
relapse) do not differ among the three treatment groups
(P = .18, log-rank test). Thus, as formally indicated by the
intimate relationship between achievement of CR and
survival (see above), the shorter survival for patients treated with CHDAC + D + GM-CSF reflects death
during induction (primarily, as noted above, from persistent

Fig 4. Kaplan-Meier remission duration plots for patients treated
with CHDAC alone, CHDAC + A/M, or CHDAC + D + GM-CSF. There
are no significant differences between the three groups (P = .43,
log-rank test). Of the 71 patients entering CR with CHDAC alone, 50
have relapsed and corresponding rates are 29 of 49 with CHDAC +
A/M and 6 of 27 with CHDAC + D + GM-CSF.
treatment group would be superior to those in the other two groups. However, there is no indication that the relapse rate is in fact lower in the CHDAC + D + GM-CSF group. Furthermore, as noted above most of the patients who received this treatment are dead and thus the censored data problem is much less with survival than it is with remission duration, influencing us to report these results now. It should be pointed out that postremission therapy differed considerably in the three groups (see Patients and Methods) and these differences may confound comparison of remission duration in the three groups.

A third issue is whether the seemingly inferior results in the CHDAC + daunorubicin + GM-CSF group result from use of daunorubicin or from use of GM-CSF because patients in the two other treatment groups received neither of these agents. One randomized trial comparing amsacrine + ara-C to daunorubicin + ara-C in newly diagnosed AML found that the amsacrine + ara-C-treated patients had a higher remission rate and a longer survival. However, a second randomized trial did not confirm this result. The doses of amsacrine used in both these studies were higher than the doses used in DM (570 to 600 mg/m² v 300 mg/m²), and the doses of ara-C were lower (0.7 to 0.825 mg/m² v 6.0 g/m²). A randomized trial comparing mitoxantrone + ara-C to daunorubicin + ara-C in newly diagnosed AML found no significant differences in CR rates or survival. Furthermore, as noted above results in patients treated with CHDAC alone were superior to those in patients treated with CHDAC + D + GM-CSF while results in the CHDAC alone and CHDAC + A/M groups were similar. Although it is possible that a trial comparing CHDAC alone to CHDAC + D would favor the former or that an interaction exists between GM-CSF and daunorubicin that does not exist between GM-CSF and amsacrine, it appears more likely that the seemingly (after covariate adjustment) inferior remission rate and survival in the CHDAC + D + GM-CSF group are caused by use of GM-CSF before and during administration of CHDAC + daunorubicin rather than to use of daunorubicin.

The seemingly negative effect of GM-CSF appears to reflect an effect on leukemia cells. Thus, the death rate per unit time (hazard) was not uniquely high in the GM-CSF group in the first 4 weeks (as might be expected if this therapy produced excess acute toxicity) but remained high throughout the initial 16 weeks after start of therapy. This continued relatively high hazard rate most likely reflected persistence of leukemia as most of the patients who died without achieving CR had persistent leukemia rather than prolonged aplasia (Table 1). In turn, persistent leukemia contributed to continued myelosuppression reflected as failure to enter CR and hence death.

Our observation that GM-CSF may decrease the in vivo sensitivity of AML blast cells to daunorubicin + ara-C is paralleled by in vitro observations of Koistinen et al. that GM-CSF protected the blast cells in 9 of 10 patients with AML from ara-C. They believe that the discrepancy between their results and other in vitro results showing that GM-CSF increases ara-C sensitivity may reflect the fact that in the latter experiments comparisons were made between cells exposed to GM-CSF + ara-C and cells exposed to no CSF + ara-C while in their experiments all cells were exposed to CSFs (either G-CSF, GM-CSF, or IL-3) + ara-C.

Several mechanisms might contribute to GM-CSF’s apparent ability to increase resistance of myelogenous leukemia cells to CHDAC + daunorubicin. GM-CSF may have an unfavorable effect on the intracellular pharmacology of the chemotherapeutic agents. In this connection W.K. Plunkett at our Cancer Center has noted (personal communication, September 1991) that in two of three patients with the myeloid blast crisis of CML the area under the curve (AUC) of ara-CTP concentration versus time was lower when the patients received GM-CSF before a dose of ara-C (median 0.87-0.88 ± 0.2254 hr) than it was when the same patients received the same dose of ara-C without GM-CSF (the AUC is identical when patients are administered two doses consecutively without GM-CSF). Use of GM-CSF before and during chemotherapy may cause the leukemic blasts to commit to differentiation, an effect that may make them less sensitive to chemotherapy, although this effect might be counterbalanced by the possibility that these blasts might therefore become less clonogenic. Clearly, if GM-CSF increases the number of blasts there must be some countervailing effect that would cause a greater increase in chemosensitivity; otherwise the effect would be fewer, and possibly shorter, remissions. As yet there are no comparative studies to address this possibility besides our own. The largest reported experience is that of Bettelheim et al in which 15 of 18 patients administered GM-CSF (250 µg/m² daily by injection for 1 or 2 days before, during, and after receiving daunorubicin + conventional-dose ara-C) achieved CR. However, the reported (Table 2, column 6 of ref 7) remission duration (50% probability of relapse by 304 days) appears short, particularly as 4 of the 18 patients had Inv(16) and none had a preleukemic phase.

Finally, we should stress that we have examined only a limited dose and schedule range of GM-CSF. Relatively few patients were treated at any one schedule, although this in part reflected necessity as 35% of the patients who received GM-CSF before chemotherapy could not receive the prescribed number of days of prechemotherapy GM-CSF because of GM-CSF-related complications such as an increase in blast count and in part reflected the need to begin the 23% of patients presenting with high blast counts or other complications of leukemia on chemotherapy without any GM-CSF pretreatment. Results may be different if other CSFs that target a different range of hematopoietic progenitors are used. However, our results suggest that the concept of recruitment of blast cells into cycle, at least using GM-CSF for this purpose, must be critically examined before being introduced into widespread practice.

ACKNOWLEDGMENT

The authors thank Jan Bole, RN and Sherry Pierce, RN for their help with data collection and Kimberly Cutchall for her expert secretarial assistance.
REFERENCES


From www.bloodjournal.org by guest on November 15, 2017. For personal use only.
Treatment of newly diagnosed acute myelogenous leukemia with granulocyte-macrophage colony-stimulating factor (GM-CSF) before and during continuous-infusion high-dose ara-C + daunorubicin: comparison to patients treated without GM-CSF

E Estey, PF Thall, H Kantarjian, S O'Brien, CA Koller, M Beran, J Gutterman, A Deisseroth and M Keating