Varying Intensity of Postremission Therapy in Acute Myeloid Leukemia

By Peter A. Cassileth, Elizabeth Lynch, John D. Hines, Martin M. Oken, Joseph J. Mazza, John M. Bennett, Philip B. McGlave, Marian Edelstein, David P. Harrington, and Michael J. O'Connell

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized trial in patients ≤65 years old (median, 44 years) to determine whether increasing the intensity of postremission therapy in acute myeloid leukemia (AML) would improve the outcome. After uniform induction therapy, patients in complete remission (CR) who were less than 41 years old and who had a histocompatible sibling underwent allogeneic bone marrow transplantation (alloBMT) (54 patients). The remainder of patients in CR were randomized to receive either 2 years of continuous outpatient maintenance therapy with cytarabine and 6-thioguanine (83 patients) or a single course of inpatient consolidation therapy consisting of 6 days of high-dose cytarabine plus 3 days of amsacrine (87 patients). The median duration of follow-up is now 4 years, and patients are included in the analyses of outcome regardless of whether they relapsed before starting the intended treatment. Four-year event-free survival (EFS) was 27% ± 10% for consolidation therapy versus 16% ± 8% for maintenance therapy (P = .068) and 28% ± 11% versus 15% ± 9% (P = .047) in patients less than 60 years old. The outcome for patients receiving alloBMT was compared with the subset of patients less than 41 years old who received consolidation therapy (N = 29) or maintenance therapy (N = 21). Four-year EFS was 42% ± 13% for alloBMT, 30% ± 17% for consolidation therapy, and 14% ± 15% for maintenance therapy. AlloBMT had a significantly better EFS (P = .013) than maintenance therapy, but was not different from consolidation therapy. In patients less than 41 years old, 4-year survival after alloBMT (42% ± 14%) did not differ from consolidation therapy (43% ± 18%), but both were significantly better than maintenance therapy (19% ± 17%, P = .047 and .043, respectively. The mortality rate for maintenance therapy was 21%, and alloBMT, 36%. Consolidation therapy caused an especially high mortality rate in the patients ≥60 years old (8 of 14 or 57%). The toxicity of combined high-dose cytarabine and amsacrine is unacceptable, especially in older patients, and alternative approaches to consolidation therapy such as high-dose cytarabine alone need to be tested. In AML, a single course of consolidation therapy or alloBMT after initial CR produces better results than lengthy maintenance therapy. Although EFS and survival of alloBMT and consolidation therapy do not differ significantly, a larger number of patients need to be studied before concluding that they are equivalent.

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INDUCTION CHEMOTHERAPY in acute myeloid leukemia (AML) yields complete remission (CR) in the majority of patients. Patients who receive no further therapy after remission rapidly relapse due to the regrowth of occult residual leukemia cells. The studies of the Eastern Cooperative Oncology Group (ECOG)1 and of others2-5 have established that after initial CR low-dose outpatient (maintenance) chemotherapy regimens can prolong CR duration compared with no further therapy (median duration of CR, 8 to 12 months vs 4 to 8 months). At the same time, a number of nonrandomized studies have suggested that increasing the intensity of postremission therapy beyond the levels used in maintenance therapy improves CR duration and long-term, disease-free survival.3,6,7 Administra-

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INTENSIVE POSTREMISSION THERAPY IN AML 1925

Cytogenetics and immunophenotyping of leukemia cells were not mandatory; these studies were performed in approximately one-third of the patients.

Induction therapy consisted of one or two courses of daunorubicin, 60 mg/m²/d intravenous (IV) push on days 1, 2, and 3; cytarabine, 25 mg/m² IV push followed by continuous IV infusion of 200 mg/m²/d on days 1 through 5; and thioguanine, 100 mg/m² orally every 4 days on days 1 through 5. Heparin therapy was recommended for patients with acute promyelocytic leukemia (FAB type M3) during early induction treatment.

At the time of complete remission, patients less than 41 years old with a histocompatible sibling were offered alloBMT; all other patients were initially randomized to one of three therapy arms: observation, maintenance therapy, or consolidation therapy. Interim analysis of the study (previously reported) after 28 patients were randomized to observation showed an inferior remission duration for these patients compared with maintenance therapy.1 Accordingly, randomization to this arm was discontinued.

Maintenance therapy consisted of thioguanine, 40 mg/m² orally every 12 hours for 4 days of the week, followed by cytarabine, 60 mg/m² subcutaneously on the fifth day of each week. Maintenance therapy was continued for 2 years. Consolidation therapy was based on our previous pilot study, and consisted of cytarabine 3 g/m² IV over 1 hour every 12 hours for 12 doses (days 1 through 6), followed by amascrine 100 mg/m²/d IV for 3 days (days 7 through 9). After this one course of treatment, no further therapy was given. The protocol for alloBMT, devised by Dr Philip McGlave, for participating ECOG BMT centers involved preparative chemotherapy with cyclophosphamide 60 mg/kg/d IV for 2 days followed by 1,320 cGy of total body irradiation (TBI) administered in fractions of 165 cGy twice daily for eight doses (4 days). Graft-versus-host disease (GVHD) prophylaxis consisted of methotrexate administered as 15 mg/m² IV on day +1, 10 mg/m² on days +3, 6, and 11, and then weekly until 100 days postmarrow reinfusion. Marrow donors had to be siblings who were fully histocompatible with the patient based on the results of HLA typing and mixed lymphocyte cultures. Patients undergoing alloBMT received no other intervening therapy after CR and before BMT.

Postremission therapy began 4 weeks after CR if patients had a performance status of 0 or 1 (ECOG scale), no persisting infection, and adequate renal (creatinine <2 mg/dL) and hepatic (serum alkaline phosphatase <2 x normal, transaminases <4 x normal, and bilirubin <2 mg/dL) function. Therapy could be delayed until these eligibility criteria were met. All patients were included for analysis of remission duration and survival, regardless of whether they actually received the randomly assigned therapy. Patients were allocated to treatment at the time of CR using randomly permuted blocks within strata. The strata included age (15–39; 40–60; 60–65), number of induction cycles (1 or 2) to achieve CR, and FAB histologic subtype (M1, M2, M3, M4, M5, M6, and M7). Institutions obtained the randomization assignment by telephoning the ECOG central office.

A total of 534 patients were initially registered for induction therapy between April 1984 and January 1988, when the study was closed. Fourteen patients were cancelled, and 39 patients were ineligible for the following reasons: no or inadequate pathologic submission in 13 cases; age greater than 65 years old in two cases; other violations of eligibility requirements in six cases; and finding of erroneous diagnosis on pathology review in 18 cases (including 11 acute lymphocytic leukemia, six myelodysplasia, and one blast phase of chronic myeloid leukemia). This left 481 eligible patients. Of these, 32 were excluded from analysis of the outcome of induction therapy because of major protocol violations in 19 cases and no follow-up data or inadequate documentation of response in 13 cases. The median age of the 449 eligible, evaluable patients was 44 years (range, 15 to 65), with an equal distribution of men and women. The distribution of FAB types was as follows: M1, 105 patients (23%); M2, 98 (22%); M3, 57 (13%); M4, 107 (24%); M5, 64 (14%); M6, 13 (3%); and M7, 5 (1%).

CR was defined as an M1 marrow status (<5% blasts, >14% erythroid elements, >25% normal granulocyte precursors, in a nonhypocellular marrow) with normal physical (P1) status (normal spleen, liver, and lymph nodes) and H1 peripheral blood (hemoglobin, >11 g/dL; neutrophils, >1,500/µL; no blasts; platelets, >100,000/µL). Relapse was defined as the appearance of circulating leukemia cells or greater than 5% blasts in the BM. BM aspiration to detect relapse was performed routinely every 2 months for the first 2 years of follow-up.

Remission duration and survival distributions were computed using the Kaplan-Meier technique.19 The Gray-Tsiatis test20 for detecting differences in cure rates was used to compare empirical curves of remission duration and survival.

RESULTS

Induction therapy. The overall CR rate was 68% (305 of 449). The remission rate was higher in patients less than 60 years old (267 of 376 or 71%) than in patients ≥60 (38 of 73 or 52%). Sixty percent of CRs were obtained after one cycle of induction therapy and 40% after two induction cycles. There was no significant difference in CR rates among the various FAB subtypes. The median time to CR from the start of therapy was 38 days (range, 16 to 139). These results are consistent with our previous study using this induction regimen.21

Postremission therapy. Of the 305 patients in CR, 28 were initially randomized to observation only. As previously reported,2 all of the 26 evaluable patients in this group relapsed with a nonactuarial median CR duration of 4 months and survival of 12 months. An additional 26 patients were not randomized because either they refused or their physicians removed them from study. The distribution of postremission therapies in the remaining 251 patients is shown in Table 1.

In all, 142 patients in CR were less than 41 years old; 58 (41%) of these patients had a histocompatible sibling, 34 (24%) had no histocompatible siblings, 13 (9%) had no available siblings, and 37 (26%) were not tested. Of the 58

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Maintenance Therapy</th>
<th>Consolidation Therapy</th>
<th>AlloBMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refused</td>
<td>6 (6%)</td>
<td>4 (4%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Ineligible</td>
<td>3 (3%)</td>
<td>6 (6%)</td>
<td>-</td>
</tr>
<tr>
<td>Major protocol violation</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Eligible, evaluable patients</td>
<td>83 (88%)</td>
<td>87 (88%)</td>
<td>54 (93%)</td>
</tr>
<tr>
<td>Patients relapsing before treatment</td>
<td>5 (6%)</td>
<td>9 (10%)</td>
<td>19 (17%)</td>
</tr>
<tr>
<td>Patients &lt;60 yr old</td>
<td>66</td>
<td>71</td>
<td>-</td>
</tr>
<tr>
<td>Patients &lt;41 yr old</td>
<td>21</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>Months from CR to treatment*</td>
<td>Median (range)</td>
<td>0.8 (0.5-3.5)</td>
<td>1.0 (0.5-3.5)</td>
</tr>
</tbody>
</table>

*After censoring out early relapsing patients.
patients who were offered alloBMT (Table 1), three refused the procedure and one is excluded from evaluability because a course of intensive consolidation therapy was administered before BMT. This patient is alive in continuous CR at 70+ months. All of the 54 eligible, evaluable patients are included in the analyses of results, even though nine patients relapsed before alloBMT. One of these nine patients died of progressive disease, one was transplanted in early relapse, and seven underwent alloBMT in second CR. The remaining 45 patients underwent alloBMT in first CR at a median time from CR of 1.6 months (range, 0.5 to 5).

Because not all patients were transplanted at ECOG member institutions, therapy was not entirely uniform. Fractionated TBI and cyclophosphamide therapy as intended by protocol were used in 71% of patients, nonfractionated TBI in 8%, and high-dose busulfan/cyclophosphamide in 20%. For GVHD prophylaxis, methotrexate as specified was used in 49% of patients, cyclosporine and methylprednisolone in 24%, cyclosporine and methotrexate in 10%, T-cell lymphocyte depletion in 10%, and methotrexate, antithymocyte globulin, and methylprednisolone in 6%. AlloBMT was performed at the University of Minnesota in 22 (41%) of patients, six procedures were performed at two other centers, and the balance was performed at eight centers, each accounting for one to four alloBMTs. There were no significant differences in patient populations, presenting features of leukemia, induction therapy characteristics, or outcome between patients transplanted as specified by protocol or at variance from protocol. These two populations are therefore combined in the analysis of results. AlloBMT involved a same sex donor to recipient in 58% of BMTs, female to male in 24%, and male to female in 18%.

Comparison of presenting features of patients and their leukemias and of induction therapy including age, sex, performance status, degree of weight loss, marrow cellularity, splenic involvement, distribution of FAB subtypes, cytogenetic analysis (performed in 38% of cases), presenting white blood cell count, number of circulating blasts and percentage of marrow blasts, number of induction therapy courses, and time to CR showed no significant differences between all patients randomized to consolidation versus maintenance therapy. Among the smaller subset of patients less than 41 years old who were either assigned to allogeneic BMT or randomized to consolidation or maintenance therapy, the age distribution differed. The median age of these patients undergoing consolidation therapy was 31 years; maintenance therapy, 34 years; and alloBMT, 26 years. Using Wilcoxon rank sum tests, the differences between the age of patients receiving consolidation therapy versus maintenance therapy did not differ \( (P = .503) \), but patients receiving these therapies were significantly older than patients undergoing alloBMT \( (P = .018 \) and .002, respectively).

The time from CR to the institution of postremission therapy also differed significantly among the treatment groups, varying directly with the intensity of therapy (Table 1). Maintenance therapy was begun at a median of 0.8 months after CR, significantly earlier than patients receiving consolidation therapy (median, 1.0 month; \( P = .016 \)) or alloBMT (median, 1.6 months; \( P < .001 \)) and the delay in starting consolidation therapy was shorter than the time elapsed from CR to alloBMT \( (P < .0001) \). The difference in lag times to initiate therapy was most likely due to varying levels of concern that residual toxicities from induction therapy had adequately resolved so that postremission therapy could be safely administered. This progressive lag in starting postremission maintenance therapy, consolidation therapy, or alloBMT was paralleled, not unexpectedly, by an increasing risk of relapse before postremission therapy, which was 6%, 10%, and 17%, respectively. To correct for this disparity, in the analyses of outcome all patients are included regardless of whether they relapsed before receiving the intended therapy.

Event-free survival duration. The median duration of follow-up of patients is now 4 years. A comparison of outcomes from this trial is displayed in Table 2. In calculating event-free survival (EFS) of patients in CR, either death or relapse is considered to be an event. Although the 4-year EFS (27% ± 10%) and survival (33% ± 11%) for all patients randomized to consolidation therapy is better than the EFS (16% ± 8%) and survival (22% ± 11%) after maintenance therapy, the differences are not statistically significant. In part, this is due to a number of deaths in patients greater than 60 years old who received consolidation therapy (see Toxicity below). If one examines the results in patients less than 60 years old, then EFS 4 years after receiving consolidation therapy (28% ± 11%) is significantly better \( (P = .047 \) by stratified Gray-Tsiatis Test) than maintenance therapy (15% ± 9%), and there is a favorable trend in overall survival (37% ± 12% v 27% ± 11% at 4 years, \( P = .195 \)) as well. The actuarial EFS curves for patients less than 60 years old are shown in Fig 1.

In the subset of patients less than 41 years old (Table 2 and Fig 2), compared with maintenance therapy, consolidation therapy produces a trend toward better EFS \( (P = .149) \)
and significantly better overall survival (P = .043) as does allogeneic BMT (P = .013 and P = .047, respectively). There is no statistically significant difference in outcome between alloBMT and consolidation therapy. In these young patients, treatment failure after consolidation or maintenance therapy was due almost entirely to relapse. In contrast, after alloBMT in first CR, treatment failure was usually due to death from complications, and relapse was uncommon, occurring in only 6 of 45 patients (13%), 8, 8, 9, 12, 13, and 31 months after CR.

Toxicity. As anticipated from a previous trial using the same therapy, the 2 years of maintenance chemotherapy were associated with minimal toxicity. Using ECOG toxicity scales, side effects rated as severe included gastrointestinal toxicity in 8% of patients, myelosuppression in 33%, and hepatotoxicity in 8%. The only life-threatening toxicity was myelosuppression in 14% of patients, requiring dose reduction. No fatalities occurred in this treatment group, and severe or life-threatening infections did not develop.

In contrast, the single course of consolidation therapy was associated with substantial toxicity. In the whole group of these patients side effects rated as severe included gastrointestinal toxicity in 4%, cerebellar toxicity in 12%, and hepatotoxicity in 17%. These side effects were largely attributable to high-dose cytarabine. Life-threatening myelosuppression occurred in virtually all patients, causing severe or life-threatening infection in 22% and bleeding in 5%. The nadir from the combined high-dose cytarabine and ammsacrine was prolonged, requiring a median of approximately 3 weeks after therapy before granulocytes were greater than 500/mm³. This lengthy nadir predisposed to serious infections and enhanced risk of superimposed fungal infections, resulting in an overall mortality rate of 21% (16 patients). The risk of a fatal outcome from consolidation therapy accrued principally to patients ≥ 60 years old. The mortality rate among patients ≥ 60 years old was 57% (8 of 14 patients) compared with a mortality rate of 13% among younger patients.

Acute complications of alloBMT included: moderate-to-severe acute GVHD in 37%; interstitial pneumonitis in 26%; liver dysfunction in 28%; and documented infection in 76%. One episode of graft failure resolved after second marrow reinfusion and one case of hepatic venoocclusive disease resolved eventuallly. Of the 45 patients undergoing alloBMT in first CR, eight died of infection less than 100 days after BMT while in CR, five died later in CR of pulmonary problems and chronic GVHD, and three died later of bacterial infections. The mortality rate of the procedure was therefore 16 of 45 patients (36%). Of the eight patients transplanted after initial relapse, four died, two of infections 6 and 7 months after BMT and two of chronic GVHD and its complications at 26 and 41 months. Of patients surviving in CR, limited chronic GVHD developed in 17% and extensive chronic GVHD in 20%. Most of these patients responded to immunosuppressive therapy, and only 11% of patients in continuing CR had substantial impairment of performance status (ECOG scale of > 2).

DISCUSSION

After CR is achieved in AML, in the absence of further therapy virtually all patients will relapse, ie, EFS will be 0. Low-dose maintenance therapy improves the EFS so that 5 to 7 years after CR, when the outcome curves have reached stable plateaus, approximately 10% to 15% of patients will still be event-free. In the current study, the EFS for patients receiving maintenance therapy is 16% at 4 to 6 years, with a median follow-up duration of 4 years. Although maintenance therapy is usually continued for a long time (2 years in the current study), the great majority of its effectiveness is probably derived from the early months of treatment after CR. In a CALGB study, in which patients in CR were randomized to 8 months or 3 years of maintenance therapy, there was no difference in long-term EFS. Similarly, when repeated courses of induction therapy were administered over 3 to 5 months after CR before randomization to maintenance therapy or observation, maintenance therapy conferred no additional benefit. In AML, as in most other cancers curable by chemotherapy, the remission established by the early phases of therapy is not enhanced by lengthy maintenance treatment.

The ECOG, in a previous trial, randomized patients to receive or not receive two dose-reduced (by approximately
courses of induction therapy before commencing the identical maintenance program used in the current study. With a 2-year median duration of follow-up, EFS for this miniconsolidation plus maintenance versus maintenance therapy alone was 28% versus 14% at 3 years. A current update of the data with a median follow-up duration of 8 years shows an EFS of 24% versus 12%, due to late relapses, suggesting that this only moderately intensive postremission therapy may have improved long-term outcome.

Subsequently, pilot studies of more intensive consolidation therapy have used one to two courses of high-dose cytarabine plus daunorubicin, a repeat of induction therapy plus either 5-azacytidine and doxorubicin or high-dose cytarabine plus daunorubicin, one course of high-dose cytarabine plus amsacrine, or two repeated courses of induction therapy alternating with two courses of amsacrine and standard dose cytarabine or high-dose cytarabine alone. With relatively short-term follow-up, the 2- to 3-year EFS in these studies was 35% to 50%. Because of late relapses in these studies, the long-term EFS will be lower than reported. For example, a recent report of high-dose cytarabine plus daunorubicin as consolidation therapy described a 30% EFS after a lengthy follow-up (median, 5.2 years).

The current study of amsacrine plus high-dose cytarabine as a single course of consolidation therapy provides an EFS at 4 years of 27% \pm 10% (median follow-up of 4 years). The EFS of this consolidation therapy is superior to maintenance therapy in patients less than 60 years old \((P = .047, \text{Table 2})\). The comparison including all patients, regardless of age, is of borderline significance \((P = .068)\) because of the inclusion of patients \(\geq 60\) years old, who experienced exceptional toxicity with consolidation therapy. Eight of the 14 patients in this age group died because of complications from the resultant prolonged myelosuppression. The mortality rate for patients less than 60 years old from high-dose cytarabine plus amsacrine was 13%. Consolidation therapy using high-dose cytarabine alone was associated with a high mortality compared with a mortality rate of 5%, 6%, and 13% when high-dose cytarabine was combined with daunorubicin. Adding other agents to high-dose cytarabine increases toxicity. It is unclear, however, whether adding daunorubicin or amsacrine to high-dose cytarabine confers any advantage in AML therapy over high-dose cytarabine alone. The current Southwest Oncology Group (SWOG) randomized study of AML in relapse compares high-dose cytarabine with or without daunorubicin, and should answer this question. Consistent with the current results, a third arm of the SWOG study using high-dose cytarabine and amsacrine was terminated prematurely because of toxicity.

A secondary aim of this study was to compare the results of alloBMT with conventional chemotherapy. We restricted the alloBMT patients to those less than 41 years old. To avoid an age-biased comparison, we analyzed the results of patients less than 41 years old receiving maintenance or consolidation therapy. As noted previously, however, patients receiving conventional chemotherapy were significantly older on average than patients undergoing alloBMT. It is unknown whether this age difference biases the results in favor of alloBMT, but an analysis of the outcome within the conventional therapy group by age showed no differences. We noted a variable delay between CR and time to institute postremission therapy. Postremission therapy began a median 0.8 months after CR for maintenance therapy, 1.0 months for consolidation therapy, and 1.6 months for alloBMT. The delays were directly correlated with pretherapy relapse rates of 6%, 10%, and 17%, respectively. These early relapsing patients exhibited adverse leukemia cell biology, ie, rapid regrowth of leukemia after CR. Whether prompt administration of chemotherapy after CR and before consolidation or alloBMT can decrease the number of early relapses in this poor prognostic subset is unknown. To compensate for the variable delay to treatment, all patients in each group were included in the analyses of outcome regardless of whether they relapsed before starting their intended therapy. In reported series of patients with AML transplanted in first CR, however, patients who relapse before alloBMT are perforce excluded. For this reason, the EFS after alloBMT in the current study is lower than those reported by transplant centers.

Despite the inclusion of patients relapsing before alloBMT, the variability in transplant and GVHD prophylaxis, and the participation of multiple alloBMT centers, the 4-year EFS of 42% \pm 13% is compatible with two other prospective studies of patients receiving uniform induction therapy and no intervening chemotherapy after CR before BMT. The 4-year EFS of these studies was 48% in the Seattle series \((N = 33)\) and 40% in the UCLA series \((N = 23)\). The current study shows that the EFS after alloBMT is superior to maintenance therapy, but not statistically better than consolidation therapy. The power of the study is too limited by the small number of patients less than 41 years old who received consolidation therapy to conclude that consolidation therapy and alloBMT are equivalent in EFS. With longer follow-up, some additional relapses will occur in patients who received consolidation therapy, whereas the alloBMT curve should remain more stable. Nevertheless, the authors believe from the results of this study and others that the long-term EFS from consolidation therapy will be approximately 25% to 30% versus 40% to 45% after alloBMT.

The decline in EFS over time after alloBMT is largely due to deaths from early and late complications from the procedure, because relapse rates are very low after alloBMT in first CR: 13% in the current study and 13% to 23% in other studies. In contrast, the fall-off in EFS curves after conventional therapy is largely due to relapse of leukemia. A proportion of patients who relapse after conventional therapy, however, can be salvaged for cure with reinduction chemotherapy followed by autologous or allogeneic BMT or by alloBMT in early relapse. For this reason, it is difficult to demonstrate statistically significant differences in overall survival between intensive conven-
tional therapy and alloBMT as shown in Table 2 and noted by others.\textsuperscript{10,26} Nevertheless, graded differences in both overall survival and EFS correlating with intensity of postremission therapy are consistently seen. Increasing the intensity of postremission therapy results in progressively improving EFS. The current intergroup study, led by the ECOG, randomizing patients to autologous BMT\textsuperscript{27,28} versus consolidation therapy with a single course of high-dose cytarabine and assigning eligible patients to alloBMT will define the value of two approaches to BMT compared with conventional consolidation chemotherapy.

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