A Randomized Comparison of Postremission Therapy in Acute Myelogenous Leukemia: A Southeastern Cancer Study Group Trial

By William R. Vogler, Elliott F. Winton, David S. Gordon, Marilyn R. Raney, Bette Go, and Leo Meyer

The Southeastern Cancer Study Group conducted a postremission induction randomized trial in adult acute myelogenous leukemia to assess the efficacy of alternate drug therapy during consolidation and of immunotherapy during maintenance. Of 508 evaluable patients entered into the study, 335 (66%) achieved a complete remission treated with a 7-day infusion of cytosine arabinoside at a dose of 100 mg/sq m/day and 3 days of daunorubicin at a dose of 45 mg/sq m/day. Those in remission were randomized to receive 3 courses of 1 of 3 consolidation regimens: (A) a continuous infusion of 5-azacytidine, 150 mg/sq m/day for 5 days; (B) 5-azacytidine plus β-deoxythioguanosine, 300 mg/sq m/day for 5 days; or (C) cytosine arabinoside, 100 mg/sq m/day intravenously, and thioguanine, 100 mg/sq m orally every 12 hr, plus daunorubicin, 10 mg/sq m every 24 hr daily for 5 days. There was no difference in remission rates. The reasons for the rare successes are increasing but this increase parallels the increase in remission rates. The reasons for the rare successes are increasing but this increase parallels the increase in remission rates.

Over the past several years, considerable progress has been made in the successful induction of complete remissions in adult acute myelogenous leukemia (AML). The remission rates from a number of series vary from 50% to over 80% and are influenced by several prominent variables, the most important being age. However, the duration of remission has remained relatively short, averaging less than a year among the larger series reported. Despite various attempts at maintenance therapy, none has proven to be vastly superior. It has been claimed that immunotherapy, such as bacillus Calmette-Guerin (BCG) with or without allogeneic leukemia cells, prolonged remissions and survival. In a recent review of collected randomized series, Vogler et al. noted a favorable effect of BCG in prolonging remission duration and survival. Although these differences were significant statistically, they did not extend the duration of remission or survival beyond a few months.

It has been known for many years that a few patients are long-term survivors. The number appears to be increasing but this increase parallels the increase in remission rates. The reasons for the rare successes are still obscure, although several attempts have been made to define the patient who is likely to be a long-term survivor. The concept of “consolidation,” that is, more intensive therapy, following remission induction was introduced when it was apparent that remission duration was usually short. Evidence that consolidation therapy prolongs remission duration is based largely on historical experience rather than randomized comparisons. In one randomized study, only marginal differences were observed when a consolidation course was added. It is known that drug resistance develops. In order to circumvent this problem, alternative drug programs were instituted. In one randomized study carried out by the Southeastern Cancer Study Group (SECSG), no difference was observed between patients randomized to continue the same drugs or alternate drugs during 6 consolidation courses. Approximately 40% relapsed on each arm. In another study in which patients were randomized to receive no therapy, BCG, or chemotherapy (consisting of cytosine arabinoside and bis-chloroethyl-nitrosourea) following 3 monthly consolidation courses, the median duration of remission was 6 mo, i.e., 3 mo after consolidation, a remission duration that was similar to that reported by Wiernik et al., who gave no treatment following remission induction.

Bodey et al. reported that late intensification was effective in prolonging remission duration and survival. However, treatment was not initiated until patients had been in remission 1 yr, a situation in which most patients will have already relapsed.

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In an attempt to improve the duration of remission and survival in AML, the SECSG designed a clinical trial to address two questions: Is alternate drug therapy during consolidation of value? Is immunotherapy combined with chemotherapy superior to either alone for maintenance?

MATERIALS AND METHODS

Criteria for Patient Selection

All previously untreated patients, 15 yr of age or older and diagnosed by bone marrow examinations as having acute myelogenous leukemia (FAB M1-M6) on the basis of histochemical stains confirmed by one of the two reference laboratories of the SECSG, were eligible. Patients 15 yr of age and older with acute undifferentiated leukemia (cytochemistry negative) were initially treated as lymphoblastic leukemia. Those who failed to reduce circulating blasts by 20% and to alter marrow cellularity following 10 days of prednisone (350 mg/sq m), twice weekly methotrexate (2 mg/sq m every 6 hr), and weekly vincristine (1 mg/sq m) were also eligible. Histochemical stains consisted of myeloperoxidase, Sudan black, combined esterase, and periodic acid-Schiff (PAS), as previously reported. Specimens submitted to the reference laboratory were technically unsatisfactory in 14 patients, but were included because they were judged to have AML by morphological criteria (Auer rods, promyelocytic granules) or by local histochemical stains that were thought to be acceptable by the authors. Patients with blastic phase of chronic myelocytic leukemia were excluded.

Remission Induction

Therapy consisted of a 7-day continuous infusion of cytosine arabinoside at a dose of 100 mg/sq m/day. Daunorubicin was administered at a dose of 45 mg/sq m/day. A bone marrow examination was performed at day 14. If the cellularity and blasts were 50% or greater, a second course was initiated; otherwise, treatment was withheld, the marrow was repeated at day 21, and if still leukemic, a second course was started. If hypoplastic, treatment was withheld and marrows were repeated at weekly intervals, or less, until remission or failure.

Criteria of Response

Complete remission (CR) and partial remission (PR) were defined as previously described. Patients failing to achieve at least a partial remission (PR) after 2 episodes of documented marrow hypoplasia were considered to be induction failures and taken off study.

Consolidation Therapy

Patients achieving a complete or partial remission were stratified on the basis of preinduction criteria, which included age (less than 60 yr or older), initial performance status (less than or more than 40%) as described by Karnofsky, initial platelet count (less than or greater than 70,000/μl), and initial blood urea nitrogen (less than or greater than 18 mg/dl). These stratifications were determined on the basis of prognostic factor analysis of a previous SECSG study. Patients were further stratified as to whether the response to induction was a CR or PR.

Patients were randomized to one of three consolidation arms. Regimen A consisted of 5-azacytidine, 150 mg/sq m/day, given by continuous intravenous infusion daily for 5 days. The drug was administered in approximately 200 ml of Ringer's lactate, infused over 8 hr. Fresh preparations were made 3 times daily. Previous studies had shown that this maximized stability of 5-azacytidine and was better tolerated by the patient.

Regimen B consisted of 5-azacytidine administered as above plus beta deoxythioguanosine given by rapid intravenous injection at a dose of 300 mg/sq m/day for 5 days. This combination had given promising results in a phase II study in refractory leukemia conducted by the SECSG and was well tolerated.

Regimen C consisted of the combination of cytosine arabinoside, 100 mg/sq m every 12 hr, by rapid intravenous injection, 6-thioguanine, 100 sq m every 12 hr orally, and daunorubicin, 10 mg/sq m/day (TAD). All were given for 5 days. Consolidation courses were repeated every 3-4 wk for 3 courses. Delayed recovery in granulocyte or platelet count permitted a 25% dose reduction for the next course. If patients relapsed during consolidation, they were taken off study.

Maintenance Program

Following recovery from the third consolidation course, remissions were documented by bone marrow examination, blood counts, physical findings, and examination of cerebral spinal fluid. Those patients in remission were randomized to receive one of three maintenance arms.

Regimen D consisted of no therapy for 13 wk, at which time patients received a continuous intravenous infusion of cytosine arabinoside, 100 mg/sq m/day for 5 days, and 2 doses of daunorubicin (DA), 45 mg/sq m, on days 1 and 2. These courses were repeated every 13 wk for 4 courses. Following this, no further therapy was given. No dose reductions were permitted with subsequent courses.

Regimen E consisted of Tice strain BCG administered by Heaf gun (0.25 ml of aqueous suspension, 108 organisms/ml, to 2 loci on each extremity twice weekly for 4 wk). Patients were skin tested with purified protein derivative (PPD) 2 wk later. Those converting to a positive skin test or demonstrating an increased positivity were given BCG once monthly for 11 mo. Those failing to change skin test reaction had a bone marrow examination to assess remission status. If still in remission, the BCG inoculations were repeated at the same schedule for 4 wk then once monthly, regardless of skin test reactivity, for 10 mo. Sequential dose reductions (30%) were permitted if any of the following occurred: local ulcerations, tender adenitis, suppurative adenitis, severe malaise, fever greater than 38.9°C, night sweats, elevated alkaline phosphatase, SGOT and/or direct bilirubin, osteomyelitis, or remote subcutaneous abscesses.

Regimen F consisted of the combination of regimens D and E. Studies done prior to therapy consisted of history and physical examination, blood count and differential, marrow aspiration and biopsy with histochemical stains, bilirubin, alkaline phosphatase, SGOT, uric acid, and an electrocardiogram. During induction, blood counts were done daily or every other day and chemistries at least weekly. During consolidation, blood counts were done at least every 2 wk and chemistries prior to each course of therapy. During maintenance, blood counts and chemistries were required at least monthly and bone marrow examinations every 2 mo.

Maintenance examination were done in every 6 mo following maintenance therapy and whenever the peripheral counts were abnormal. Patients were followed for relapse and survival.

Prognostic Factors

A number of pretreatment prognostic variables were considered to delineate those of predictive value for remission duration and survival. These included sex, age, performance status, associated diseases (cardiac, respiratory, hepatic, renal, diabetes), and physical findings (CNS symptoms, gum hypertrophy, bleeding, bone pain, fever, proven infection, and weight loss). In addition, the initial hematologic findings considered were blood counts (platelet count,
WBC, percent bands and segmented neutrophils, percent blasts, hemoglobin concentration, marrow cellularity, and percent leukemic cells and histochemistry (FAB classification).

Statistical Methods

Survival and remission duration curves were calculated with the Kaplan and Meier techniques \(^\text{29}\) and compared for significance by the Gehan method. \(^\text{30}\) Prognostic factors related to remission duration and survival were modeled using a stepwise proportional hazards general linear model (PHGLM) regression technique. \(^\text{31,32}\) Other comparisons were made using chi-square statistics.

RESULTS

Induction Arm

The protocol was open to accession from September 1977 to April 1981. During that interval, 691 patients were registered by 21 institutions in the SECSG. The distribution of registrations by institutions is shown in Table 1. There were 92 patients subsequently excluded from the analysis because they were judged ineligible, failing to meet diagnostic criteria. The majority of these were excluded because the investigator failed to submit histochemistry stains for review. Of the 599 eligible patients, 33 were excluded because of major protocol violations, and 58 were judged not adequate because of death within the first week of treatment, inadequate data, treatment refused, or loss to follow-up. Thus, 508 patients were considered evaluable. The ages ranged from 15 to 80.6 yr. Fifty-two percent (266) were males, and 48% (242) were females.

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. Registered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emory University</td>
<td>150 (22)</td>
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<tr>
<td>University of Alabama</td>
<td>91 (13)</td>
</tr>
<tr>
<td>Duke University</td>
<td>66 (10)</td>
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<tr>
<td>Vanderbilt University</td>
<td>53 (8)</td>
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<tr>
<td>University of Puerto Rico</td>
<td>48 (7)</td>
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<tr>
<td>St. Louis University</td>
<td>37 (5)</td>
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<tr>
<td>Rush Medical College</td>
<td>34 (5)</td>
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<tr>
<td>University of Cincinnati</td>
<td>32 (5)</td>
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<tr>
<td>Case Western Reserve University</td>
<td>31 (4)</td>
</tr>
<tr>
<td>Temple University</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Miami University</td>
<td>23 (3)</td>
</tr>
<tr>
<td>University of Florida</td>
<td>21 (3)</td>
</tr>
<tr>
<td>University of Kentucky</td>
<td>18 (3)</td>
</tr>
<tr>
<td>University of South Florida</td>
<td>13 (2)</td>
</tr>
<tr>
<td>University of Tennessee—Memphis</td>
<td>11 (2)</td>
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<tr>
<td>Veterans Administration Hospital—</td>
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</tr>
<tr>
<td>Durham, NC</td>
<td>10 (1)</td>
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<tr>
<td>New Jersey Medical College</td>
<td>8 (1)</td>
</tr>
<tr>
<td>University of Tennessee—Knoxville</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Veterans Administration Hospital—</td>
<td></td>
</tr>
<tr>
<td>Brooklyn, NY</td>
<td>5 (&lt;1)</td>
</tr>
<tr>
<td>Washington University</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>University of Louisville</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Total</td>
<td>691 (100)</td>
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</table>

There were 335 complete remissions (66%) and 14 partial remissions. The median time to remission was 33 days, the mean was 42 days, and the mean number of induction courses was 1.3.

Consolidation Arm

Of the 349 remissions (CR and PR), 338 patients were randomized to the consolidation arms, but 33 were ineligible. Protocol violations occurred in 25 instances, and the trial was inadequate in 4. Thus, there were 276 patients evaluable; 106 received regimen A, 64 regimen B (NCI stopped supplying beta deoxythioguanosine midway through the study), and 106 received regimen C. There was no difference in relapse rate among the three arms. The percentages completing consolidation and remaining in remission were 74% on regimen A, 80% on regimen B, and 83% on regimen C. Figures 1 and 2 show that remission and survival were not significantly different among the three arms.

Maintenance Therapy

There were 215 patients registered on the maintenance arms. Thirty-seven were not eligible, 7 were ineligible because of protocol violations, and 8 had inadequate data. Of 163 evaluable cases, 54 were randomized to regimen D (DA), 57 to regimen E (BCG), and 52 to regimen F (DA + BCG). Figures 3 and 4 show the remission duration and survival. Regimen D appears to have an advantage over regimens E and F. The median duration of remission was 17.4 mo on regimen D compared to 9.4 and 9.5 mo on regimens E and F, respectively. The median survival on regimen D was 29 mo compared to 21 for both regimens E and F. The survival differences were not statistically significant.

The effect of the consolidation regimen on each of the subsequent maintenance regimens was analyzed to
determine if patients receiving different drugs during consolidation fared better than those receiving similar drugs. Azacytidine consolidation significantly prolonged remission duration ($p = 0.001$, Fig. 5) and survival ($p = 0.009$, Fig. 6) in those receiving regimen D when compared to regimen F. Figure 5 illustrates a borderline statistically significant difference between D and E in remission duration. Figure 6 shows no difference in survival. The difference between regimens E and F were of borderline significance concerning remission durations ($p = 0.14$) and survival ($p = 0.06$). Consolidation with regimen B gave a mixed picture regarding maintenance. Regimen D was superior to F ($p = 0.04$, median 24 mo versus 10 mo) but not to E ($p = 0.18$, median 11 mo) regarding remission duration, and no significant differences were observed in survival. However, those patients consolidated with regimen C showed no significant differences among the 3 maintenance arms.

Although it is too early to know how many patients will be in remission at 5 yr, 4 of 156 at risk were in remission 4 or more yr (3%), 16 of 227 (7%) between 3 and 4 yr, and 44 of 328 (13%) between 2 and 3 yr.

**Toxicity**

The majority of patients failing to achieve remission died of complications of the disease or treatment. No unusual toxicities were noted. During induction, 125 patients died; only 1 patient died of toxicity during consolidation and 6 during maintenance therapy. All were related to hemorrhage or infection during periods of aplasia. Fever and ulcerations were the major side effects of BCG therapy.

**Prognostic Factors**

Applying the same variables as before and using a proportional hazards general linear model, the effects of the variables on remission duration and survival were assessed (Table 2). For remission duration, hemoglobin, platelets, respiratory disease, M4 marrow, and bone pain were identified as significant factors. For survival, respiratory disease, age, bleeding diathesis, platelets, and fever were significant.
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Those receiving azacytidine consolidation.

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obtained in the majority of adults with acute leukemia generally give higher remission rates than those obtained by cooperative groups. For instance, Foon et al.34 reported a 76% CR rate in 107 patients treated at their institution using a 3-drug combination of cytosine arabinoside, daunorubicin, and thioguanine. On the other hand, a multiple institutional cooperative study reported a CR rate of 60%, using a similar 5-drug combination.5 Our 66% rate appears to be approaching the results of single institutions.

We explored three different consolidation programs in an effort to prolong remission duration. All had been proven to have activity in AML in SECSG trials.8,27,35 The idea of using drugs different from those in induction was to delay the onset of drug resistance. As the data show, we could not demonstrate an advantage of any consolidation program in itself. However, when combined with the best maintenance arm, there appeared to be some advantage in using drugs the patients had not received during induction. As noted, azacytidine consolidation followed by DA maintenance gave the longest remission duration and survival. The combination of azacytidine and beta deoxythioguanosine followed by DA gave better results than TAD followed by DA. Thus, we observed that switching drugs during consolidation was helpful. However, Clarkson et al.36 used different drugs during maintenance and observed only a 10-mo median duration of remission, suggesting that this approach was not a significant advance.

Although it is generally believed that maintenance therapy is necessary, few randomized trials have addressed this point. In our previous study, the duration of remission and survival were no different when immunotherapy, chemotherapy, and no treatment were compared following three consolidation courses.8 The median remission duration was 6 mo and survival 16 mo in 32 patients randomized to no treatment. In a small series reported by Embury et al.,37 in which patients were randomized to maintenance chemotherapy or no treatment following four consolidation courses, the median remission duration of 13 patients receiving no further treatment was 6.7 mo. This was significantly less than the 10.3 mo observed in 13 patients continued on chemotherapy. However, survival was not different, 15.6 mo versus 13.4 mo, respectively. With increasing emphasis on early intensive therapy, the issue of maintenance therapy remains open. A current SECSG protocol addresses this issue.

At the time this study was planned, the BCG arm of our earlier study appeared to have an advantage in prolonging survival.38 For this reason, it was selected as one of the maintenance arms. The remission duration and survival of those patients receiving BCG in the current study and the previous study were virtually identical (9.4 versus 8 mo for remission duration and 21 versus 22 mo for survival, respectively). Thus, the current study not only confirms the results of BCG therapy, but clearly demonstrates the advantage of the chemotherapy maintenance arm.

When this protocol was initiated, other series had suggested that the combination of chemotherapy and immunotherapy would be the optimal maintenance program. Powles et al. demonstrated the survival advantage of immunotherapy plus chemotherapy over chemotherapy alone.39 We observed similar results.40 However, no comparisons of immunotherapy versus the combination of immunotherapy and chemotherapy had been made. We conducted a trial concurrent with our previously reported study8 at two SECSG institutions in which 33 patients were given a combination of

Table 2. Stepwise PHGLM Regression

<table>
<thead>
<tr>
<th>Dependent variable: overall survival</th>
<th>Favorable Factors</th>
<th>χ²</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Absence of respiratory disease</td>
<td>9.98</td>
<td>0.0016</td>
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<tr>
<td>Age &lt;50</td>
<td>14.59</td>
<td>0.0001</td>
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</tr>
<tr>
<td>Absence of bleeding</td>
<td>6.58</td>
<td>0.0103</td>
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<tr>
<td>Platelets &gt;72.5 x 1,000</td>
<td>5.66</td>
<td>0.0173</td>
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<tr>
<td>Absence of fever</td>
<td>4.69</td>
<td>0.0303</td>
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<table>
<thead>
<tr>
<th>Dependent variable: remission duration</th>
<th>Favorable Factors</th>
<th>χ²</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Hemoglobin &gt;9.22</td>
<td>11.52</td>
<td>0.0007</td>
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<tr>
<td>Platelets &gt;72.5 x 1,000</td>
<td>8.94</td>
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<tr>
<td>Absence of respiratory disease</td>
<td>12.64</td>
<td>0.0004</td>
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<tr>
<td>M4 marrow</td>
<td>9.15</td>
<td>0.0025</td>
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<tr>
<td>Absence of bone pain</td>
<td>4.68</td>
<td>0.0304</td>
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Fig. 6. Survival from date on study by maintenance arm of those receiving azacytidine consolidation.

DISCUSSION

The results of this clinical investigation confirm the work of others in demonstrating that remissions can be obtained in the majority of adults with acute myelogenous leukemia.1,11

Reports from centers specializing in the treatment of acute leukemia generally give higher remission rates than those obtained by cooperative groups. For instance, Foon et al.34 reported a 76% CR rate in 107 patients treated at their institution using a 3-drug combination of cytosine arabinoside, daunorubicin, and thioguanine. On the other hand, a multiple institutional cooperative study reported a CR rate of 60%, using a similar 5-drug combination.5 Our 66% rate appears to be approaching the results of single institutions.

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immunotherapy and chemotherapy. The results of this study showed a median remission duration of 10.2 mo and median survival of 12.7 mo, identical to Powles et al. and not significantly different from the combination in the current study. These data would indicate that the combination of immunotherapy and chemotherapy is not superior to immuno-suppressive programs alone. The superiority of chemotherapy over the combination has yet to be explained. It would appear that the addition of BCG to chemotherapy had an adverse effect on remission duration. Bekesi et al. noted an adverse effect of MER on remission duration when added to chemotherapy and neuraminidase-treated allogeneic myeloblasts. This was thought to be related to the appearance of suppressor monocytes. In our previous study, we demonstrated a reduction in T and B cells during maintenance therapy. These observations suggest that such maintenance programs may be immuno-suppressive.

Our data support the results of others that intensification programs after obtaining remission prolongs the duration of remission. Although not a randomized study and restricted to patients less than 50 yr of age, of whom the majority were less than 17, Mayer et al. reported a median duration of remission of 22.4 mo in 74 patients in remission treated with intensive courses of cytosine arabinoside, Adriamycin, vincristine, and prednisone over a 15-mo period, a time not dissimilar to ours. In a recent update of this study, a median remission duration of 27 mo for 30 adults was reported.44 In a randomized study, Glucksberg et al. reported a 22.9-mo remission duration in 23 patients given 2 additional induction courses at 6 and 12 mo during maintenance treatment. In contrast, in 16 patients not given intensification, the median remission duration was 9.1 mo. These results will stimulate more investigation utilizing intensification programs either early in remission or intermittently during maintenance.

Although it is too early to know how many of the 64 patients in remission more than 2 yr will be long-term survivors, the results are clearly better than the six 24+ mo survivors from our previous study.9

Despite the progress made in remission induction in AML and the increasing numbers of patients who are long-term disease-free survivors, the fact remains that the majority succumb to their illness, so better treatment is still needed.

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REFERENCES

POSTREMISION THERAPY IN ACUTE LEUKEMIA


A randomized comparison of postremission therapy in acute myelogenous leukemia: a Southeastern Cancer Study Group trial

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