Comparison of Three Remission Induction Regimens and Two Postinduction Strategies for the Treatment of Acute Nonlymphocytic Leukemia: A Cancer and Leukemia Group B Study

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Patients with acute nonlymphocytic leukemia were randomized to receive remission induction therapy consisting of seven days of cytosine arabinoside and three days of daunorubicin (“7 + 3”) or to receive the same regimen intensified by either the addition of 6-thioguanine or by extension of the administration of cytosine arabinoside to ten days. Additionally, all patients were randomized to receive or not to receive cotrimoxazole antibacterial prophylaxis during the remission induction phase. Neither an increase in intensity of chemotherapy nor the antibacterial prophylaxis increased the remission rate above the 53% for patients treated with the standard “7 + 3” regimen.

The treatment of acute nonlymphocytic leukemia (ANLL) consists of a remission induction phase designed to return hematopoiesis to normal and a postinduction phase designed to prolong the remission. The first part of the study to be reported here was designed to determine whether an increase in the intensity of the standard seven days of cytosine arabinoside and three days of daunorubicin (DNR) (“7 + 3”) remission induction regimen used by the Cancer and Leukemia Group B (CALGB) since 1974 and/or the administration of cotrimoxazole antibacterial prophylaxis would result in an increase in the complete remission (CR) rate. The second phase of the study was designed to determine whether prolonged maintenance therapy of moderate intensity during the postinduction phase was necessary. Accordingly, all patients received maintenance chemotherapy for 8 months, at which time half were randomized to discontinue all therapy and the other half to continue monthly courses of maintenance therapy for a total of 3 years.

The data described in this paper demonstrate that neither an increase in the intensity of 7 + 3 therapy, as described here, nor the administration of cotrimoxazole results in an improvement in the CR rate and that maintenance chemotherapy beyond 8 months is unnecessary. In addition, data are presented that reinforce an earlier hypothesis that leukemic relapse may occur as a result of at least two distinct biologic processes.

MATERIALS AND METHODS

Study Design

CALGB study 7921 was activated in November 1979 and was closed to accrual in November 1982.

Eligibility

Any patient with acute nonlymphocytic leukemia (ANLL) according to the criteria established by the French-American-British (FAB) working party was eligible for study. Patients with life-threatening infections were eligible only upon control of such infections. Informed consent was required prior to entry into the study.

Patients were ineligible if they had inadequate renal function. Although the protocol specified maximum permissible levels of 30 mg/dL for BUN and 1.5 mg/dL for creatinine levels, a number of patients were entered who had levels slightly above these limits. Although technically ineligible, these patients were included in the study, with careful analyses being performed to determine whether they showed any differences in response or toxicity. Any patient whose BUN was >40 mg/dL or whose creatinine level was >2.0 mg/dL was excluded from analysis. Patients with a history of neoplastic disease and associated cytotoxic therapy were not eligible for randomization (See Statistical Methods).

Treatments Under Study

Remission induction therapy. Figure 1A provides the schema for the induction phase of the study. Patients were initially randomized to induction therapy with the standard 7 + 3 regimen (cytosine arabinoside, 100 mg/m²/d by continuous infusion for seven days, and DNR, 45 mg/m² on days 1, 2, and 3) or with induction therapy...
whose intensity was increased either by extending the administration of cytosine arabinoside to ten days ("10 + 3") or by the addition of 6-thioguanine (6-TG; TAD) at 100 mg/m² every 12 hours for seven days concurrent with cytosine arabinoside. These two modifications of the 7 + 3 regimen were based upon reports in the literature that the therapeutic efficacy of our standard regimen might be improved by extending cytosine arabinoside administration to ten days12 or by the addition of 6-TG.1315

A second course of therapy was administered, as indicated in Fig 1A, if the patient's leukemia failed to enter remission. The only exceptions were patients who achieved a partial remission and in whom the severity of toxicity during the first course of therapy was felt to preclude the administration of course 2. Half of the patients on each program were randomized to receive cotrimoxazole, two regular-strength tablets (80 mg trimethoprim and 400 mg sulfamethoxazole), by mouth twice a day starting on the day before initiation of chemotherapy and continuing until remission occurred or until the patient was removed from the study as a treatment failure.

The study was amended in November 1980 so that the DNR dose in all three regimens was reduced to 30 mg/m²/d for patients over 60 years old. This modification was introduced as a consequence of the previous CALGB protocol in ANLL that suggested that this change would increase the CR rate and reduce the death rate for older patients.2

Patients who entered CR or partial remission following the second course of induction therapy advanced to the maintenance phase. The remaining patients were considered to be treatment failures and were removed from the study.

Dose reductions of 50% and/or dose interruptions were permitted for severe gastrointestinal toxicity, hepatic dysfunction, or renal dysfunction. A lumbar puncture was performed on the day prior to the initiation of chemotherapy and every 6 months for 5 years. If any leukemic cells were seen on a cytocentrifuge preparation, the patient received 50 mg of cytosine arabinoside intrathecally every four days until leukemic cells were no longer detectable in the CSF, and this was followed by the same dose of cytosine arabinoside every 4 weeks for 8 months.

**Maintenance therapy.** As indicated in Fig 1B, maintenance therapy consisted of a series of monthly five-day courses of combination chemotherapy. Each cycle was composed of four such courses. Sequential courses consisted of five days of administration of cytosine arabinoside together with 6-TG (course 1), prednisone/vincristine (courses 2 and 4), or DNR (course 3) administered on a rotating
schedule. When a cumulative dose of 500 mg/m² of DNR was reached, the third course of each cycle was modified by replacement of DNR with 6-TG, 100 mg/m² orally every 12 hours for ten times.

Following two cycles of maintenance therapy (8 months), marrow aspiration and biopsy were performed. Patients who were still in CR at this time were randomized either to stop maintenance chemotherapy immediately or to continue maintenance for an additional seven cycles (for a total duration of maintenance therapy of 3 years) or until the time of relapse if that occurred before the seven cycles were completed.

Bone marrow aspiration was repeated every 4 months until relapse for all patients regardless of their maintenance treatment assignment.

Evaluation of Response

A CR was defined by the criteria previously reported by Rai et al. In brief, a bone marrow aspirate had to contain <5% abnormal cells, with a normal cellularity and normal granulopoiesis, thrombopoiesis, and erythropoiesis. Additional requirements included a peripheral blood count within normal limits and clearing of all signs and symptoms attributable to leukemia.

Relapse was defined as a return of leukemic cells to the marrow in excess of 25%.

Statistical Methods

Patients who were clearly ineligible were excluded from this analysis. Patients who were registered but withdrawn prior to the initiation of protocol therapy and patients with no follow-up data after registration were also excluded. Patients with prior cancer were not eligible for randomization but were nonrandomly assigned to treatment with 7 + 3 without cotrimoxazole and have been excluded from this report. Seven hundred forty-nine patients were registered in the study. Their study status is shown in Table 1. Six hundred sixty-eight (95.8%) of the 697 patients with primary leukemia were eligible and evaluable.

The primary end points of interest for the induction questions were response rates and duration of survival. Analysis of these end points were stratified by age (60 and under vs over 60). Comparisons of the three induction regimens were also stratified by the randomized assignment of cotrimoxazole, and the evaluations of this antimicrobial agent were stratified by the induction regimen assigned.

For the maintenance phase of the study, the primary end points were time to relapse and survival. Both end points were measured from the date of CR and from the time of maintenance randomization (ie, after two cycles of maintenance). These comparisons were stratified by the induction chemotherapy regimen assigned since the maintenance randomization was stratified in that way.

All P values reported are two sided. Survival and response duration curves as well as any rates computed from these curves were calculated by using the life table method (product limit estimator) of Kaplan and Meier. Survival comparisons were made using the Mantel-Haenszel (log rank) test. The chi-square test for contingency tables was used for overall comparisons of response rates across strata. A number of patients were deemed "not evaluable for response," usually as a result of inadequate documentation of marrow status posttreatment. For purposes of estimating and comparing response rates, a conservative approach was used with respect to these patients. They were assumed to have been treatment failures, ie, they were included in the denominators of the rates, but not in the numerators.

A number of patients entered bone marrow transplantation programs prior to completion of this study. Patients who entered transplantation programs while in their initial remission were considered censored at the date of entry into that program for calculation of the remission duration but continued to be followed for survival.

Toxicity of the treatments under study was assessed by using previously reported CALGB toxicity criteria. Specific comparisons of infection rates between the cotrimoxazole-treated and the control groups were used to determine the efficacy of prophylactic administration of cotrimoxazole.

RESULTS

Remission Induction Therapy

The Outcome of Remission Induction Therapy

Fifty-six percent of the 668 eligible patients entered CR, 4% achieved a partial remission, 24% expired during therapy, 14% survived but did not enter remission, and 1% were ineligible because of a lack of definitive marrow studies. The CR rates for 7 + 3, TAD, and 10 + 3 regimens were 52.6%, 56.9%, and 57.3%, respectively (Table 2) (P = .6).

Fewer patients treated with 10 + 3 required two courses of therapy to enter remission (15% of complete responders) than did patients treated with 7 + 3 (29%) or TAD (28%) (P = .011), but the median time to remission was not significantly different for the three regimes (10 + 3, 4.8 weeks; 7 + 3, 4.4 weeks; TAD, 4.1 weeks). The toxicity of the three regimens was identical, with all patients experiencing life-threatening hematopoietic toxicity, and 7 to 11% of patients experiencing severe or life-threatening renal, hepatic, and/or cardiac toxicity.

Three hundred twenty-three patients were randomized to receive cotrimoxazole, and 345 patients were randomized to receive no antimicrobial prophylaxis during remission induction therapy. The CR rate was 56% whether or not the patient received cotrimoxazole. In addition, cotrimoxazole

<table>
<thead>
<tr>
<th>Table 1. Study Status of Patients in the Study</th>
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<tbody>
<tr>
<td>With Cotrimoxazole</td>
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<tr>
<td>---------------------</td>
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<tr>
<td>7 + 3 TAD 10 + 3</td>
</tr>
<tr>
<td>Patients entered</td>
</tr>
<tr>
<td>Prior cancer</td>
</tr>
<tr>
<td>Patients randomized</td>
</tr>
<tr>
<td>Ineligible</td>
</tr>
<tr>
<td>Cancelled</td>
</tr>
<tr>
<td>No follow-up</td>
</tr>
<tr>
<td>Cases analyzed</td>
</tr>
</tbody>
</table>

*Number of patients (%).
†Patients whose leukemia proved to be resistant to the chemotherapy administered.
‡Death during remission induction therapy.
had no effect on patient survival or on the toxicity associated with each of the chemotherapy treatment arms.

**Prognostic Factors for the Outcome of Remission Induction Therapy**

Table 3 lists the patient characteristics that were evaluated for possible relationship to the outcome of remission induction therapy. Only five of these 20 characteristics were significantly related to treatment outcome, and one was of borderline significance (Table 4). Age was by far the single most important factor, with only 41% of 104 patients >60 years old entering remission as compared with 65% of patients ≤60 years old (P < .00001). The next most important factor was serum creatinine levels. Only 36% of patients with a creatinine level of 1.6 to 2.0 mg/dL entered remission as compared with 56% for patients whose creatinine level was <1.6 (P = .006). An SGOT level of ≥40 mU/mL was associated with a CR rate of 47% compared with 59% for patients whose SGOT level was <40 mU/mL. A WBC count at diagnosis of >100,000/μL was associated with a CR rate of only 38% as compared with 58% for patients with a count below this value (P = .041). The presence of skin or gingival involvement was an unexpectedly good prognostic sign, being associated with a CR rate of 68% as compared with a CR rate of 54% for patients without such extramedullary involvement (P = .032).

Forty-three percent of patients presented without fever or infection. These patients tended to have a higher CR rate than the 57% of patients who were febrile and/or had a documented infection at the time of diagnosis (60% v 52.6% CR rates respectively, P = .07). The presence of severe infection was also of prognostic significance, being associated with a CR rate of only 40% as compared with a CR rate of 57% for patients without severe infection (P = .057). The administration of cotrimoxazole had no effect on the outcome of treatment or on the survival of patients whether or not they were afebrile or febrile, infected or not infected at diagnosis. The incidence of severe or life-threatening infection during induction therapy for patients who were afebrile at diagnosis was reduced from 73% to 59% by the administration of cotrimoxazole (P = .013), but as noted earlier, this had no effect on treatment outcome. Table 5 provides information regarding the types of infection experienced by patients who received or did not receive cotrimoxazole. Bacterial infections were the predominant cause of first infections. Fungal infections were frequent causes of second infections and were more common in the cotrimoxazole group (50%) than in the control group (29%).

**Miscellaneous Observations Regarding the Outcome of Remission Induction Therapy**

One year after the study was initiated, the protocol was modified so that patients >60 years of age would receive 30 mg/m²/d of DNR rather than 45 mg/m²/d. One hundred eleven patients in this age group received the higher DNR dosage, whereas 139 patients received the lower dosage. Although the CR rates were not significantly different (39% v 43% respectively), fewer patients treated at the lower dosage died during therapy (31% v 45% respectively, P = .028).

### Table 4. Factors of Prognostic Significance

<table>
<thead>
<tr>
<th>Age</th>
<th>WBC count</th>
<th>Infection</th>
<th>Infection</th>
<th>Remission Outcomes</th>
<th>Remission Duration</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
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<td>&lt;.0001</td>
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<td>.023</td>
<td>.023</td>
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</table>

**Table 5. Types of Induction Infections**

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>With Cotrimoxazole (n = 323)</th>
<th>Without Cotrimoxazole (n = 345)</th>
<th>Severe Infection</th>
<th>Life-Threatening Infection</th>
<th>Severe Infection</th>
<th>Life-Threatening Infection</th>
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<td>Bacterial</td>
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<td>Fungal</td>
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<td>11</td>
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<td>Viral</td>
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<tr>
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<td>3</td>
<td>1</td>
<td>5</td>
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<td>5</td>
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<tr>
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<td>49</td>
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<tr>
<td>Type not reported</td>
<td>54</td>
<td>25</td>
<td>66</td>
<td>13</td>
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<td></td>
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</table>

**Table 3. Patient Characteristics at Diagnosis Evaluated for Potential Prognostic Significance**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>WBC count</th>
<th>Number of circulating leukemic cells</th>
<th>Hematocrit</th>
<th>Hemoglobin level</th>
<th>Platelet count</th>
<th>Bleeding</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>CNS involvement</td>
<td>Skin or gingival involvement</td>
<td>Hepatomegaly</td>
<td>Splenomegaly</td>
<td>Lymphadenopathy</td>
<td>BUN</td>
<td>Creatinine</td>
<td>SGOT</td>
<td>Bilirubin</td>
</tr>
</tbody>
</table>

Abbreviation: FUO, fever of undetermined origin.

*Local or visceral infection with systemic signs and/or a fever of 38°C.
†Fulminant local or visceral infection with sepsis, shock, or other system failure.
‡Type of infection documented by culture or by biopsy.
Remission Duration

Figure 2A provides the remission duration curve for all patients who entered CR. The median was 52.4 weeks; 22% of patients were projected to be in remission at 3 years. There was no statistically significant difference in remission duration between patients treated on the three induction arms. The overall remission duration was related to the number of courses necessary to induce a CR. Patients who required a single course of therapy had longer remissions than those who required two courses (median remission durations of 55.9 v 45.4 weeks respectively, \( P = .02 \)). Patients who entered partial remission status relapsed at a median of 20.7 weeks, with no patient remaining in this status beyond 100 weeks.

One hundred forty-eight patients relapsed or died before reaching the point of second randomization to stop or to continue maintenance therapy. Of the remaining patients, 151 were randomized, and 73 were not. There were no statistically significant differences in remission duration between patients who were or were not randomized. The median duration of remission for all patients after randomization was 67 weeks, with 38% of patients projected still to be in remission 3 years later (Fig 2b). This figure also provides the remission duration curve for patients randomized to continue or to stop therapy. The curves diverged 3 months after randomization but converged and became persistently superimposable 75 weeks after randomization. The median time to relapse after randomization for patients in whom therapy was discontinued was 45 weeks compared with 71 weeks in patients who continued therapy (\( P = .62 \)). The type of remission induction therapy had no statistically significant effect on the time to relapse for patients randomized to stop or to continue maintenance chemotherapy.

Toxicity Associated With Maintenance Chemotherapy

Toxicity data were available for 329 patients for the first cycle of maintenance therapy and for 220 patients on the second cycle. Seventy-five percent of patients experienced severe or worse hematologic toxicity at some time during cycle 1 with a reduction of the blood counts to life-threatening levels (WBC count reduced to <1,000/μL, granulocyte count to <500/μL, and/or platelet count to <25,000/μL) occurring in 51% of patients. Sixty-six percent of patients who received cycle 2 of therapy had severe hematologic toxicity, with 31% having life-threatening reductions in blood counts to the levels just described.

Death in remission occurred only during cycles 1 and 2 and was clearly age related, with a 3% death rate in remission for patients <40 years old, 9% for patients 41 to 60 years old, and 14% for patients >60 years old (\( P = .03 \)).
Clinical Prognostic Factors for Remission Duration

Of the various factors evaluated, only age at diagnosis and initial hemoglobin level were statistically significantly prognostic factors for remission duration (Table 4). Figure 2C demonstrates that patients between 41 and 60 years of age had the longest remission durations (median, 68.3 weeks). Older and younger individuals had significantly shorter remissions (medians of 49.9 and 42.7 months respectively, \( P = .026 \)). Patients with a hemoglobin value of 8 to 12 g/dL had a median remission duration of 57.6 weeks; those with hemoglobin values <8 had a median of 51 weeks, and those with hemoglobin values of 12 to 18 had a median of 36 weeks (\( P = .002 \)).

Survival

Figure 3A presents the survival curve for the 668 evaluable patients. The median duration of survival is 41.2 weeks; 18% of patients are alive at 3 years. The survival curve has three components, each with a characteristic slope. The first component, which has the steepest slope, represents death during remission induction therapy. The second component represents death subsequent to relapse during the first 2 years of remission, and the third component represents late relapses and death. As noted earlier, the only deaths seen in remission occurred during the first two cycles of maintenance therapy and were age related.

Table 4 lists the factors that were prognostically important for survival. From the data provided it can be seen that the majority of factors were important because of their relationship to the outcome of remission induction therapy. Figure 3B illustrates this effect. Note that as the severity of infection increases, the fall in the first part of the survival curve becomes greater, thus indicating increasing mortality during remission induction therapy. Once the period of induction
death is passed, all the curves are parallel, which indicates that infection at diagnosis has no effect on events subsequent to the patient entering remission. The hemoglobin level, on the other hand, is prognostically important because of its relationship to remission duration. In this case, the survival curves for patients with different hemoglobin levels at diagnosis are virtually identical for the first phase of the curve but diverge thereafter (data not shown). The survival curves for patients treated with the three different remission induction regimens were virtually identical.

In contrast, age was of prognostic importance with respect to both the outcome of remission induction therapy and remission duration. Figure 3C demonstrates that patients <40 years old are more likely to survive remission induction therapy than are older patients, whereas patients over 60 years of age are not only more likely to die early in therapy but also have a higher death rate during the first year of remission. When these data are considered together with the data presented in Fig 2C, it is apparent that older patients are at a disadvantage because of a higher relapse rate and a higher death rate both during remission induction therapy and subsequent to relapse. Although younger patients also have a higher relapse rate than patients 40 to 60 years old, it is likely that their greater ability to survive after relapse offsets any survival advantage that the patients 40 to 60 years of age might have had from their longer remission durations.

Figure 3D gives the survival curve of the 151 patients randomized to stop or to continue maintenance therapy after the first 32 weeks of maintenance. The median survival time is 150.7 weeks, with 48% of patients projected to be alive at 3 years after randomization. Figure 3D also provides the survival curves for patients randomized to stop or to continue therapy. There appears to be a trend for greater survival for those who stopped therapy, but the current P value is .11.

DISCUSSION

The examination of remission induction therapy in this study demonstrated that all three regimens produced the same CR rate. The administration of cotrimoxazole, although reducing the incidence of severe infection, did not improve either the remission induction or survival rates. Evaluation of the types of treatment failure demonstrates that almost two thirds of the treatment failures were associated with death during therapy and one third were characterized by persistent leukemia in patients who survived therapy. Given that the former patients might have benefited from a less intensive and therefore less toxic induction regimen and the latter patients might have benefited from more intensive therapy, it is clear that no single alteration in the induction regimens studied here is likely to produce a dramatic increase in the CR rate. Rather, selectivity in treatment with the design of regimens tailored to the needs of the individual patients may be the most likely approach to improve the overall CR rate.

The study reported here failed to demonstrate any therapeutic benefit from the addition of 6-TG to the “7 + 3” cytosine arabinoside/DNR combination. Although others have reported very high remission rates with TAD regimens, the doses and schedules used for the cytosine arabinoside and DNR differ from that used. Any differences that might exist in therapeutic efficacy between these TAD regimens and “7 + 3” therapy would appear to be most likely due to differences in the cytosine arabinoside and DNR dose/schedules rather than to the addition of 6-TG. The observations reported here with respect to cotrimoxazole confirm previous observations that the administration of the antimicrobial agent to severely granulocytopenic patients reduces the incidence of severe infections and appears to be associated with an increase in fungal infections. Perhaps the latter reason together with the fact that cotrimoxazole treatment reduced bacterial infections only to a modest extent accounts for the failure of cotrimoxazole administration to improve the CR rate.

The median duration of remission for the patients treated here was 52.4 weeks, with 22% of patients projected to be in remission at 3 years. In contrast, data presented elsewhere suggest that patients who receive similar remission induction therapy and who do not receive any therapy after having entered remission have median duration of remissions in the range of 7 months. The remission duration curves for those patients randomized to stop or to continue maintenance therapy began to diverge approximately 3 months after randomization due to an increase in the relapse rate of those patients in whom therapy was discontinued. The relapse curves then began to converge 6 months after randomization as a result of a significant fall in the relapse rate of those patients whose therapy had been discontinued. The curves became superimposable at 13/2 years after randomization and remained so thereafter. Both relapse curves have a point of inflection indicative of a change from a high rate of relapse to a lower relapse rate. This change in relapse rate occurred earlier in patients in whom maintenance therapy was discontinued. Once the lower relapse rate phase began, the continued administration of chemotherapy had no effect on the rate of relapse. Hence, the data reported here demonstrate that the administration of conventional maintenance chemotherapy for 3 years retards leukemic relapse during the first 2 years of administration but has no effect on the rate of relapse thereafter or on the proportion of patients in long-term remission over and above that produced by 8 months of therapy. Patients in whom therapy was discontinued at 8 months appear to have survived longer than patients who receive 3 years of therapy, perhaps because of a survival advantage after relapse.

The relatively modest therapeutic efficacy of maintenance chemotherapy has resulted in the introduction of intensive consolidation chemotherapy. In one Roswell Park Memorial Institute study, three courses of intensive consolidation chemotherapy were administered followed by 3 years of maintenance therapy. The median duration of remission was 17 months, with over 30% of patients remaining in remission beyond 5 years. A successor study, which provided for three or four courses of intensive consolidation therapy and no maintenance therapy, has produced similar results. Similar results for intensive consolidation therapy have been reported by other investigators, but the follow-up times have
been shorter.\textsuperscript{27-29} At the present time CALGB is engaged in a prospective randomized comparison of the efficacy of intensive consolidation chemotherapy.\textsuperscript{30} One problem with the intensive consolidation therapies has been that they are associated with significant morbidity, with mortality rates ranging from 5\% to 20\%.\textsuperscript{27-29} Hence, the net beneficial effects of intensive therapy in remission is less than one might expect on the basis of reduced relapse rates. Given recent observations regarding the prognostic significance of the cytogenetic characteristics of the leukemic cells,\textsuperscript{31} cell surface markers,\textsuperscript{32} and the potential significance of both molecular biologic\textsuperscript{33} and cell cycle characteristics of leukemic cells,\textsuperscript{34} perhaps pretherapy assessments of these leukemic cell characteristics could be used to identify patients who will have a long remission when treated with maintenance therapy. This would allow these patients to avoid the risks of intensive consolidation therapy.

Age was the most important prognostic factor, with advanced age being associated with a low remission rate. Age >60 or <40 was associated with shorter remissions. The latter observation is curious since a recent review of 760 patients treated with very similar maintenance therapies failed to demonstrate an effect of age on remission duration.\textsuperscript{8} An elevated serum creatinine or SGOT level, the presence of infection, and a WBC count greater than 100,000/μL at the time of initiation of treatment were all associated with death during remission induction therapy. Of interest is the unexplained observation that a hemoglobin level between 8 and 12 g/dL was a good prognostic sign with respect to remission duration. Since there was no provision for a central review of slides, no comment can be made regarding the possible relationship between FAB type and response.

The observations reported here also have implications regarding the interpretation of other studies. Therapies such as allogeneic bone marrow transplantation in remission\textsuperscript{35-37} may also have their primary effects on the first part of the relapse curve and may be associated with a similar low but significant late relapse rate. Should this prove to be the case, then the hypothesis that at least some late relapses are in fact “new leukemias” may gain support. Finally, the somewhat unexpectedly long subsequent remission durations and survivals of patients who were selected by having remained in remission at 8 months (Figs 2B, 3D) demonstrate the necessity of a control arm in interpreting the efficacy of therapeutic interventions performed several months to years after remission has been attained, be these interventions bone marrow transplantation\textsuperscript{35-37} or “late intensification” chemotherapy.\textsuperscript{38}

APPENDIX

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REFERENCES

TREATMENT OF ANLL


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