Treatment of Acute Nonlymphocytic Leukemia: Use of Anthracycline-Cytosine Arabinoside Induction Therapy and Comparison of Two Maintenance Regimens

By Harvey D. Preisler, Youcef Rustum, Edward S. Henderson, Sigurdur Bjornsson, Patrick J. Creaven, Donald J. Higby, Arnold Freeman, Salman Gailani, and Carl Naeher

Patients with acute nonlymphocytic leukemia were given remission induction therapy consisting of cytosine arabinoside and an anthracycline. Those patients who experienced complete remission received two courses of consolidation therapy and were randomized to receive maintenance therapy consisting of either daily chemotherapy with reinforcements every 3 mo or reinforcement therapy only every 6 wk. The overall complete remission rate was 66%, with 80% complete remission for previously untreated patients less than 60 yr of age who did not have a prior history of malignancy. Remission durations were the same for patients treated with both maintenance regimens. The major determinant for successful remission induction therapy was patient age, with older patients frequently succumbing to intercurrent infection. Documented leukemic cell resistance to the therapy employed was only rarely encountered. Once remission was achieved, age was no longer a determinant of patient survival, since duration of remission was independent of age. Remission durations were directly related to leukemic cell retention of cytosine arabinoside triphosphate. Hence therapy for acute nonlymphocytic leukemia can be divided into two separate areas: remission induction and remission maintenance.

Progress in the treatment of childhood acute lymphocytic leukemia has been made possible by the development of chemotherapeutic regimens that are highly effective in inducing complete remission. Once a significantly high complete remission rate has been attained, it becomes possible to develop remission maintenance, consolidation, and sanctuary regimens, all of which have led to very long disease-free periods and perhaps even cure in more than half of the affected children. Efficient remission induction regimens have also led to the recognition of subpopulations of patients who relapse early and to alternate approaches to the treatment of these patients.

Progress in the treatment of acute nonlymphocytic leukemia has not been as rapid, although remission rates have climbed and are now between 60% and 70%. The present communication reports our experience with chemotherapy consisting of cytosine arabinoside (ara-C) and an anthracycline (adriamycin [ADR] or daunorubicin [DNR])—a combination regimen capable of inducing complete remission in 80% of patients who are less than 60 yr of age. This rate of remission induction is in the same range as that for childhood acute lymphocytic leukemia. A comparison of intermittent and continuous maintenance chemotherapy has also
been carried out to evaluate differences in remission duration, toxicity, and patient acceptibility of these two regimens.

MATERIALS AND METHODS

All patients less than 70 yr of age admitted to the Medicine A service between July 1975 and June 1977 with acute nonlymphocytic leukemia were entered into this study. The only exclusions were patients who had previously been treated with an anthracycline or whose life expectancy was less than 24 hr. Only complete remissions were considered to be significant responses, and these were defined by the Cancer and Acute Leukemia Group B criteria. The patient characteristics are given in Table 1.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Morphologic subtype, Dx:</th>
<th>Age: range 2½–70 yr, median 43 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>238, 229</td>
<td>Acute myelocytic leukemia 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute promyelocytic leukemia 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute myelomonocytic leukemia 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute erythrocytic leukemia 4</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic Regimens (Fig. 1)

**Remission induction.** All patients (save 8) received ara-C 100 mg/m²/day by 24-hr infusion on days 1–7 (these 8 patients received a 10-day infusion on this drug). Patients were initially randomized to also receive on days 1, 2, and 3 either ADR 30 mg/m²/day or DNR 45 mg/m²/day intravenously. Bone marrow aspiration and biopsy (to judge cellularity) was performed 7 days after the end of therapy. If the marrow was still leukemic (≥25% cellularity with ≥5% myeloblasts), a second course of the same induction therapy was administered. If the marrow was consistent with complete remission, the patient advanced to the consolidation phase. If the patient’s marrow was neither frankly leukemic nor remission marrow, no further therapy was administered. Bone marrow examinations were performed at 3–4-day intervals until it was clear that either there was persistent leukemia or the patient entered complete remission status. Randomization to the DNR arms was discontinued when it became apparent that given the number of patients available to us no distinction between the efficacy of these two anthracyclines could be made. Patients who failed to enter complete remission after two courses of induction therapy were considered to be induction failures.

**Remission consolidation.** On achieving complete remission (marrow cellularity ≥25% with <5% myeloblasts with normal erythropoiesis, myelopoiesis, and megakaryocytopoiesis, peripheral blood granulocytes ≥1000/µl, and platelets ≥100,000/µl), patients received two courses of remission consolidation. Course No. 1: ara-C 100 mg/m² every 12 hr for 10 doses subcutaneously and ADR 40 mg/m²/day intravenously on day 1. After recovery from drug toxicity produced by course No. 1, the patient received a second course of consolidation therapy: ara-C 100 mg/m² every 12 hr for 10 doses subcutaneously, Adriamycin 40 mg/m²/day intravenously on day 1, and 5-azacytidine 120 mg/m²/day as a continuous infusion on days 1–5. On recovery from the toxicity produced by the second course of consolidation therapy, the patients were randomly allocated to one of two different maintenance regimens.

**Maintenance therapy.** Regimen A—(continuous therapy). Therapy was divided into quarter-year cycles. Patients received 6-thioguanine (6TG) 100 mg/m²/day by mouth and methylglyoxalbisguanylyl-hydrazone (MeGAG) 300 mg/m² intramuscularly each week for 8 wk of each 12-wk quarter. Dosages were adjusted to maintain a peripheral white blood cell count greater than 3500/µl and a platelet count greater than 100,000/µl. No chemotherapy was given during the ninth week, and during the tenth week the patients received a 5-day reinforcement course that varied from quarter to quarter. At the end of quarters 1, 3, 5, and 7, patients received ara-C 100 mg/m² q 12 hr for 10 doses subcutaneously and ADR 60 mg/m² intravenously on day 1 of the 5-day ara-C course. At the end of quarters 2, 4, 6, and 8, patients received ara-C 100 mg/m² q 12 hr for 10 doses subcutaneously and 5-azacytidine 120 mg/m²/day as a continuous i.v. infusion for 5 days. After recovery from the 5-day courses of reinforcement therapy, administration of 6-TG and MeGAG was resumed.

Regimen B (intermittent therapy). Patients received only reinforcement therapy every 6 wk. Course No. 1 and every odd course thereafter: ara-C 100 mg/m² q 12 hr for 10 doses subcutaneously, 6-TG 100 mg/m² q 12 hr for 10 doses subcutaneously.
Fig. 1.  (A) Remission induction. (B) Remission maintenance.
mg/m² q 12 hr for 10 doses orally, and MeGAG 300 mg/m² intramuscularly on day 1. Courses No. 2, 6, 10, 14, and 18: ara-C as above, ADR 40 mg/m² intravenously on day 1 of course, and MeGAG as above. Courses No. 4, 8, 12, 16, and 20: ara-C as above, 5-azacytidine 120 mg/m²/day as a continuous infusion for 5 days, and MeGAG as above. Dosage was modified to ensure that the platelet count did not fall below 50,000/µl or granulocyte count below 500/µl.

Additional therapy. All patients received methanol-extracted residue of BCG (MER) 1 mg intradermally in five divided sites prior to remission induction therapy and 1 wk before each course of reinforcement therapy. Following recovery from consolidation therapy, all patients received on days 1, 5, 9, 13, and 17 ara-C 50 mg and methotrexate 4 mg administered intrathecally in 5 ml of Elliott's B solution.

Classification of remission induction failures. Remission induction failures were classified according to a schema proposed previously:

Type I. Absolute drug resistance. No evidence of marrow hypocellularity at any time during or after therapy.

Type 2. Relative drug resistance. Attainment of marrow hypocellularity (<1 + cellularity) during or after a course of therapy with regrowth of leukemic cells within 4 wk of cessation of therapy.

Type 3. Regeneration failure. Disappearance of leukemic cells from the marrow with failure of marrow to completely regenerate so that complete remission is never achieved.

Type 4. Death during period of severe marrow hypoplasia.

Type 5. Inadequate trial of therapy. Patient expires sooner than 7 days after the end of a course of treatment. This period of time was chosen because the maximum effect of chemotherapy is seen 7-10 days after cessation of a 7- or 10-day course of ara-C therapy in combination with 3 days of anthracycline therapy.


All patients who were treated and who failed to enter complete remission were classified as clinical treatment failures. The purpose of using the above classification is to distinguish between the various causes of treatment failure. The leukemic cells of patients who were Type 1, 2, or 6 failures showed evidence of resistance to the chemotherapy employed. Patients who were classified as Type 4 or 5 failures died of intercurrent disease either before their marrow had had time to regenerate (Type 4) or before enough time had passed to evaluate the antileukemic effect of chemotherapy (Type 5). In Type 2 and 4 failures the majority of leukemic cells are sensitive to the therapy employed, since severe marrow hypoplasia resulted from therapy. The majority of the leukemic cells in Type 1 failure appeared to be resistant to the chemotherapeutic agents employed, since there was little evidence of an antileukemic effect.

### Table 2. Complete Remission Induction Rates With ara-C-Anthracycline Therapy. Effects of Age, Previous Treatment, and Prior Malignancy on Response

<table>
<thead>
<tr>
<th></th>
<th>Eligible*</th>
<th>Previous Rx ANLL†</th>
<th>ANLL† + PM‡</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. CR</td>
<td>No. CR</td>
<td>No. CR</td>
<td>No. CR</td>
</tr>
<tr>
<td>&lt;20</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>20–29</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>30–39</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>40–49</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50–59</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60–69</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥70</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>24</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

*Eligible: no prior treatment for AML or previous malignancy.
†ANLL: acute nonlymphocytic leukemia.
‡PM: prior malignancy.

The difference in remission induction rate for eligible patients who were ≤59 yr of age (20/25) and for those who were >59 yr of age (4/11) is statistically significant (p = 0.01).
### Table 3. Response by Treatment. No Malignancy Other Than ANLL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>&lt;1 Course*</th>
<th>1 Course</th>
<th>2 Courses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. CR</td>
<td>No. CR</td>
<td>No. CR</td>
<td>No. CR</td>
</tr>
<tr>
<td>DNR + ara-C (7 days)†</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>ADM + ara-C (7 days)</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>ADM + ara-C (10 days)</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>DNR + ara-C (7 days)‡</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ADM + ara-C (7 days), second</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>0</td>
<td>24</td>
<td>19</td>
</tr>
</tbody>
</table>

*Patients who expired during the first 7 days of therapy.
†(7 days) = 7 days of therapy with ara-C. (10 days) = 10 days of therapy with ara-C.
‡Patient received an initial course of DNR-ara-C and achieved complete hematologic remission. He was judged to be a Type 6 failure because of persistence of leukemic infiltrates in the skin and hepatosplenomegaly. He achieved complete remission after a second course of chemotherapy consisting of ara-C and adriamycin.

### RESULTS

#### Remission Induction

The remission induction results are given in Table 2. For all patients the remission induction rate was 60%, with 68% of patients less than 60 yr of age attaining complete remission, but only 33% of patients who were 60–70 yr of age entering complete remission. For 36 previously untreated patients without a prior history of malignancy there was an overall complete remission rate of 66%, with 80% of the patients less than 60 yr old attaining complete remission status. Three of four previously treated patients attained complete remission, whereas none of 5 patients with a previous history of malignancy achieved remission.

Table 3 gives the remission results according to the remission induction regimen, excluding those patients with a prior malignancy. There are no differences between the efficacies of induction with ara-C (7 days) and DNR (67%), ara-C (7 days) and

![Survival graph](image-url)

**Fig. 2.** Survival of patients who received one or more doses of chemotherapy. Life table plot. Eligible patients are those who were previously untreated without a prior history of malignancy.
Table 4. Causes of Death in Treated Patients

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>9</td>
</tr>
<tr>
<td>Infection and hemorrhage</td>
<td>6</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Fulminant hepatic failure*</td>
<td>1</td>
</tr>
</tbody>
</table>

*Patient expired 1 wk after complete remission was obtained.
Two additional patients failed remission induction therapy and survived.

ADR (65%), and ara-C (10 days) and ADR (71%). Nineteen of 27 complete remissions were attained after a single course of therapy. The median time to remission for patients receiving a single course was 28 days, whereas for those receiving two courses it was 56 days. Figure 2 gives the survival curves for all patients treated with this protocol. The median survival time for all patients was 32 wk, whereas for previously untreated patients without a prior history of malignancy it was 52 wk. The causes of death for patients who failed to achieve complete remissions are given in Table 4. The presence of an abnormal karyotype indicated a decreased likelihood of successful remission induction therapy, with only 6 of 16 such patients achieving complete remission, as compared with 11 of 14 complete remissions in patients whose karyotype was normal (Table 5). The difference in complete remission rate for patients with and without karyotypic abnormality was

\[ p = 0.06 \]

The patients who failed to attain complete remission status were classified according to the schema presented in the Methods section, and the results are shown in Table 6. Considering the ultimate type of remission induction failure (regardless of the number of remission induction courses administered), leukemic cell resistance to therapy was documented in only 3 patients (one case of absolute and two cases of relative drug resistance). Whether or not the leukemic cells of the remaining 15 treatment failures would have been resistant to therapy could not be determined, since 7 of the patients died during a period of severe marrow hypoplasia (and could have been Type 2 failures or entered remission had they survived long enough) and 8 patients died during or immediately after therapy, so that the effect of the therapy on the leukemic cells could not be determined.

Duration of Remissions

Five of the 27 patients who attained complete remission failed to be randomized to the maintenance arms. One patient had systemic candidiasis and thus did not receive consolidation or maintenance therapy and relapsed at 30 wk. One patient expired as a result of viral hepatitis after attaining complete remission. Three patients relapsed during the consolidation phase at 1, 11, and 11 wk after attaining complete remission. In one patient the site of initial relapse was in the central

Table 5. Effect of Pretreatment Karyotype on Response

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>No. of Patients</th>
<th>No. CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Abnormal*</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>27</td>
</tr>
</tbody>
</table>

*Some or all metaphases.
Table 6. Causes of Remission Induction Failure After One and Two Courses of Chemotherapy

<table>
<thead>
<tr>
<th>Course 1</th>
<th>Course 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>14</td>
</tr>
<tr>
<td>Absolute drug resistance</td>
<td>8</td>
</tr>
<tr>
<td>Relative drug resistance</td>
<td>4</td>
</tr>
<tr>
<td>Extramedullary persistence of leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Expired</td>
<td>12</td>
</tr>
<tr>
<td>Relative drug resistance</td>
<td>1</td>
</tr>
<tr>
<td>Died during marrow hypoplasia</td>
<td>4</td>
</tr>
<tr>
<td>Died during therapy</td>
<td>7</td>
</tr>
</tbody>
</table>

Criteria for classification are given in Methods section.

Fig. 3. Duration of complete remission. Life table analysis. Prime indicates patients still in remission. (a) All patients whether or not they received maintenance therapy. (b) Previously untreated patients who received either continuous intermittent (B) maintenance therapy.
nervous system, and one additional patient developed meningeal leukemia subse-
quent to marrow relapse.

Ten patients were randomized to the continuous maintenance regimen and 12
patients to the intermittent regimen. Three patients on the continuous arm remain
in complete remission at 58+, 112+, and 129+ wk, with a median duration of remis-

sion for the entire group of 54 wk. Seven patients on the intermittent arm
remain in complete remission at 37+ to 72+ wk. The median for this patient group
has not yet been reached. A life table plot of remission duration for all patients is
given in Fig. 3a. Figure 3b compares the remission durations of the two mainte-
nance regimens. At the present time there is no apparent difference between the
two different maintenance regimens. Comparison of remission duration according
to whether DNR or ADR was administered during remission induction failed to
reveal a difference nor was there a difference in remission duration between those
patients who required one or two remission induction courses.

DISCUSSION

The treatment of nonlymphocytic leukemia now appears to be resolvable into two
separate areas: remission induction and remission maintenance. The remission
induction regimens reported in this paper produced an overall complete remission
rate of 66% in previously untreated patients. For previously untreated patients
under 60 yr of age without a prior history of malignancy, the remission rate was
80%. These regimens were clearly less effective in two groups of patients: those who
were over 60 yr of age and those with a prior history of malignancy. Analysis of the
remission induction failures for the group of previously untreated patients who did
not have a history of prior malignancy shows that failure was the result of
demonstrable leukemic cell resistance to the therapy employed in only 2 of the 12
failures (one case of absolute and one case of relative drug resistance). Failure in
the remaining 10 patients resulted from the fact that the patients did not survive
long enough either for marrow to regenerate after therapy or for the full effect of
the therapy on the leukemic cells to be manifested. Patients with a prior history of
malignancy fared very poorly, with no complete remission among the
S


This problem has been extensively discussed elsewhere.11

Of particular interest is our observation that the leukemic cells of 6 of the 8
patients who required two courses of induction therapy to attain complete remission
would have been classified as being absolutely resistant to the chemotherapy
employed had they expired before or during the second course of remission
induction therapy. Furthermore, the duration of remission for patients requiring
two courses of therapy to attain remission was identical to that of patients who
attained remission after a single course of therapy (and whose cells, therefore,
seemed to be more sensitive to the drugs employed). Hence, failure to enter
remission after a single course of therapy is not necessarily indicative of a poor
prognosis, providing, of course, that the patient does not expire prior to a second
course of therapy. Taken together, these observations suggest that, with the
currently employed regimens, better remission induction rates and survivals will be
obtained when death due to intercurrent diseases (largely infection) is prevented so
that one or more full courses of chemotherapy can be administered and the normal
marrow can be given an adequate chance to regenerate.
The median duration of remission for the entire group of previously untreated patients was comparable to that obtained by other investigators. To the present time the remission durations of patients on the continuous and intermittent maintenance arms are indistinguishable. Patients preferred the continuous arm, since on this regimen they were made ill by the side effects of drugs every 12 wk, whereas patients on the intermittent arm experienced side effects twice as frequently (every 6 wk). The duration of complete remission was unrelated to the number of courses required to achieve remission, to the age of the patients, or to the anthracycline used to induce remission.

Remission duration appeared to be greatest for patients who received a 10-day course of ara-C during remission induction. Although the number of patients involved is small, the prolonged remission among this group of patients is reminiscent of the report of Burke et al., several of whose patients experience prolonged unmaintained remissions after receiving remission induction therapy also covering 10 days (days 1, 2, 3, 8, 9, and 10); these investigators ascribed the prolonged remission to the recruitment of leukemic cells into cycle by chemotherapy administered on days 1–3, followed by the destruction of these recruited cells by the therapy administered on days 8–10. Perhaps the administration of a 10-day course of ara-C (which by definition covered days 1–3 and 8–10) had effects similar to those postulated by Burke et al.

The problem of maintenance of remission appears to be separable from that of remission induction. For example, the single greatest risk factor with respect to remission induction is advanced age, an observation confirmed in the present study. However, once remission is obtained, the duration of remission in the older patients is indistinguishable from that in younger patients. In studies reported elsewhere by Rustum and Preisler, we have demonstrated a clear-cut association between the 4-hr retention of cytosine arabinoside triphosphate (ara-CTP) by leukemic cells in vitro and the duration of remission. The subjects of these studies were 28 of the patients reported in the present article. The median duration of remission for this group of patients was 57 wk. The median duration of remission for patients whose leukemic cells' 4-hr ara-CTP retention was less than 30% was 28 wk, whereas that for patients whose leukemic cells retained more than 30% is projected to 110 wk, with 7 of 11 patients still in complete remission between 55+ and 129+ wk. Hence, the high relapse rate in the first 40 wk that is apparent in Fig. 3a appears to be due primarily to relapse of patients whose leukemic cell retention of ara-C was low. This measurable parameter is independent of a patient's age. Patients with poor ara-CTP retention appear to be similar to patients with T-cell acute lymphocytic leukemia in that their remission rate is good (9 of 15 patients at risk attained complete remission) but their remission duration is short.

The studies presented here report reasonably effective remission induction and maintenance regimens. Of greater importance, however, is the recognition that at the present time the treatment of acute nonlymphocytic leukemia presents two distinct problems, each requiring a different approach. With respect to remission induction, barring the appearance of less toxic drugs or treatment regimens, in order to improve remission induction rates, better means must be found to prevent or treat infection, so that a higher proportion of patients will survive remission induction therapy. This is particularly true for older patients and patients with a
previous history of malignancy. The factors that determine the duration of remission are different from those that determine whether or not a patient achieves remission. Since a maintenance regimen that emphasizes ara-C (as do most reported in the literature) appears to be inadequate for patients whose leukemic cells retain ara-CTP poorly, perhaps maintenance regimens that do not employ ara-C should be tested in this group of patients.

ACKNOWLEDGMENT

The authors wish to express their gratitude to the fellows, nursing staff, and secretarial and technical staff of Medicine A. without whose assistance this study could not have been carried out. The authors would also like to thank Dr. A. A. Sandberg for performing the karyotypic analysis.

REFERENCES

Treatment of acute nonlymphocytic leukemia: use of anthracycline-cytosine arabinoside induction therapy and comparison of two maintenance regimens

HD Preisler, Y Rustum, ES Henderson, S Bjornsson, PJ Creaven, DJ Higby, A Freeman, S Gailani and C Naehler