Chemotherapy for Acute Myelogenous Leukemia in Children and Adults: VAPA Update

By Howard J. Weinstein, Robert J. Mayer, David S. Rosenthal, Felice S. Coral, Bruce M. Camitta, and Richard D. Gelber

We designed a protocol (VAPA) that featured 14 mo of intensive postremission induction chemotherapy in an effort to improve remission durations for patients with acute myelogenous leukemia (AML). One hundred and seven patients under 50 yr of age were entered into this study. The rate of complete remission is 70%. A Kaplan-Meier analysis of patients entering remission predicts that 56% ± 7% (± SE) of patients less than 18 yr and 45% ± 9% of patients aged 18–50 yr will remain in remission at 3 yr

MAJOR PROGRESS in the treatment of acute myelogenous leukemia (AML) has occurred during the past decade. Advances in chemotherapy and supportive care have been associated with an increase in the complete remission rate for AML patients under age 60 from 35% to 55% to approximately 75%. The median duration of complete remission and the percentage of patients in long-term continuous complete remission has steadily improved. This has resulted from postinduction combination chemotherapy or chemoradiotherapy and transplantation of marrow from histocompatible siblings. In 1976, we initiated an AML protocol with the acronym VAPA, which was designed to circumvent two central obstacles to cure: (1) inadequate leukemia cytoreduction, and (2) the emergence of drug-resistant leukemia cells. We previously reported encouraging results obtained with this approach. With 2.5 yr of additional follow-up, and a total of 107 patients entered on study, new information indicates that: (1) the VAPA protocol continues to offer a promising approach to treatment of AML, (2) there is a poorer duration of remission for patients with the monocytic subtype (M5), and (3) there is a high incidence of meningeal leukemia in patients less than 18 yr of age.

MATERIALS AND METHODS

Patients

One hundred and seven consecutive, previously untreated patients less than 50 yr of age were evaluated and entered into this study between February 1976 and May 1980. The diagnosis of AML was based on morphological examination of bone marrow and a study of histochemical stains.

Treatment

Remission was induced with two courses of vincristine, doxorubicin, prednisolone, and cytosine arabinoside (ara-C). Patients achieving complete remission were treated with intensive sequential combination chemotherapy for 14 mo (Table 1). The first and last sequences were designated as early and late intensification. Central nervous system prophylaxis was not included, but surveillance lumbar punctures were performed throughout remission. Details of the treatment protocol have previously been published.

Statistical Analysis

The duration of survival was measured from the time of initial therapy, while the duration of remission extended from the time bone marrow remission was confirmed. Kaplan-Meier analyses were performed for survival and continuous complete remission (CCR) estimates. Statistical tests of significance were made with the log-rank test or the Cox model when appropriate. Remission deaths were counted as relapses and withdrawals were considered until the time they were electively removed from the protocol.

RESULTS

Induction of Remission

The results of remission induction therapy are presented in Table 2. Rates of complete remission were similar for children and adults and did not differ significantly according to morphological subtype of AML (see Table 3).

Duration of Remission

Among the 75 complete responders, there have been 8 withdrawals for reasons including nonhematopoietic drug toxicity, bone marrow transplantation, and physician–patient desire to discontinue therapy. Two of five
### Table 1. Intensive Sequential Maintenance Schema

<table>
<thead>
<tr>
<th>Sequence I</th>
<th>Sequence II</th>
<th>Sequence III</th>
<th>Sequence IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin, 45 mg/sq m/day, day 1, intravenous</td>
<td>Adriamycin, 30 mg/sq m/day, day 1, intravenous</td>
<td>Vincristine 1.5 mg/sq m/day, day 1, intravenous</td>
<td>Cytosine arabinoside, 200 mg/sq m/day, days 1–5, continuous infusion</td>
</tr>
<tr>
<td>Cytosine arabinoside, 200 mg/sq m/day, days 1–5, continuous infusion</td>
<td>Azacytidine 150 mg/sq m/day, days 1–5, continuous intravenous infusion</td>
<td>Methylprednisolone, 800 mg/sq m/day, days 1–5, intravenous</td>
<td>6-Mercaptopurine, 500 mg/sq m/day, days 1–5, intravenous</td>
</tr>
<tr>
<td>Methotrexate, 7.5 mg/sq m/day, days 1–5, intravenous</td>
<td>Given 4 times at 3–4 wk intervals</td>
<td>Given 4 times at 3-wk intervals</td>
<td>Given 4 times at 3–4 wk intervals</td>
</tr>
</tbody>
</table>

Given 4 times at 3–4 wk intervals

Given 4 times at 4-wk intervals

Given 4 times at 3-wk intervals

Given 4 times at 3–4 wk intervals

children who were withdrawn are known to be in CCR at last report; conclusions are unchanged if withdrawals are included to latest follow-up. There have been two deaths during remission, and a total of 34 patients have relapsed (Table 2).

The median follow-up for patients in CCR is 43 mo (range 32–80 mo) from the day on which complete remission was achieved. Figure 1 shows Kaplan-Meier plots of the probability of remaining in CCR for the pediatric and adult patients. For patients less than age 18, the 3-yr actuarial CCR probability (± SE) is 56% (± 7%), with only one relapse observed between 36 mo and 80 mo in remission. For patients age 18–50, 3-yr actuarial CCR probability (± SE) is 45% (±9%), but this probability decreases to 27% at 5 yr. The curves in Fig. 1 are not statistically significantly different (p = 0.39). The late fall in the adult curve is a reflection of two bone marrow relapses at 51 and 55 mo. The morphology of the late marrow relapses indicates probable recurrence of the original leukemia.

No patient who had a bone marrow relapse on therapy reentered remission, whereas 4 of 9 patients who had bone marrow relapses off therapy achieved a second remission.

*Elective Cessation of Treatment*

Twenty-six patients less than 18 yr of age have completed therapy and only 5 of these 26 patients have relapsed. Fifteen adults have completed treatment and 5 have relapsed.

*Overall Survival*

Figure 2 shows Kaplan-Meier plots of the probability of survival for all patients. The 5-yr survival probability estimates are 44% for patients less than 18 yr old and 25% for the older patients.

*Prognostic Factors*

Factors that may have influenced the duration of remission were analyzed using the log rank test. These factors included white blood count at the time of diagnosis, age, sex, morphological subtype of AML, and the number of courses of therapy required to induce a complete remission. Morphological subtype was the only presenting feature that correlated significantly with remission duration. Patients with monocytic leukemia had shorter lengths of complete remission (2-sided p < 0.05) (Fig. 3). Six of 9 patients in our study with monocytic leukemia who achieved CR were less than 2 yr of age (Table 3).

Within the pediatric group, children <2 yr compared to those between 2 and 17 yr had a statistically significant shorter remission duration. However, when we controlled for morphological subtype in a Cox

### Table 2. VAPA Update as of January 1, 1983

<table>
<thead>
<tr>
<th>Age</th>
<th>No. entered</th>
<th>No. complete remissions</th>
<th>Withdrawals</th>
<th>Deaths in remission</th>
<th>Total relapses</th>
<th>CNS</th>
<th>Bone marrow</th>
<th>Myeloblastoma</th>
<th>Completed therapy</th>
<th>Relapses off therapy</th>
</tr>
</thead>
</table>
proportional hazard regression model, the influence of age was no longer statistically significant.

Central Nervous System Relapse

Eight of 19 pediatric relapses occurred in the central nervous system (CNS). In contrast, only 1 of the 15 relapses in the adult group occurred in the CNS (Table 2). Seven of the 8 children with primary CNS relapse were asymptomatic. All 8 children had bone marrow relapses 2 wk to 5 mo after CNS relapse. The monocytic subtype was associated with a high risk for primary CNS relapse (p = 0.07).

Toxicity

Toxic manifestations during the intensive sequential chemotherapy phase were limited primarily to nausea, vomiting, and fever (or infection) associated with granulocytopenia. Hospitalization time during this phase of therapy was either for administration of chemotherapy or antibiotics and averaged 80 days. After 1978, patients received continuous subcutaneous infusions of ara-C outside the hospital by means of a portable infusion pump (Auto-Syringe, Hooksett, NH) instead of continuous intravenous infusions in the hospital, thereby reducing the number of hospital days for administration of chemotherapy. Three of 75 patients followed in remission developed adriamycin cardiomyopathy, with one fatality.

Hematologic toxicity was most pronounced during sequence I of the intensive sequential maintenance therapy. All patients had nadirs of 0–100 polymorphonuclear neutrophil leukocytes (PMNs)/cu mm (<200 PMNs/cu mm for 4–10 days) and less than 20,000 platelets/cu mm after each course of sequence I. During the granulocyte nadir of these early intensification courses, there was a 40% likelihood of a patient developing a fever and a 15% documented infection rate (one fatal infection). Sequence I courses were repeated every 21–30 days. There was no dose modification for previous myelosuppression.

After the adriamycin and azacytidine courses (sequence II), there was often a long interval before the granulocyte and platelet nadirs and slow hematopoietic recovery. The depth of pancytopenia was moderate when compared to sequence I. Hospital admissions occurred after 5% of these courses. The interval between courses averaged 4–5 wk (range 3–8 wk). Sequence III and IV courses were well tolerated, with very few hospital admissions for fever and granulocytopenia.

<p>| Table 3. Results of Therapy Compared With AML Subtype |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>AML Subtype</th>
<th>No. Entered</th>
<th>No. in CR (%)</th>
<th>No. of Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML (M1, M2)</td>
<td>54</td>
<td>37 (69)</td>
<td>16</td>
</tr>
<tr>
<td>APL (M3)</td>
<td>16</td>
<td>9 (56)</td>
<td>3</td>
</tr>
<tr>
<td>AMML (M4)</td>
<td>27</td>
<td>20 (74)</td>
<td>10</td>
</tr>
<tr>
<td>AMOL (M5)</td>
<td>10</td>
<td>9* (90)</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>75 (70)</td>
<td>36†</td>
</tr>
</tbody>
</table>

* Six patients <2 yr of age.
† Includes 2 remission deaths.

DISCUSSION

Seventy percent of patients with AML in this study entered complete remission. This result is consistent with the experience of others who have employed a combination of cytosine arabinoside and an anthracycline with or without vincristine and prednisolone. In an effort to improve duration of remission, the VAPA protocol included 14 mo of intensive sequential postremission induction chemotherapy. The program included early and late intensification with ara-C designed to exploit the steep dose–response curve and maximize leukemic cytoreduction. The early intensification was followed by sequential treatment with non-crossresistant combinations designed to prevent the emergence of drug-resistant lines.

Our overall data are very encouraging. In the pediatric age group, the probability of CCR is 56% at 3 yr. There was only one relapse observed between 2 and 6

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**Fig. 2.** Kaplan-Meier plots of probability of survival for pediatric and adult age groups (107 patients). Tick marks indicate patients still being followed.

**Fig. 3.** Kaplan-Meier plots of probability of CCR for morphological subtypes of acute myelogenous leukemia. Tick marks indicate patients continuing in remission. AML, myelocytic; AMML, myelomonocytic; AMOL, monocytic; APL, promyelocytic.
yr in remission. These results are much better than those reported in other chemotherapy trials for childhood AML.6,19,30

For adults between 18 and 50 yr of age, the median duration of remission is 27 mo, and the 3-yr CCR probability is 45%. These results are substantially better than previously achieved with most other chemotherapy protocols.9,21,22 Preliminary results of other more recent intensification chemotherapy programs for adults with AML at other centers are also encouraging.23,24

There have been no consistently identified features that have predicted for duration of remission in previously reported trials of therapy for AML.2,25 This is not surprising, as there have been so few long-term survivors. In this treatment program, sufficient numbers of survivors allow such an analysis, and we find that morphological classification predicts for duration of remission. Patients with monocytic leukemia (FAB subtype M5) had a statistically significant shorter duration of remission. As noted previously, the majority of patients with monocytic leukemia were under 2 yr of age.

Although the CCR curves for the adults versus the children appear to be different, the differences occur largely in the tails of the distributions and are not statistically significant. It is not possible from these data to conclude whether there are biologic differences between AML in children and adults less than age 50.

The central nervous system was the initial site of leukemic relapse in 8 of 19 children. In contrast only one adult experienced a CNS failure among 15 adult relapses. Primary CNS relapse has been reported to account for 10%-15% of the relapses in both children and adults with AML.20,26 Our protocol did not include CNS prophylaxis, but cytosine arabinoside penetrates into the CSF when administered by continuous intravenous or subcutaneous infusion.27 The high incidence of primary CNS relapse in children, however, indicated that continuous ara-C infusions at a dose of 200 mg/sq m/day did not provide effective CNS prophylaxis. The higher CNS relapse rate observed in children was, in part, related to the greater incidence of the monocytic subtype in this age group. Other investigators have also observed a correlation between the monocytic subtype and CNS relapse.28 In the modification of the VAPA program currently in use, patients less than 18 yr of age receive intrathecal chemotherapy with ara-C for CNS prophylaxis.

The only other therapy that appears to maintain long durations of remission for patients with AML is chemoradiotherapy followed by allogeneic bone marrow transplantation performed early in first remission. This approach is currently limited to patients with a histocompatible sibling. Results of current transplant studies project 55%-70% leukemia-free survival at 2-5 yr for patients with AML transplanted in first remission.12-15 A direct comparison between marrow transplantation and the VAPA program is difficult because of bias in the selection of patients for transplantation. In particular, children less than 2 yr of age were a poor-risk group in our AML study, but have not been included in most of the reported transplant studies.

The VAPA experience indicates that many patients with AML, especially children, may hopefully be cured by aggressive chemotherapy. The data also indicate that it is possible to discontinue intensive therapy in patients with AML after a finite period (15 mo in our study) and to demonstrate that the majority (31 of 41 patients) may remain in prolonged remission without maintenance therapy. In our study, primary CNS relapse in children and bone marrow relapse before completion of treatment were obstacles to long-term remission. Future studies, therefore, should focus on early intensification therapy, improved methods for delivery of noncrossresistant combinations of drugs, and a more effective approach to CNS leukemia in children.

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