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The Treatment of Acute Myelogenous Leukemia in Children and Adults: VAPA Update*

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A. Introduction

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 of patients under the age of 60 with AML from 35%–55% [5, 7] to approximately 75% [2, 9, 16]. More importantly, 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 [10, 13, 18, 20] or chemoradiotherapy and transplantation of marrow from histocompatible siblings [4, 15, 21]. In 1976 the VAPA protocol was initiated to specifically improve the duration of complete remission for children and adults (< 50 years) with AML. In 1980 we reported encouraging results obtained with this approach [12, 22], and this report is an update of the study.

B. Materials and Methods

I. Patients

One hundred and seven consecutive, previously untreated patients less than 50 years of age were evaluated and entered onto this study between February 1976 and October 1979. The diagnosis of AML was based on morphologic examination of bone marrow and a study of histochemical stains.

II. Treatment

Remission was induced with two courses of vincristine, adriamycin, prednisolone, and cytosine asrabinoside (araC). Patients achieving complete remission were treated with intensive sequential combination chemotherapy for 14 months. This phase of therapy was divided into four sequences of drug combinations: adriamycin/araC, adriamycin/azacytidine, prednisolone/vincristine/mercaptopurine/methotrexate, and araC. Central nervous system prophylaxis was not included but surveillance lumbar punctures were performed throughout remission. Details of the treatment protocol have previously been published [22].

III. 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. Statistical tests on this distribution were made with the log-rank test [14]. Deaths during remission were treated as relapses and withdrawals were considered up until the time they were electively removed from the protocol.

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C. Results

I. Induction of Remission

The results of remission induction therapy are presented in Table 1. Rates of complete remission were similar for children and adults and did not differ significantly according to morphologic subtype of AML (data not shown).

II. Duration of Remission

Among the 75 complete responders there have been eight withdrawals for reasons including nonhematopoietic drug toxicity, bone marrow transplantation, and physician-patient desire to discontinue therapy. There have been two deaths during remission in the adult group. A total of 34 patients have relapsed. Eight of 19 pediatric relapses have occurred in the central nervous system (CNS). In contrast, only one of the relapses in the adult group occurred in the CNS (Table 1).

Figure 1 is a Kaplan-Meier plot of the probability of remaining in continuous complete remission (CCR). The median follow-up period for patients less than age 18 is 41 months and 52% remain in CCR at 38 months. For patients age 18–50 the median follow-up period is 33 months, and there is a 42% probability of CCR at 36 months but this decreases to 14% at 51 months. This late fall in the adult curve is a reflection of the small number of adults at risk beyond 3 years and two late relapses.

Table 1. VAPA update as of 1 April 1982

	Age 0 – 17	Age 18 – 50
No. entered	61	46
No. of complete remissions	45 (74%)	30 (65%)
Withdrawals	5	3
Deaths in remission	0	2
Total relapses	19	15
CNS	8	1
Bone marrow	10	13
Myeloblastoma	1	1
Completed therapy	26	15
Relapses of therapy	5	5

III. Cessation of Treatment

Twenty-six patients less than 18 years of age have completed therapy and only 5 of these 26 patients have relapsed (median follow-up time after cessation is 21+ months). Fifteen adults have completed treatment and five have relapsed (median follow-up after cessation is 18+ months).

IV. Overall Survival

Figure 2 is a Kaplan-Meier plot of the probability of survival for all patients: the median survival remains undefined for patients less than 18 years of age and the median survival for patients 18–50 years of age is 16.5 months.

V. 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, morphologic subtype of AML, and the number of courses of therapy required to induce a complete remission. The monocytic subtype was the only presenting feature that correlated significantly with remission duration. Patients less than 18 years of age with monocytic leukemia had shorter lengths of complete remission ($P = 0.007$).

VI. Central Nervous System Relapse

Seven of the eight children with primary CNS relapse were asymptomatic. All eight children had bone marrow relapses 2 weeks to 5 months after CNS relapse. The monocytic subtype was associated with a high risk for primary CNS relapse ($P = 0.07$).

VII. Toxicity

Toxic manifestations during the intensive sequential chemotherapy phase were limited primarily to nausea, vomiting, and fe-

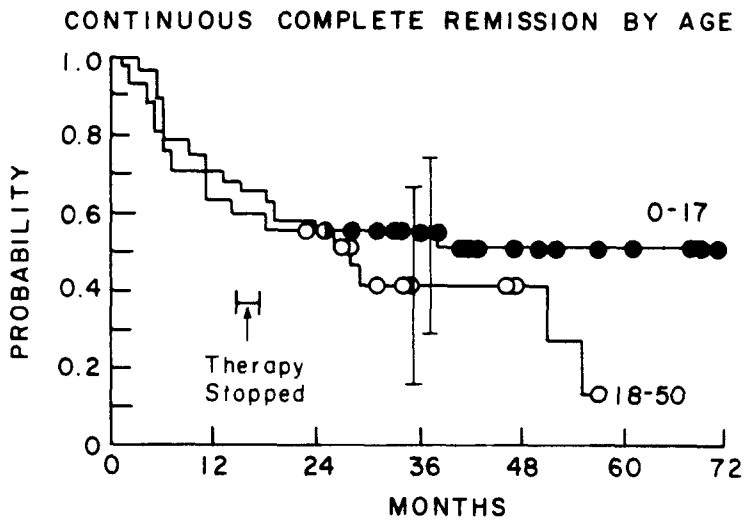

Fig. 1. Kaplan-Meier plot of probability of CCR. The *vertical bars* represent two standard deviation confidence limits

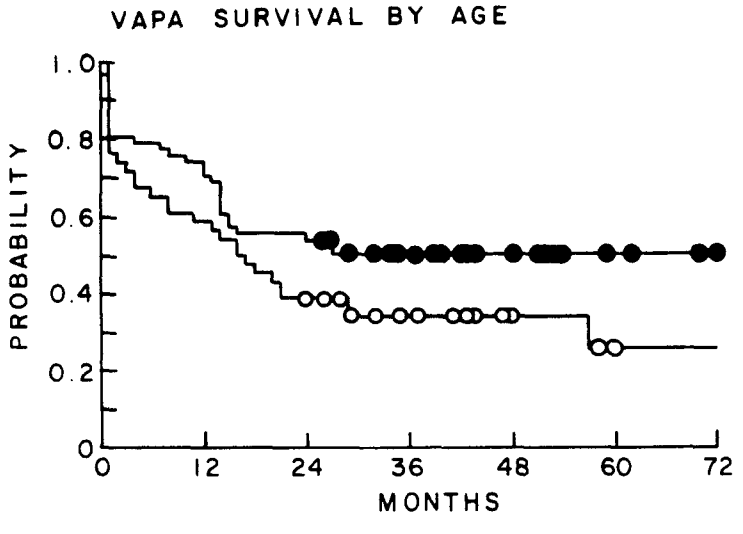

Fig. 2. Kaplan-Meier plot of probability of survival for all patients ($n = 107$)

AGE	ALIVE	DEAD	TOTAL	MEDIAN
● 0-17 YRS	31	30	61	UNDEF
○ 18-50 YRS	15	31	46	16.5

ver (or infection) associated with granulocytopenia. The average hospital time during this phase of therapy was approximately 60 days. After 1978, patients received continuous subcutaneous infusions of araC outside the hospital by means of a portable infusion pump (autosyringe) instead of continuous intravenous infusion as inpatients. Three of 75 patients followed in remission developed adriamycin cardiomyopathy, with one fatality in this group. There was one death during remission secondary to pneumonia during a period of granulocytopenia. There was a 5% incidence of reversible cholestatic liver disease observed during the maintenance phase.

D. Discussion

In this study, 70% of patients with AML 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. The goal of our study was to improve durations of complete remission by specifically addressing the problem of relapse. The VAPA protocol included 14 months of intensive sequential chemotherapy after remission was achieved. The programm was designed to maximize leukemic cytoreduction and to circumvent the problem of

the development of drug resistance by leukemia cells [19].

The overall data appear very encouraging. In the pediatric group, the probability of CCR is 56% at 2 years, and only one relapse has been observed beyond this time. Twenty-six of 45 children who entered complete remission had therapy electively stopped at 14 months in CCR and 21 of these patients remain in remission. These results are significantly better from those reported in other chemotherapy trials for childhood AML [2, 6, 8].

For adults between 18 and 50 years of age, the median duration of remission was 28 months, which is substantially longer than previously achieved with most other chemotherapy protocols [1, 11]. There have been, however, two late relapses (after 3 years of CCR) in the adult group. Due to the small number of patients at risk beyond 3 years, one cannot predict with certainty the percentage of adults who will remain in long-term remission. Preliminary results of other intensive chemotherapy programms for adults with AML support our treatment approach [3, 17].

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 amongst 15 adult relapses. Primary CNS relapse has been reported to account for 10%–15% of the relapses in both children and adults with AML [8, 24]. The VAPA protocol did not incude CNS prophylaxis, but cytosine arabinoside penetrates into the CSF when administered by continuous intravenous or subcutaneous infusion [23]. The high incidence of primary CNS relapse in children indicated that continuous araC infusions at a dose of 200 mg/m^2 per day were not effective for CNS prophylaxis. There were many more children than adults with monocytic leukemia in our study and this may have contributed to the higher CNS relapse rate observed in the younger group. In our new AML study patients less than 18 years of age receive intrathecal chemotherapy for CNS prophylaxis.

The VAPA experience indicates that AML, especially in children, can be controlled and hopefully cured by chemotherapy alone in many patients. 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 the first remission. This approach is currently limited to patients with a histocompatible sibling. With continued advances in supportive care, chemotherapy, and bone marrow transplantation, long-term control of AML in the majority of cases is a reasonable goal in the near future.

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