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VAPA[10]: A Treatment Program for Acute Myelocytic Leukemia*

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A. Introduction

During the past decade, the combination of an anthracycline and continuous infusion cytosine arabinoside chemotherapy has been associated with an increase in the complete response rate of patients under age 60 having acute myelocytic leukemia (AML) from 35%–55% (Carey et al. 1975; Clarkson et al. 1975) to approximately 75% (Evans et al. 1975; Gale 1979; Haghbin et al. 1977; Preisler et al. 1979; Rees and Hayhoe 1978; Yates et al. 1973). This encouraging advance, however, has not led to prolonged periods of remission and indefinite survival as seen in childhood acute lymphocytic leukemia. The median duration of complete remission in most recent studies in AML is in the range of 12–14 months (Armitage and Burns 1976; Evans et al. 1975; Haghbin et al. 1977; Moreno et al. 1977; Peterson and Bloomfield 1977; Preisler et al. 1979; Rees and Hayhoe 1978; Spiers et al. 1977). In early 1976 a therapeutic program (VAPA[10] protocol) was initiated in an attempt to overcome the causes of relapse in patients with AML. It was postulated that the high failure rate in AML patients in complete remission might be the result of inadequate cytoreduction during the maintenance period, the development of drug resistance, the presence of "sanctuaries" into which effective chemotherapy could not penetrate, and the presence of a mutant myeloid progenitor cell which over a period of time would progressively replace or even suppress the growth of the differentiated product of normal hematopoiesis. It was appreciated that if the latter possibility were true, it would be unlikely that intensive chemotherapy would have any long-term beneficial effect in patients with AML and that the only rational therapeutic option would be replacement of these progenitor cells through a maneuver such as bone marrow transplantion. Others are presently testing the utility of marrow transplantation in patients with AML shortly after complete remission is obtained (Blume et al. 1980; Powles et al. 1980; Thomas et al. 1979).

This report reviews the status of the VAPA[10] protocol at the time of an 1 April 1980 analysis. The protocol, designed with curative intent, has resulted in a complete remission rate of 70%. Among the complete responders, it is projected that 71%±13% of the patients will be alive 24 months after diagnosis was made and 49%±17% will continue disease free 24 months after their initial complete remission was documented.

B. Materials and Methods

I. Patients

One hundred and six consecutive previously untreated patients less than 50 years of age with AML were evaluated and entered onto this study between February 1976 and 1 April 1980. The diagnosis of AML was based on examination of bone marrow aspirate morphology and histochemical stains. When such a diagnosis was confirmed, patients were entered onto the program and all patients receiving any amount of protocol drug therapy, regardless of their clinical condition, were considered evaluable for analysis.

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II. Treatment Program

Chemotherapy consisted of two phases: a remission induction phase followed by an intensive sequential combination chemotherapy phase. The remission induction program (Fig. 1) was similar to the treatment plan of others, administering 3 days of an anthracycline (adriamycin) and 7 days of continuous infusion cytosine arabinoside with the addition of vincristine and prednisolone. Marrow status was assessed on the 14th day of the treatment program with another 5 days of therapy instituted at that time if the bone marrow was hypercellular or if leukemic blasts were still readily identifiable. Patients were removed from study and considered induction therapy failures if they did not achieve complete remission following these two courses of therapy.

Patients who achieved complete remission were treated with intensive sequential combination chemotherapy during a 14-month "maintenance" period (Fig. 2). This period of treatment was subdivided into four sequences of drug combinations. Sequence I, designated as "early intensification", consisted of 5-day courses of adriamycin and cytosine arabinoside given every 3–4 weeks for four courses. Treatment was resumed after each course when the circulating granulocyte count had reached 500/mm^3 and the platelet count was greater than 100,000/mm^3. Sequence II consisted of adriamycin and azacytidine given as 5-day courses every 4 weeks for four courses. This was followed by Sequence III, which included 6-mercaptopurine, vincristine, methotrexate, and methyl prednisolone (POMP) given in 5-day courses every 3 weeks on four occasions. Sequence IV was designated as "late intensification" and consisted of 5-day courses of cytosine arabinoside given every 3–4 weeks on four occasions. Treatment was discontinued after the completion of Sequence IV, approximately 15 months after the onset of "maintenance" therapy.

Central nervous system prophylaxis was not included per se in the protocol design. Intensification courses with continuous infusions of cytosine arabinoside were given in part to provide therapeutic concentrations of cytosine arabinoside in the central nervous system, thereby potentially eradicating microscopic disease at that site.

III. Criteria for Response

Patients were considered to be in complete remission if they were asymptomatic, had no physical findings suggestive of leukemia, and had normal bone marrow examinations and normal peripheral counts. Relapse was defined as the presence of 5% marrow blasts or the documentation of any extramedullary sites of leukemia. Bone marrow aspirations were performed every 8 weeks during the intensive sequential phase and every 3 months for the 1st year after the discontinuation of chemotherapy. Surveillance lumbar punctures were performed initially at the time complete bone marrow remission was documented and subsequently every 2–3 months during the intensive therapy phase.

IV. Statistical Analysis

The duration of survival was measured from the time of diagnosis, while the duration of remission extended from the date complete bone marrow remission was confirmed. Kaplan-Meier analyses of survival and continuous complete remission intervals were plotted on a semilogarithmic scale so as to compare the failure rates during successive monthly intervals. Deaths during remission were treated as failures, while withdrawals were considered evaluable up until the time they were electively removed from the protocol.

C. Results

One hundred and six patients were entered onto this study over a 4-year period. At the time of an 1 April 1980 review (Table 1), 105

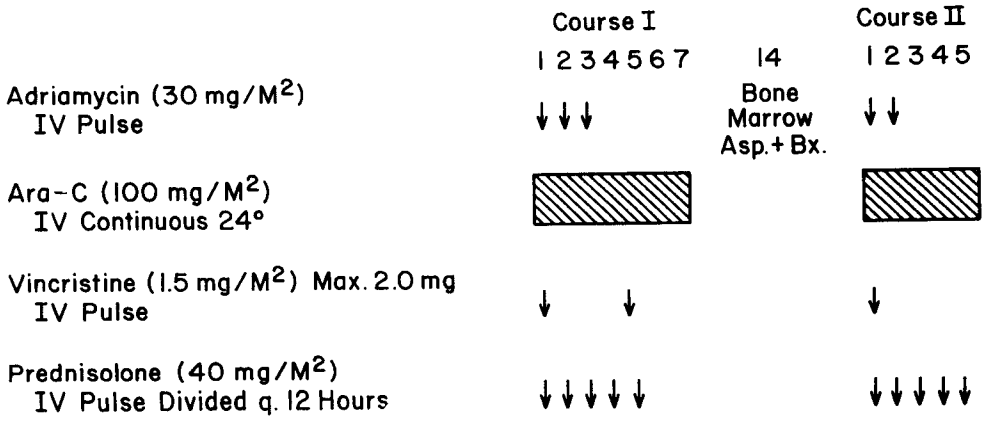


Fig. 1. VAPA[10]: remission-induction schema

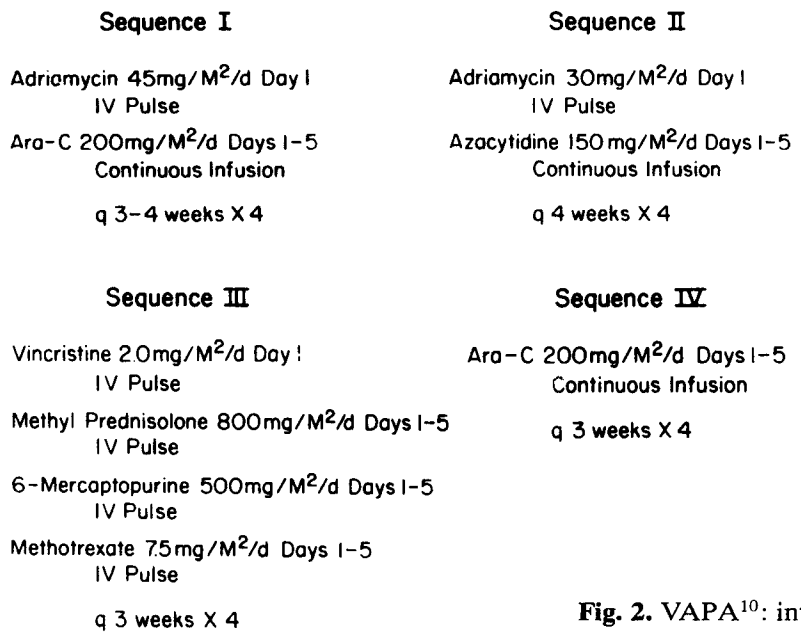


Fig. 2. VAPA[10]: intensive sequential maintenance schema

were evaluable for analysis, with 61 being 17 years of age or younger and 44 being between ages 18–50. The median age for the entire group of 105 evaluable patients was 14.5 years. This unusual age distribution for AML patients reflects the referral patterns of the Longwood Avenue area hospitals and the fact that most pediatricians throughout New England send their children with this disease to a tertiary care facility such as the Sidney Farber Cancer Institute-Children's Hospital Medical Center. Complete remissions have been achieved in 74/105 (70%) of evaluable patients with younger patients having a slightly increased chance of achieving a complete remission (74%) than their older counterparts (66%). These data are similar to the reports of others (Evans et al. 1975; Gale 1979; Haghbin et al. 1977; Preisler et al. 1979; Rees and Hayhoe 1978; Yates et al. 1973).

I. Remission Duration and Survival

Among the 74 complete responders there have been eight (11.0%) withdrawals for reasons including cardiomyopathy, bone marrow transplantation, and physician-patient desire to discontinue therapy. Of these eight patients, seven remain in their initial complete remission. There have been two remission deaths, one occurring in a 33-year-old woman who developed a fatal pneumonia at the time of drug-induced myelosuppression and another in a 31-year-old woman who expired from

Table 1. VAPA update as of 1 April 1980

	AGE 0–50	AGE 0–17	AGE 18–50
# Entered	106	61	45
Too early	1	0	1
Inevaluable	0	0	0
# Evaluable	105	61	44
# Complete remissions	74 (70%)	45 (74%)	29 (66%)
Withdrawals	8	5	3
Remission deaths	2	0	2
Relapses	24	16	8
Bone marrow	14	7	7
CNS	8	8	0
Myeloblastoma	2	1	1
# Continuous complete remission	40	24	16
Completed therapy	22	15	7
Relapses off therapy	4	3	1

refractory congestive heart failure presumably induced by adriamycin. Among the remaining 64 patients who entered complete remission, 40 remain disease free, while 24 have relapsed. All relapses in the adult age group have occurred in bone marrow, with one patient showing his first sign of recurrence by the development of a pleural myeloblastoma but with myeloblasts detected shortly thereafter in the bone marrow. In contrast, one-half of the 16 pediatric age relapses have occurred in the central nervous system. Six of these recurrences were detected through surveillance lumbar punctures. The median time to central nervous system relapse after documentation of complete bone marrow and spinal fluid remission was 4.5 months (range: 1.5–13.5). Six of the eight central nervous system relapses were followed within 0.5 months to 7.0 months by the reappearance of leukemic cells in bone marrow.

Figure 3 presents a Kaplan-Meier plot of the probability of remaining in complete remission among the complete responders. The median followup for these 74 patients is 9 months (range: 1+to 48+months) following the date they achieved complete remission. As previously noted, treatment was discontinued at approximately 15 months. The median duration of complete remission in 22.4 months. Utilizing two standard deviation confidence limits, the probability for complete responding patients to remain in remission at 12 months and 24 months is 67%±13% and 49%±17% respectively. Figure 4 presents a Kaplan-Meier plot of the same data comparing the pediatric and adult age groups. There is no significant difference in remission duration based on age.

Twenty-two patients have completed the VAPA[10] program. Of these 22, four have relapsed "off therapy", while 18 remain in unmaintained complete remission. The median duration of time following the completion of therapy for this group of 22 patients is 11+months. Three of the four late recurrences were noted in the bone marrow, while the other patient developed a nasopharyngeal myeloblastoma. All three patients who developed a bone marrow relapse entered a second remission following a single course of the VAPA[10] induction regimen and remain alive and disease free.

As seen in Fig. 5, the median survival for the entire group of 105 patients is 26.1 months. The 31 nonresponders had a median survival of only 0.5 months, while the median time to death among the complete responders has not yet been reached with a Kaplan-Meier plot suggesting a plateau in the 65%–70% range. Two standard deviation confidence limits indicate the probability of survival among complete responding patients to be 85%±9%, 71%±13%, and 66%±15% at 12, 24, and 36 months respectively.

II. Toxicity

The major toxicity during VAPA[10] remission induction in essentially all patients has been fever, necessitating the use of broad-spectrum

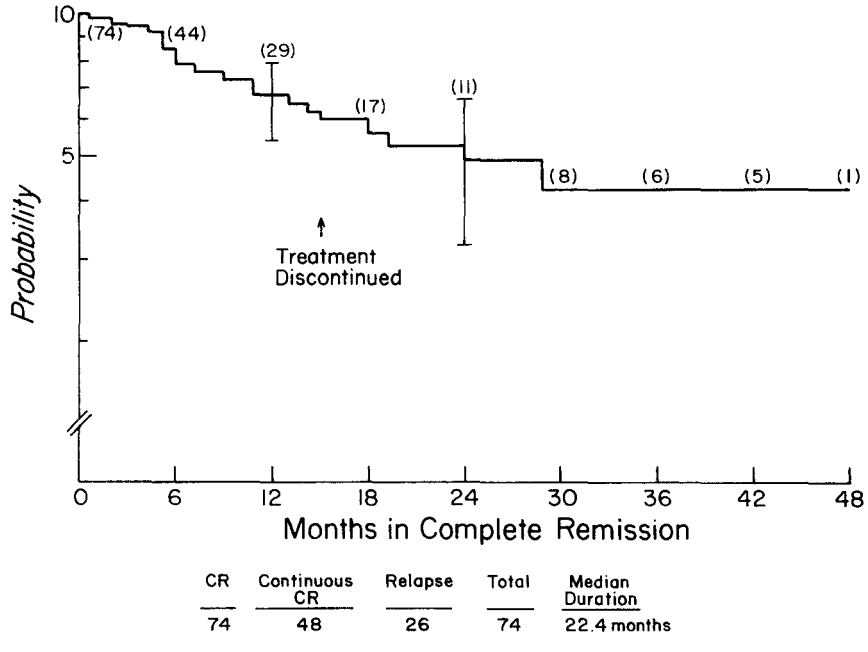
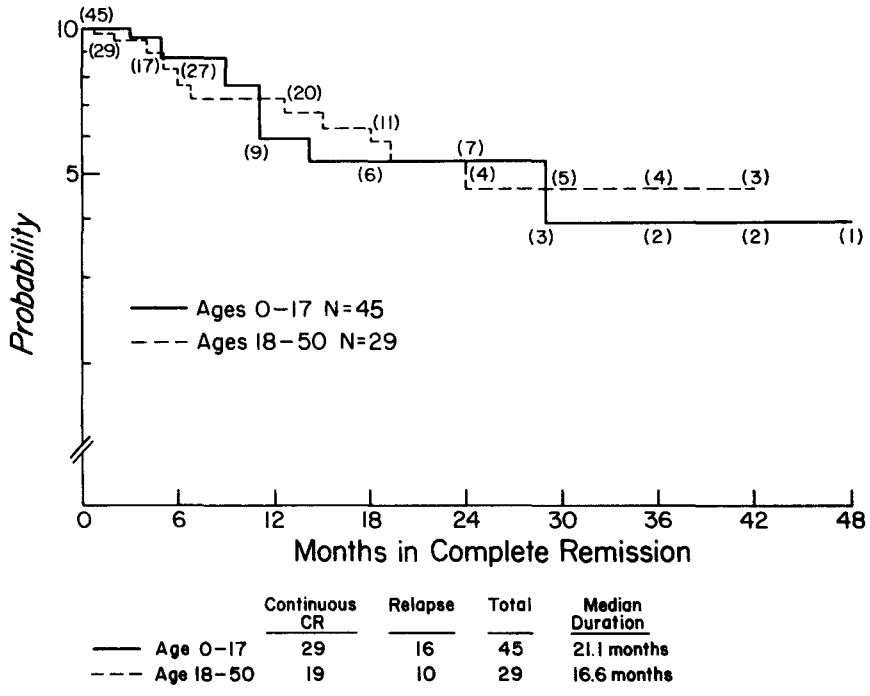


Fig. 3. VAPA[10]: Kaplan-Meier plot of probability of remaining in complete remission among all complete responders. The *vertical bars* at the 12 and 24 month points represent two standard deviation confidence limits



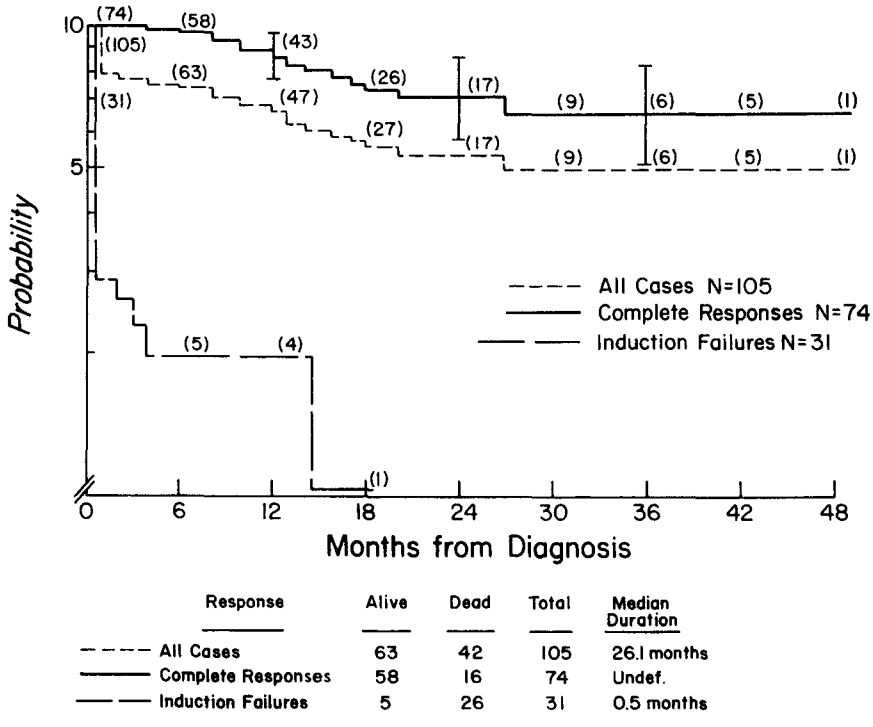
	Continuous CR	Relapse	Total	Median Duration
Age 0–17	29	16	45	21.1 months
Age 18–50	19	10	29	16.6 months

Fig. 4. VAPA[10]: Kaplan-Meier plot of probability of remaining in complete remission comparing pediatric and adult age groups

antibiotics. Culture-documented bacteremias have been present in about 20% of patients. In addition, approximately 25% of the pediatric patients under age 10 have experienced life-threatening gastrointestinal difficulties characterized by bloody diarrhea, esophagitis, ileus, bowel distension, and the development of signs of peritoneal irritation. These episodes of typhlitis resolved when bone marrow function recovered.

The early intensification phase of the maintenance program (Sequence I) was associated with severe thrombocytopenia requiring platelet transfusions in 70% of courses and neutropenia to the point of agranulocytosis. The drug-induced myelosuppression was most severe between the 12th and 17th day of each treatment cycle and usually resolved by the 21st day. Fevers occurring at times of granulocytopenia necessitated short-term hospitalizations and the use of broad-spectrum antibiotics in 30% of the courses, but a culture-documented infection was only present in 17% of these febrile episodes.

The use of azacytidine and adriamycin in the second 5-day cycle phase of the maintenance



Response	Alive	Dead	Total	Median Duration
All Cases	63	42	105	26.1 months
Complete Responses	58	16	74	Undef.
Induction Failures	5	26	31	0.5 months

Fig. 5. VAPA[10]: Kaplan-Meier plot of probability of survival. The *vertical bars* at the 12, 24, and 36 month points in the curve representing complete responders represent two standard deviation confidence limits

period (Sequence II) was generally well tolerated with the extreme nausea and vomiting associated with "bolus" azacytidine administration rarely present. Severe thrombocytopenia and granulocytopenia induced by this drug combination were rare, but in about 10% of courses the myelosuppression did not resolve by the 28th day of a given treatment cycle as was expected but was occasionally prolonged, lasting as long as 7 weeks. This lengthy bone marrow depression necessitated the delay of chemotherapy in several instances, but such patients were able to tolerate further azacytidine-adriamycin without difficulty and have enjoyed similar remission durations as have other patients.

There have been no major toxicities associated with "POMP" (Sequence III) except for a rare case of cholestatic jaundice thought to be related to the 6-mercaptopurine. The late intensification treatments (Sequence IV) with cytosine arabinoside led to severe myelosuppression, but only 12% of the courses have been associated with fever necessitating hospitalization.

The length of the treatment period including remission induction and the sequential chemotherapy phase averaged 450 days. Initially, 120 of these days were spent in the hospital for the administration of intravenous chemotherapy or for systemic antibiotics. During this study, the pharmacokinetics of continuous intravenous and continuous subcutaneous infusions of cytosine arabinoside were evaluated (Weinstein et al. 1978). The results indicated comparable drug levels and myelosuppression with both routes of administration. Because of these data, patients were no longer admitted to the hospital for 5-day intravenous infusions of cytosine arabinoside, but instead received outpatient subcutaneous infusions via a portable infusion pump (Auto Syringe, Inc., Hooksett, New Hampshire). Time of hospitalization was thereby reduced from 120 to 80 days.

D. Discussion

The major thrust of the VAPA[10] program was directed not at remission induction where a 65%–75% complete response rate was anticipated, but rather at the "maintenance" period where it was hoped that intensive therapy might lead to a significant prolongation in remission duration and survival. Protocol design was specifically directed at circumventing major potential obstacles to long-term remission. These include:

1. *Inadequate cytoreduction during the maintenance period.* The VAPA[10] program offered intensive therapy at drug doses higher than the remission induction levels at the beginning (Sequence I) and at the conclusion (Sequence IV) of the 15-month maintenance period. As seen in Figure 1, four cycles of cytosine arabinoside given by continuous infusion for 5 days at a dose of 200 mg/m^2/day were administered at the start and at the end of "maintenance". The initial four cycles were accompanied by a single administration of adriamycin. Each of these treatment cycles was administered on a 21–28 day schedule with no dose de-escalation made for myelosuppression or infection. The rationale for early and late intensification was data from experimental murine models demonstrating a steep dose response curve for cytosine arabinoside (Skipper 1978). Clinical data to support this concept comes from a recent AML study in which patients received only a single cycle of intensive induction chemotherapy which resulted in a median, unmaintained remission of 10 months (Vaughn et al. 1980).

2. *The development of drug resistance.* In experimental in vitro and in vivo leukemia models, there is evidence that relapse results from the selection and overgrowth of drug resistant cell lines (Skipper 1978). Initially, during treatment with a given program the majority of chemotherapeutically-sensitive cells are progressively eliminated, but at some point ("nadir") further leukemic cell kill is counterbalanced by the overgrowth of resistant cells which eventually results in clinical relapse. By back extrapolation from the kinetics of remission induction and relapse in patients with AML, this "nadir" was estimated to occur at approximately 3–4 months of treatment with a given regimen. Hence, two different drug programs (Sequences II and III) of non-cross-resistant agents were interposed between the early and late intensification periods. In the first of these, azacytidine, an active agent in the treatment of AML which has been reported to be non-cross-resistant with cytosine arabinoside (Van Hoff et al. 1976), was given at induction level doses in combination with adriamycin. In the second of these two drug programs, 6-mercaptopurine and methotrexate, each having some degree of

activity in AML (Ho and Frei 1971), were introduced along with vincristine and prednisone.

3. *The presence of pharmacologic "sanctuaries"*. While meningeal leukemia has been reported in patients with AML (Pippard et al. 1979; Wolk et al. 1974; Zachariah et al. 1978), it is far less common than in acute lymphocytic leukemia. The central nervous system is the initial site of recurrence in only 10%–15% of relapsing AML patients and is far more often seen in pediatric than in adult age groups (Chard et al. 1978; Pizzo et al. 1976). It was thought conceivable, however, that prolonging survival of patients with AML might yet be associated with an increased incidence of meningeal leukemia (Wolk et al. 1974). The VAPA[10] program did not include treatment directed solely at the central nervous system. Cytosine arabinoside, however, when administered by continuous infusion, has been shown to pass readily through the blood brain barrier, reaching cytotoxic concentrations when administered in doses such as those employed in the early and late intensification plans (Ho and Frei 1971). This approach, especially in the pediatric age group, will require re-examination in the future, since 8 of the 16 relapses in patients under age 18 have occurred in the central nervous system.

A preliminary analysis of the VAPA[10] experience suggests that age at presentation, sex, or height of the initial white blood count up to 200,000/mm^3 does not have prognostic significance in terms of either remission induction rate or remission duration. The duration of complete remission was further uninfluenced by the number of courses (i.e., whether a second induction treatment was begun on day 14) required to achieve a complete remission. The remission induction rate may be slightly reduced among patients having the acute promyelocytic leukemia subtype (8/15), while the relapse potential seems higher in patients having acute monocytic leukemia (5/10).

These data are extremely encouraging and indicate that intensive, sequential combination chemotherapy given to patients with AML who have achieved complete remission can extend the median duration of that remission for 2 years, prolong survival in these individuals for an indefinite period of time, and allow a subsequent period of unmaintained remission in excess of an additional year. The Kaplan-Meier plots (Figs. 3–5) furthermore suggest that a plateau has been achieved among patients who have remained in complete remission for greater than 24 months, making the likelihood of late relapse less and raising the possibility of cure in a significant number of such individuals. The only other therapeutic modality that appears to achieve a similar result for patients with AML is intensive chemotherapy and total body irradiation followed by allogeneic bone marrow transplantation when performed early during the initial remission (Blume et al. 1980; Powles et al. 1980; Thomas et al. 1979). This approach, however, is limited to patients who not only achieve a complete remission, but also have a histocompatible sibling.

The VAPA[10] experience suggests that AML, even if it is a disease caused by an abnormal bone marrow clone, can be suppressed for extended periods of time by chemotherapy alone in at least 33% of patients under age 50. It will now be possible to examine factors affecting durations of remission and to design specific therapeutic strategies based on these findings.

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