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Treatment of Acute Myelocytic Leukemia: A Study by Cancer and Leukemia Group B

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In a randomized study of acute myelocytic leukemia (AML), 352 patients of all ages were treated for remission induction by one of the four regimens: 7 days of cytosine arabinoside (ara-C) by continuous intravenous (i.v.) infusion or bolus injection every 12 hr, together with daunorubicin (DNR) by rapid i.v. injection on days 1, 2, 3; or 5 days of ara-C by infusion or bolus injection and DNR for 2 days only. The regimen of 7 and 3 infusion was significantly superior to the other 3 regimens, resulting in 56% complete remission (CR). For remission maintenance, ara-C was given for 5 days every month and each month one of the following four drugs added on a cyclic rotational basis: thioguanine, cyclophosphamide, CCNU, or DNR. Although ara-C dosage each month was the same, the route of ara-C administration by random allocation was either rapid i.v. bolus or subcutaneous (s.c.) injection. The median duration of CR was significantly longer for s.c. ara-C group: 14 mo for patients less than 60 yr old (versus 8 mo for i.v.) and 31 mo for 60 or older age group (versus 9 mo for i.v.). Patients who received a combination of the best of the four induction regimens (7 and 3 infusion) and the better of the two maintenance schedules (s.c. ara-C) had a median remission duration of 22 mo and a median survival of 35 mo (the longest reported in a prospective randomized trial of therapy for AML). These results establish the validity of an intensive chemotherapy to produce rapid marrow aplasia followed by a sequential maintenance therapy for achieving prolonged disease-free survival in AML.

IN REMISSION INDUCTION therapy of acute myelocytic leukemia (AML) with cytotoxic agents, it is necessary to ablate the leukemic cells in the bone marrow before regrowth of normal marrow cells occurs. A patient with AML is at greatest risk of morbidity and mortality from the consequences of an aplastic marrow during the period of remission induction. With induction therapies in current use, this period lasts several weeks. The frequency of death from infection, bleeding, and other complications usually exceeds 25%.[1] When the study reported here was initiated, treatment regimens for AML usually consisted of 5 days of cytosine arabinoside (ara-C) administered together with a second drug. A minority of patients reached remission after a single course. A second course was ordinarily administered 10–20 days later when residual leukemic cells were found in the marrow, independent of levels of peripheral blood counts. Yates et al.[2] suggested that a more intensive schedule of chemotherapy, which produced more consistent marrow aplasia sooner, might reduce the period at risk for patients with AML. In a pilot study using ara-C for 7 days and daunorubicin (DNR) for the first 3 days, they reported that of 15 patients with AML who were between 15 and 60 yr of age, 13 achieved complete remission. The period of hospitali-

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zation for these patients was shorter than for patients on regimens previously used. The Cancer and Leukemia Group B (CALGB) undertook the present study in 1974 based on this concept and the pilot findings. During the period when this study was being planned, two methods for administration of ara-C were in common use: intravenous (i.v.) infusion continuously for several days, or rapid bolus i.v. injections at 12-hr intervals for several days. Since the relative superiority of these methods had not been established, the two methods of administration of ara-C were compared in a randomized fashion as a subsidiary question.

Maintenance chemotherapy in this study was accomplished as 5-day cycles of ara-C given every 4 wk with each of four drugs, thioguanine, cyclophosphamide, CCNU, and DNR in rotational sequence. Such a rotational cycle using multiple drugs was chosen to avoid development of resistance. Two methods of administration of ara-C for maintenance were randomly compared: (1) a rapid bolus i.v., and (2) subcutaneous (s.c.) injection. Some patients also received a single i.v. injection of the interferon-inducer Poly I:Poly C. This injection was given by random allocation during the third month of maintenance. The results of the Poly I:Poly C portion of this investigation have already been reported.[3]

MATERIALS AND METHODS

Patients

Three-hundred and eight-five patients of all ages from 27 member institutions of CALGB in North America, Europe, and South Africa entered into this study between April 25, 1974 and May 7, 1975. Of these 352, 91% were evaluable and 33 were considered unevaluable for the following reasons: major treatment violation: 16, died before treatment could be started: 6, ineligible, not AML: 6, improper randomization: 5.

All patients with acute myelocytic leukemia (myeloblastic, myelomonocytic, promyelocytic, monocytic, or erythroleukemia) were eligible for this study provided: (1) they had never received any of the drugs prescribed in this study or treatment with corticosteroids; (2) efforts to bring systemic signs of infection under control had begun; and (3) written informed consent was obtained prior to institution of this study.

Treatment

The first course of induction chemotherapy consisted of four regimens of combinations of ara-C and DNR as detailed below.

Regimen I (5 and 2 with ara-C infusion). Ara-C, 100 mg/sq m/day continuous infusion from day 1 through day 5, plus DNR, 45 mg/sq m/day by rapid i.v. injection on days 1 and 2.

Regimen II (5 and 2 with ara-C bolus). Ara-C, 100 mg/sq m every 12 hr for a total of 10 injections (5 days) by rapid i.v. injection (bolus) plus DNR, 45 mg/sq m/day by rapid i.v. injection on days 1 and 2.

Regimen III (7 and 3 with ara-C infusion). Ara-C, 100 mg/sq m/day by continuous i.v. infusion from day 1 through day 7, plus DNR, 45 mg/sq m/day by rapid i.v. injection on days 1, 2, and 3.

Regimen IV (7 and 3 with ara-C bolus). Ara-C, 100 mg/sq m every 12 hr for a total of 14 injections (7 days) by rapid i.v. injection (bolus), plus DNR, 45 mg/sq m/day by rapid i.v. injection on days 1, 2, and 3.

If after a minimum waiting period of 7 days following completion of the first course a complete bone marrow remission (CR) was not achieved, a second course of induction chemotherapy was given. All second courses were given as 5 and 2, maintaining the same technique of ara-C administration as in their respective first courses.

Patients who received 5 and 2 as their first course received a third course of 5 and 1 if after two courses they failed to achieve CR and showed adequate cellularity of repopulation marrow. There was no provision for a third course for patients who received either of the 7 and 3 regimens as the first course.

Therapeutic End-points of Induction Regimens

The criteria for evaluating response were those established by CALGB and have been described in detail by Ellison et al.[4] According to these criteria the marrow cellularity in complete remission (CR) as well as in partial remission (PR) was normal with evidence of normal erythropoiesis, granulopoiesis, and megakaryopoiesis. The marrow in CR showed no more than 5.0% blast cells, and the range of blast cells in marrow was from 5.1% to 25.0% for PR status.[4] An attempt was made to put every patient into CR unless adverse reactions were so severe after induction of PR with one course of therapy that clinical judgment precluded further therapeutic efforts to achieve CR.

Definition of failure of induction therapy. All patients who did not achieve either a complete or a partial remission after the three prescribed courses in regimen I and II or after the two prescribed courses in regimens III and IV, or those who died during induction treatment were considered as induction failures.

Statistical Analysis

All disease-free and overall survival curves are calculated using the actuarial life-table technique.[5] Differences in patterns of recurrence or death were determined using Breslow's modification of the Kruskal-Wallis test.[6] Differences among treatments in distributions of patient and disease features were examined using the chi-square test for contingency tables.[7] Multivariate regression analyses using Cox's[8] linear logistic model were performed to identify features prognostic of response.

Assignment of Induction Therapy

Patient assignment to induction therapy was accomplished by random allocation within each institution from a centrally determined sequence of treatments. Patients who were under 60 yr of age were randomized separately from those who were 60 or older. Those who were less than 60 yr of age were randomized to receive one of the four regimens detailed above, whereas, the older-aged patients were assigned to either regimen I or II.

Assignment to Maintenance Therapy

Patients in complete or partial remission at the conclusion of induction therapy were randomly allocated to one of two maintenance therapies, which differed in the method of administration of ara-C (i.v. or s.c., 100 mg/sq m q 12 hr × 10 doses every month); in all other respects the regimens were identical: *Month 1:* Ara-C plus thioguanine 100 mg/sq m q 12 hr × 10 doses (from day 1 to day 5) given p.o. *Month 2:* Ara-C plus cyclophosphamide 1000 mg/sq m by i.v. bolus on day 1. *Month 3:* Ara-C plus CCNU 75 mg/sq m in 1 dose on day 1, given p.o. *Month 4:* Ara-C plus DNR 45 mg/sq m/day by an i.v. bolus on days 1 and 2.

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This four month cycle was repeated throughout maintenance. Then, an addendum was introduced in 1979, whereby all maintenance therapy was stopped for patients reaching their fourth or fifth anniversary of continuous remission. Blood and bone marrow examinations were performed prior to each monthly therapy to assure a continued CR status. All drugs except DNR were obtained from commercial sources. DNR (NSC#82151) was obtained from the National Cancer Institute. Because of its potential cardiotoxicity, total dosage of DNR was kept less than 225 mg/sq m during the induction therapy and less than 540 mg/sq m overall. After this maximum dosage of DNR was reached, DNR was omitted; subsequent cycles consisted of three instead of four months.

Drug Dosage Modification During Maintenance

Persistent neutropenia (total neutrophils <2000/cu mm) or thrombocytopenia (platelets <100,000/cu mm) during maintenance therapy, even when therapy was delayed by a week, or two episodes of severe hypoplasia justified permanent 50% reduction in the dosage of all drugs.

Concurrent Therapy

Transfusions of blood and blood products (platelets and leukocytes) were given when indicated. Platelet transfusions were given prophylactically when possible to all patients with platelet counts below 20,000/cu mm. Antibiotics, allopurinol, acetazolamide, phenothiazines, and other drugs were used when indicated.

RESULTS

The randomization of patients resulted in comparable characteristics in each age set (Table 1). Of the 352 patients evaluated, 76% were classified as acute myeloblastic or AML, 14% acute myelomonocytic or AMML, 5% acute promyelocytic, 2% acute monocytic, and 3% acute erythroleukemia. None of these patients had a history of preleukemia or had received chemotherapy or radiation therapy for a previous malignancy.

Table 2.

Age Group	Regimen	No. of Patients	Percent CR
<60	5 and 2 Infusion	40	45
<60	5 and 2 Bolus	39	36
<60	7 and 3 Infusion	35	57
<60	7 and 3 Bolus	37	68
≥60	5 and 2 Infusion	35	20
≥60	5 and 2 Bolus	27	11

Induction Therapy

An interim analysis of remission induction results was performed after the first 7 mo of study when 213 patients had been accrued (151 in the < 60 yr and 62 in the ≥ 60 yr age group). These results are given in Table 2.

The 5 and 2 regimens were significantly inferior to 7 and 3 regimens ($p < 0.01$) in the less than 60 age group. The 7 and 3 regimens were initially not offered to the ≥60 age group patients because of a general belief that the more intensive therapy would be excessively hazardous for the elderly patients. However, this interim analysis revealed that the 5 and 2 regimens were clearly inadequate for these elderly patients as well as for the younger age group. The 5 and 2

Table 1. Comparability of Patient Groups in Induction

Induction Therapy	Age <60 yr (n = 247)				Age >60 yr (n = 105)			
	5 and 2		7 and 3		5 and 2		7 and 3	
ara-C method	Infusion	Bolus	Infusion	Bolus	Infusion	Bolus	Infusion	Bolus
No. of patients	n = 40	n = 39	n = 82	n = 86	n = 35	n = 27	n = 22	n = 21
Percent male	55	62	52	51	66	70	41	48
Median age	42	43	36	34	67	69	69	70
Diagnosis								
% Myeloblastic	80	71	72	78	86	78	68	71
% Myelomonocytic	12	13	15	12	11	11	27	24
% Promyelocytic	5	11	4	6	3	4	5	0
% Monocytic	0	5	2	2	0	4	0	0
% Erythroleukemia	3	0	7	2	0	3	0	5
% ≥ 90% leukemic cells in marrow	49	37	34	40	21	15	20	26
% c̄ Packed marrow	3	11	14	12	21	8	5	21
% c̄ Any initial infection	31	37	44	40	30	70	55	55
% c̄ Liver enlargement (≥3 cm)	23	15	23	31	27	30	17	24
% c̄ Spleen enlargement (≥3 cm)	15	13	17	22	15	22	14	10
% c̄ Nodes enlargement	35	28	40	29	18	19	9	10
Median hemoglobin (gm/dl)	10.0	9.1	9.2	9.2	9.3	8.3	9.7	8.2
Median platelets (× 10^3)	54	31	50	44	45	41	63	44
% <25,000 platelets initially	18	44	32	27	33	41	18	29
Median WBC (× 10^3)	20.0	7.5	18.7	30.0	9.2	27.5	16.7	17.5
% ≥ 75% leukemic cells in blood	38	11	27	35	18	35	14	20

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Table 3. Outcome of Induction Therapy

Schedule	Method of Ara-C Administration	Age	No. of Evaluable Patients	Percent of Evaluable Patient With Different Outcomes* of Induction Therapy			
				CR	PR	NR	Died
5 and 2	Infusion	<60	40	45	13	12	30
5 and 2	Bolus	<60	39	36	13	18	33
7 and 3	Infusion	<60	82	59	13	8	20
7 and 3	Bolus	<60	86	51	10	12	27
5 and 2	Infusion	≥60	35	20	6	6	68
5 and 2	Bolus	≥60	27	11	11	11	67
7 and 3	Infusion	≥60	22	45	9	18	28
7 and 3	Bolus	≥60	21	38	5	14	43

*CR, Complete remission; PR, partial remission; NR, no response.

regimens were discontinued, and in the subsequent 5 mo of the study, all patients were randomized to receive one of the two 7 and 3 regimens to test the relative superiority of the two methods of ara-C administration.

The results of induction therapy for the 352 evaluable patients are detailed in Tables 3 and 4. For patients under 60 yr of age, 7 and 3 infusion resulted in 59% complete remission, an incidence superior to the other 3 regimens ($p < 0.05$). Deaths during induction therapy were fewer with 7 and 3 regimens (23%) compared to 5 and 2 regimens (32%). For patients 60 yr of age and older, 7 and 3 infusion resulted in 45% complete remission, in sharp contrast to the 16% remission seen earlier with the 5 and 2 regimens. The frequency of deaths during induction for these older age patients decreased from 68% for the 5 and 2 regimens to 35% for the 7 and 3 regimens. The frequency of achieving only a PR was similar among the 4 induction regimens for those under and over 60 (Table 3).

When the relative frequencies of complete remissions are standardized for age and time of entry to study, the overall estimates of the probabilities of CR are: 39% for 5 and 2 infusion, 29% for 5 and 2 bolus, 55% for 7 and 3 infusion, and 46% for 7 and 3 bolus (Table 4). Multivariate analyses,[8] including age, time of entry, initial blood total leukocyte count, and initial infection status as standardization variables in addition to dosage and schedule of drugs, confirm that the 7 and 3 regimens are significantly superior to 5 and 2 schedules ($p < 0.01$). The apparent superiority of continuous infusion of ara-C over i.v. bolus every 12 hr fails to satisfy customary significance criteria ($p = 0.13$). For patients under the age of 60, the CR frequency for 7 and 3 infusion was 57% during the first 7 mo of study and was 59% in the subsequent 5 mo. For the 7 and 3 bolus group, there was a decrease in the CR frequency from 68% to 39% over the same periods. This unexpected low frequency of CR with 7 and 3 bolus during the latter part of the study is unexplained. There were no discernible differences in patient characteristics during the two periods.

Seventy-one percent of the complete responders to the 7 and 3 programs achieved CR after one course (78/110), while only 36% of the responders to the 5 and 2 schedules did so ($p < 0.001$). Administration of ara-C by infusion or bolus did not influence the speed at which remissions occurred, 61% of the CRs arrived at that status after only one course of therapy by each method. CR was reached in a mean time of 38 days with the 7 and 3 schedules, and 47 days with the 5 and

Table 4. Relative Frequency of Complete Remissions According to Treatment Regimen and Age for All Patient Entries

Age at Entry	Induction Regimen							
	5 and 2 Infusion		5 and 2 Bolus		7 and 3 Infusion		7 and 3 Bolus	
	No. Evaluable	% CR	No. Evaluable	% CR	No. Evaluable	% CR	No. Evaluable	% CR
<20	10	60	5	40	13	54	19	58
20-29	4	75	7	29	19	58	16	56
30-39	4	75	5	40	16	81	21	57
40-49	9	44	8	38	15	53	14	43
50-59	13	15	14	36	19	47	16	38
60-69	26	27	15	13	12	50	11	27
70-84	9	0	12	8	10	40	10	50
Totals <60 yr	40	45	39	36	82	59	86	51
Totals ≥60 yr	35	20	27	11	22	45	21	38
Totals	75	33	66	26	104	56	107	49
Standardized % CR	39%		29%		55%		46%	

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Table 5. Relative Frequency of Significant Complications During Induction According to Treatment Group and Age for All Patient Entries

	Treatment Group							
	5 and 2				7 and 3			
	Infusion		Bolus		Infusion		Bolus	
Age Group:	<60	≥60	<60	≥60	<60	≥60	<60	≥60
No. Evaluated:	40	35	39	27	82	22	86	21
Complication								
Hemorrhage	23%	17%	15%	33%	11%	14%	15%	14%
Infection	40%	63%	41%	70%	50%	68%	41%	38%
Hepatic	8%	6%	0	0	2%	0	2%	0
Renal	5%	6%	3%	15%	2%	9%	2%	10%
GI	0	0	3%	4%	1%	0	6%	5%
Cardiac	0	9%	0	0	0	0	1%	5%

2 schedules ($p < 0.05$). The frequency of significant hemorrhage, sepsis, and other complications were similar in the four treatment regimens (Table 5). The cause of death of patients during induction therapy phase was invariably sepsis and hemorrhage. Sepsis alone was the most common cause of death and bleeding was associated with sepsis in about 15% of fatalities. The marrow status was recorded for only about one-third of the patients who died during induction therapy. It is not possible to compare the relative frequency of deaths with aplastic marrow in the four induction regimens because of small numbers of patients whose marrow status was recorded at the time of death.

Morphological Diagnosis and CR

Ninety percent of patients had a morphological diagnosis of either acute myeloblastic (AML) leukemia (76%) or acute myelomonocytic (AMML) leukemia (14%). Among those with AML, 32% achieved CR with the 5 and 2 regimens compared to 57% with 7 and 3 regimens. Among those with AMML, 39% achieved CR with 5 and 2 regimens and 50% with 7 and 3 regimens. Complete remission was achieved in only 2 patients (out of 17) with acute promyelocytic leukemia, in only 1 patient (out of 8) with acute monocytic leukemia and in 5 patients (out of 11) with acute erythroleukemia. As is evident, these numbers are too small to allow a definitive comparison of the 4 induction regimens and of overall duration of remission.

Overall Survival Duration

For 152 patients with CR, the median duration of survival was 19 mo, for 38 patients with PR, 13 mo, and for 162 patients with NR (no response) or who

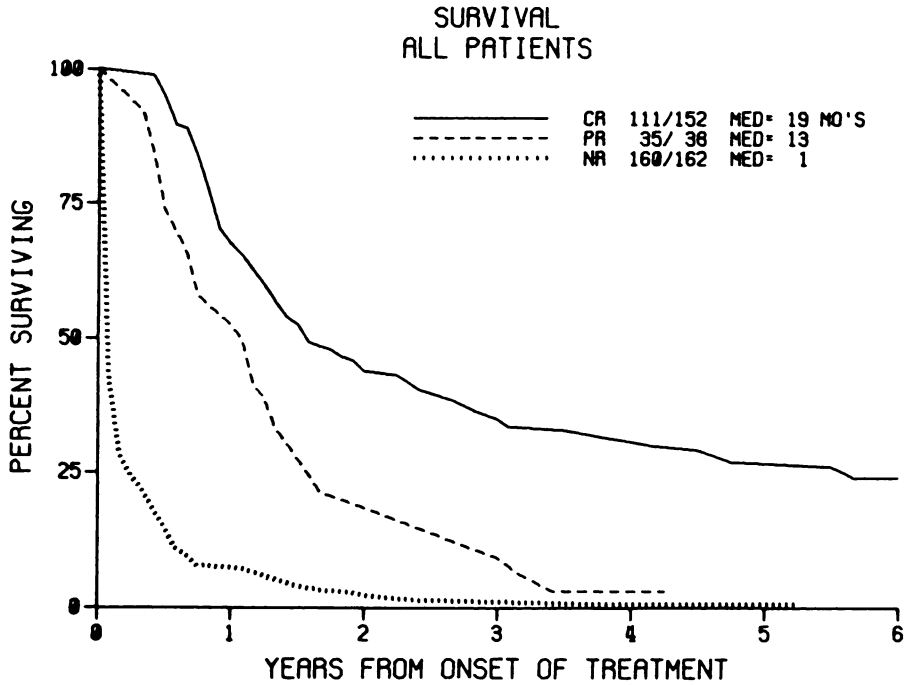

Fig. 1. Duration of survival according to the outcome of remission induction therapy in 352 patients with AML. CR, Complete remission; PR, partial remission; NR, no response. Number of patients at risk for each 1 yr interval is as follows:

Year	0	1	2	3	4	5	6
CR	152	105	67	53	44	36	11
PR	38	21	7	5	1	0	0
NR	162	12	4	2	1	1	0

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died during induction therapy, the median survival time was 1 mo (Fig. 1).

Maintenance Therapy

There were 155 patients who were randomized to maintenance therapy with either i.v. bolus injection or s.c. injection of ara-C in addition to another drug each month as previously described. There were 35 additional responders who either refused maintenance therapy or received therapy with drugs and schedules not according to this study. They were not evaluable for this analysis because of improper randomization or inapplicability of the treatments used. One-hundred and twenty-five patients entered maintenance after achieving CR and 30 after achieving PR. The remission duration of the 30 patients who achieved PR was uniformly poor (20 wk) no matter which maintenance therapy regimen was used. Therefore, all analyses of results detailed in this report are those performed on the 125 patients who received maintenance therapy after achieving CR. The patients randomized to s.c. or to i.v. ara-C were similar with respect to distribution according to age, sex, and induction therapy.

Duration of Response and Survival of Responders

Remission duration with the multidrug cycle using s.c. ara-C was significantly longer than with the group given i.v. ara-C ($p = 0.05$). As shown in Fig. 2, the median duration of CR was 18 mo for the subcutaneous ara-C and 8 mo for the i.v. ara-C groups. At 32 mo, the curves converge, and at 60 mo, both regimens had approximately 25% patients in complete remission. The median duration of remission with the s.c. route of ara-C was superior in the age group less than 60 (median s.c. 14 mo versus i.v. 8 mo) as well as in patients age 60 or over (s.c. 31 mo versus i.v. 9 mo) ($p < 0.01$).

As shown in Fig. 3, those patients who received ara-C by continuous i.v. infusion during the induction phase and then received ara-C by s.c. route during maintenance had a significantly longer duration of remission than with other combinations of induction and maintenance regimens ($p < 0.01$). Patients induced with continuous infusion followed by s.c. maintenance ara-C also sustained the highest frequency of severe hematologic toxicity during maintenance therapy, thus necessitating a sharper reduction of drug dosage. One-half to two-thirds of the patients in the i.v. ara-C maintenance subgroups continued to receive full dosage of maintenance drugs for up to 4 yr, but because of hematologic toxicity, only one-fifth to one-fourth of patients in the s.c. ara-C maintenance could tolerate the full dosage during prolonged remission.

The survival data parallel the remission duration data; median survival time for 60 patients on s.c. ara-C maintenance was 26 mo and for 65 patients on i.v. ara-C 15 mo ($p = 0.02$). As shown in Fig. 4, patients with ara-C by continuous infusion in induction and s.c. maintenance had the longest median survival (35 mo) as compared to the other three combinations ($p = 0.02$).

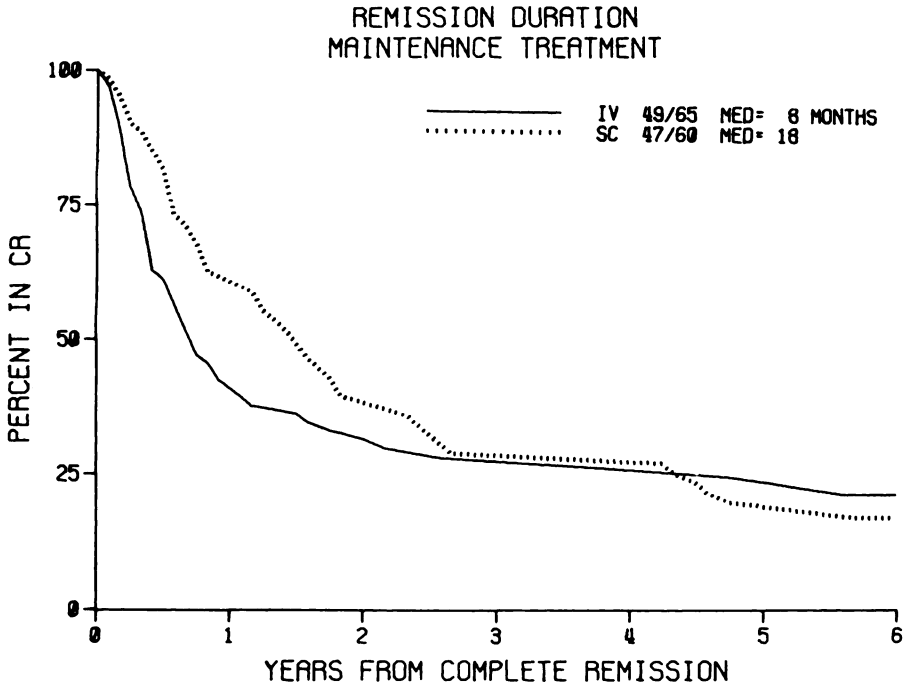

Fig. 2. Complete remission durations for patients receiving ara-C in maintenance by intravenous route (IV) or subcutaneous route (SC). Fractions show the number relapsed from the number beginning treatment. Number of patients at risk for each 1 yr interval is as follows:

Year	0	1	2	3	4	5	6
IV	65	27	20	16	15	13	5
SC	60	35	22	16	16	11	3

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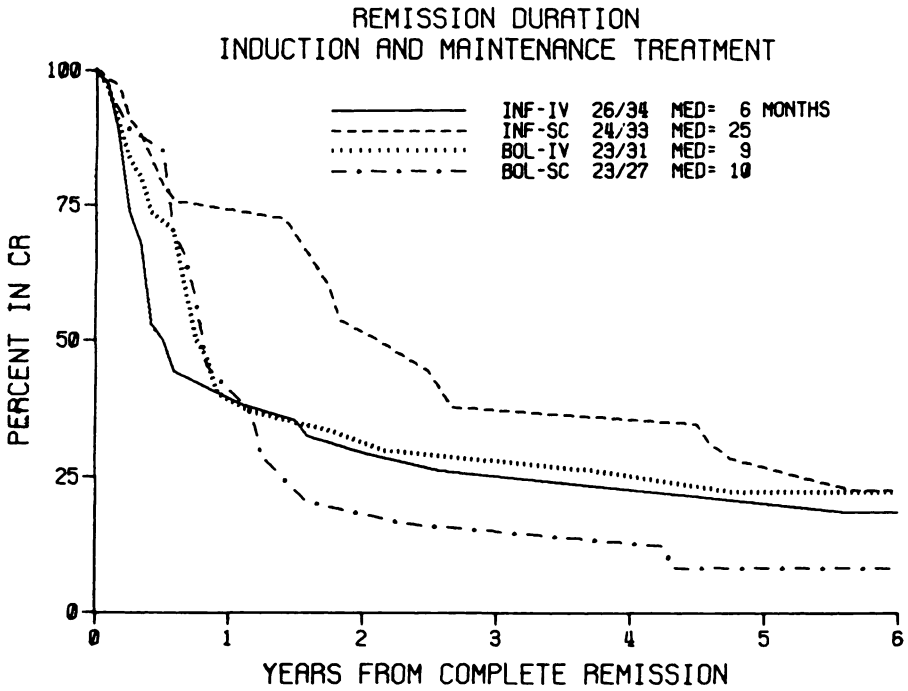

Fig. 3. Complete remission durations for patients receiving ara-C induction by continuous infusion (INF) or every 12 hr bolus (BOL) and in maintenance by the intravenous (IV) or subcutaneous (SC) route. Fractions show number relapsed from the number beginning maintenance treatment. Number of patients at risk for each 1 yr interval is as follows:

Year	0	1	2	3	4	5	6
INF-IV	34	15	11	8	8	7	2
INF-SC	33	24	17	12	12	9	1
BOL-IV	31	12	9	8	7	6	3
BOL-SC	27	11	5	4	4	2	2

Long-Term Remissions

Of the 125 patients with CR who were started on maintenance therapy, the number of patients who remained in CR at 30 mo, 36 mo, 48 mo and 60 mo were 38, 37, 34, and 18, respectively. These long-term remitters are represented in the two curves of Fig. 2 from the point where the curves converge and plateau. The two maintenance therapy regimens are identical in the relative proportion of patients who remain in long-term remission. Data on duration of maintenance therapy on these 38 patients are given in Table 6. These data do not demonstrate a significant difference in duration of CR in patients treated for more than 2 yr. Thus, 70%, 75%, and 78% of patients remain in remission for 4 yr or more when maintenance was discontinued in their third, fourth, or fifth year of

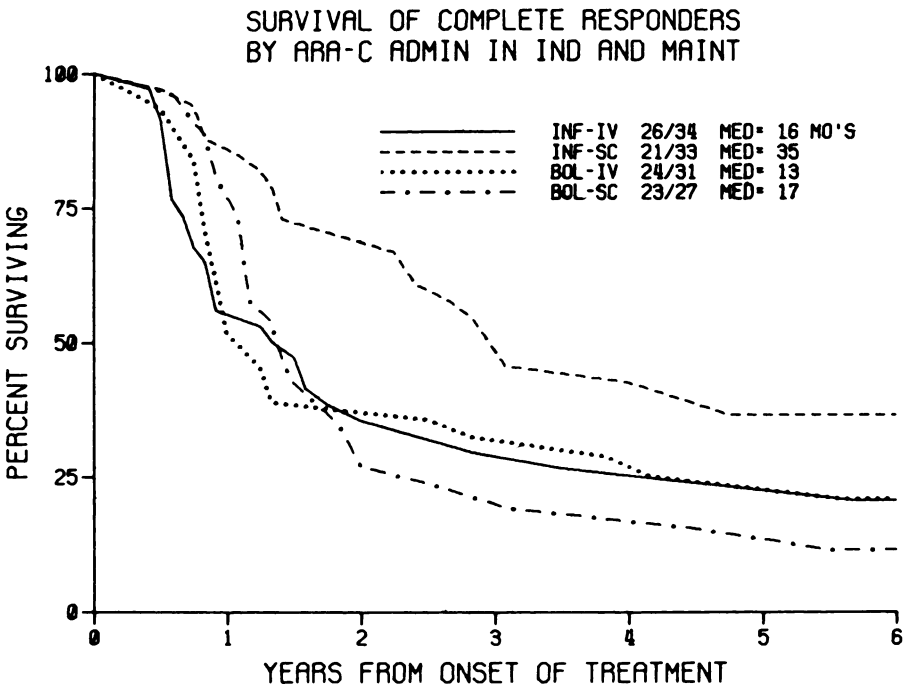

Fig. 4. Survival from beginning of protocol of complete responders who received ara-C in induction by continuous infusion (INF) or every 12 hr bolus (BOL) and in maintenance by the intravenous (IV) or subcutaneous (SC) route. Fractions show deaths among the number beginning maintenance treatment. Number of patients at risk for each 1 yr interval is as follows:

Year	0	1	2	3	4	5	6
INF-IV	34	19	13	10	9	7	2
INF-SC	33	29	23	18	15	12	3
BOL-IV	31	19	12	10	8	7	3
BOL-SC	27	21	8	6	5	4	2

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Table 6. Data on Long-Term Remission Durations (Duration of Remission According to the Duration of Maintenance Therapy)

Duration of Maintenance Therapy	Number of Patients	Number Relapsed	Duration of Remission (mo)*
<1 yr	1	1	53†
1-2 yr	3	2	47, 52, 63+
2-3 yr	8	4	30, 40, 44, 65+, 65+, 67, 70+, 71+
3-4 yr	8	2	48+, 50, 51+, 52+, 53, 65+, 68+, 74+
5-6 yr	18	4	51, 52, 56, 64+, 65+, 65+, 65+, 66+, 67, 67+, 67+, 68+, 70+, 71+, 71+, 72+, 76+, 76+

*Each number represents one patient's duration of remission (in months) as of October 1980. (+) Indicates patient still in CR; absence of + indicates time in months when relapse occurred.

†Stopped maintenance after 9 mo: relapsed 44 mo later—died within a few days with leukemia and sepsis.

treatment, respectively. Only one relapse has occurred after 60 mo, with 18 patients at risk.

DISCUSSION

An objective of this study was to test whether in AML, a rapid ablation of bone marrow would reduce the time at risk for morbidity and mortality from chemotherapy and if this would result in increased incidence of complete remissions. For rapid marrow ablation we used ara-C for 7 days and DNR for 3 days (7 and 3 schedule) and compared the results with 5 and 2 schedule. The results of outcomes of induction therapies, detailed in Tables 3 and 4, validate this premise. The frequency of CR was higher with 7 and 3 schedules as compared to the 5 and 2 schedules. Whereas 68% of patients over 60 yr died during the induction phase with 5 and 2 schedules, only 35% of the corresponding group died with 7 and 3 schedules. Mortality among younger patients was also less with the 7 and 3 schedules, but not significantly so. Twice as many patients achieved CR following only one course of induction therapy with 7 and 3 schedules as with 5 and 2 schedules (71% versus 36%). The frequency of severe toxicity was equal in the two treatment schedules.

The original study reported by Yates et al.,[2] the combined treatment of Crowther et al.,[9] and the study reported by Gale and Cline[10] were based on the same premise as the present series. They demonstrated that more intensive drug administration, or a combination of 3 drugs, induced rapid marrow ablation and rapid remission status. It is not unexpected that small series with unusually high response rates are reported; small series with standard response rates rarely are prepared for publication. It is of note in this regard that our interim results for patients less than 60 yr with the 7 and 3 schedule showed a 77% response frequency.[11]

The remission induction results with 7 and 3 infusion in patients over 60 yr of age are the best reported so far in a large series. In the present study, there were 22 patients in the 60 and over age group who received 7 and 3 infusion. Six of 12 between 60 and 69 yr and 4 of 10 between 70 and 84 yr achieved a CR; results with 7 and 3 bolus were also favorable (Table 4). The results with the 5 and 2 regimens were distinctly inferior. Peterson et al.,[12] utilizing the same 7 and 3 infusion schedule, obtained CR in 4 of 6 patients between the ages of 61 and 70 and none of 5 patients between 71 and 86 yr old. Our results confirm the previously reported observations of CALGB[13] as well as of other investigators[10,12] that in AML old age alone should not be considered a reason to withhold intensive induction therapy.

Ara-C is an analog of pyrimidine 2′-deoxycytidine. The cytotoxic activity of ara-C rests in its ability to inhibit DNA synthesis, which is explained most probably by a competitive inhibition of DNA polymerase.[14] Used as a single agent, ara-C produces remission in about 30% of patients with AML.[15-17] When ara-C is combined with 6-thioguanine or with DNR, the incidence of CR in AML is increased to between 40% and 54%.[17-24] When ara-C is combined with both 6-thioguanine and DNR or doxorubicin, the reported incidence of CR in AML is 35%–50% in multiinstitutional randomized studies involving a large number of patients[23,24] and 82% in a single institutional nonrandomized trial involving a smaller number of patients.[10]

Although ara-C has been in clinical use as a chemotherapeutic agent for more than a decade, the optimal regimen for administration of this drug had not been established in 1974 when this study was undertaken. For an S-phase-specific drug, the optimal schedule for remission induction in AML should be one that provides effective serum levels of the drug continuously (or at intervals less than the median time of DNA synthesis of the leukemic cells) for as long as is tolerated by the host.[25,26] The calculated generation time for leukemic cells in AML varies greatly in different reports, but ranges from 2 days to greater than 10 days, with a mean time of DNA synthesis of

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about 10 hr.[27-30] In man, ara-C administered by i.v. bolus injection disappears from the blood within 20–60 min, with a plasma T½ of less than 5 min.[14,31,32] When given by i.v. infusion over a period of 30 min in patients with AML, the plasma T½ ranged from less than 3 min to 9 min after cessation of the infusion.[33] Frei et al.[34] showed a linear and steep dose–response curve when they gave ara-C continuous i.v. infusion for 48 or 96 hr in patients with various cancers. A continuous i.v. infusion of ara-C for 5 days in patients with AML resulted in a constant plasma level of the drug for the duration of the infusion after a plateau was achieved (which occurred between 8 and 24 hr after starting the infusion).[35]

The results of the present study are in conformity with the cell kinetics and pharmacologic considerations of ara-C in AML discussed above. Our results (Tables 3 and 4) demonstrate superiority of 7 and 3 infusion schedule over 7 and 3 bolus, 5 and 2 infusion and 5 and 2 bolus schedules. The 7 and 3 infusion schedule was the most effective for ages under and over 60 yr. Remission durations were significantly longer with subcutaneous ara-C in maintenance therapy than intravenous bolus ara-C, both given at the same dose q 12 hr for 5 days with the same accompanying drugs. This is consistent with the observation that plasma concentrations of ara-C fell rapidly in patients receiving the drug by i.v. bolus, and that peak blood levels were reached 1 hr after subcutaneous injection where they remained at a plateau for 6 hr.[36]

A recent report[37] of intensive sequential maintenance therapy in a younger population of patients with AML projects a 23-mo median duration of CR, a result consistent with the CR duration in the best combination of regimens (Fig. 3) in the present study conducted in an older population. The long-term results available from the present study (Table 6) lend further support to the therapeutic strategy of intensive sequential therapy for maintenance of remission. Of the 38 patients who were in continuous CR at 30 mo, an evaluation at 60 mo (when all patients had been off maintenance therapy for a period ranging from 6 mo to more than 2 yr) revealed that only 7 patients had relapsed by this time. These are very encouraging results in AML, which demonstrate that an increasing number of patients, off chemotherapy, are now disease-free survivors for longer than 5 yr. This trend presents a substantial progress in our movement towards a successful long-term control of acute myelocytic leukemia.

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