Comparison of Three Remission Induction Regimens and Two Postinduction Strategies for the Treatment of Acute Nonlymphocytic Leukemia: A Cancer and Leukemia Group B Study

By Harvey Preisler, Roger B. Davis, Jeffrey Kirshner, Eloise Dupre, Frederick Richards III, H. Clark Hoagland, Samuel Kopel, Robert N. Levy, Robert Carey, Phillip Schulman, Arlan J. Gottlieb, O. Ross McIntyre, and the Cancer and Leukemia Group B

Patients with acute nonlymphocytic leukemia were randomized to receive remission induction therapy consisting of seven days of cytosine arabinoside and three days of daunorubicin ("7 + 3") or to receive the same regimen intensified by either the addition of 6-thioguanine or by extension of the administration of cytosine arabinoside to ten days. Additionally, all patients were randomized to receive or not to receive cotrimoxazole antibacterial prophylaxis during the remission induction phase. Neither an increase in intensity of chemotherapy nor the antibacterial prophylaxis increased the remission rate above the 53% for patients treated with the standard "7 + 3" regimen.

The second part of this study addressed the issue of the utility of long-term maintenance chemotherapy. To this end, patients were randomized to discontinue all treatment after 8 months of maintenance chemotherapy or to continue maintenance therapy for a total of 3 years. Although there was a transient increase in the relapse rate for patients who discontinued therapy, the proportion of long-term remitters was identical in the two patient groups. Additionally, there is a suggestion of a survival advantage for patients randomized to discontinue all therapy at 8 months.

THE TREATMENT of acute nonlymphocytic leukemia (ANLL) consists of a remission induction phase designed to return hematopoiesis to normal and a postinduction phase designed to prolong the remission. The first part of the study to be reported here was designed to determine whether an increase in the intensity of the standard seven days of cytosine arabinoside and three days of daunorubicin (DNR) ("7 + 3") remission induction regimen used by the Cancer and Leukemia Group B (CALGB) since 1974[1,2] and/or the administration of cotrimoxazole antibacterial prophylaxis[3-5] would result in an increase in the complete remission (CR) rate. The second phase of the study was designed to determine whether prolonged maintenance therapy of moderate intensity during the postinduction phase was necessary.[6] Accordingly, all patients received maintenance chemotherapy for 8 months, at which time half were randomized to discontinue all therapy and the other half to continue monthly courses of maintenance therapy for a total of 3 years.

The data described in this paper demonstrate that neither an increase in the intensity of 7 + 3 therapy, as described here, nor the administration of cotrimoxazole results in an improvement in the CR rate and that maintenance chemotherapy beyond 8 months is unnecessary. In addition, data are presented that reinforce an earlier hypothesis that leukemic relapse may occur as a result of at least two distinct biologic processes.[7,8]

MATERIALS AND METHODS

Study Design

CALGB study 7921 was activated in November 1979 and was closed to accrual in November 1982.

Eligibility

Any patient with acute nonlymphocytic leukemia (ANLL) according to the criteria established by the French-American-British (FAB) working party was eligible for study.[9] Patients with life-threatening infections were eligible only upon control of such infections. Informed consent was required prior to entry into the study.

Patients were ineligible if they had inadequate renal function. Although the protocol specified maximum permissible levels of 30 mg/dL for BUN and 1.5 mg/dL for creatinine levels, a number of patients were entered who had levels slightly above these limits. Although technically ineligible, these patients were included in the study, with careful analyses being performed to determine whether they showed any differences in response or toxicity. Any patient whose BUN was >40 mg/dL or whose creatinine level was >2.0 mg/dL was excluded from analysis. Patients with a history of neoplastic disease and associated cytotoxic therapy were not eligible for randomization (See Statistical Methods).[10,11]

Treatments Under Study

Remission induction therapy. Figure 1A provides the schema for the induction phase of the study. Patients were initially randomized to induction therapy with the standard 7 + 3 regimen (cytosine arabinoside, 100 mg/m^2/d by continuous infusion for seven days, and DNR, 45 mg/m^2 on days 1, 2, and 3) or with induction therapy

From the Roswell Park Memorial Institute, Buffalo; Harvard School of Public Health and Dana-Farber Cancer Institute, Boston; Frontier Science and Technology Research Foundation, Buffalo; Bowman-Gray School of Medicine, Winston-Salem, NC; Mayo Clinic, Rochester, MN; Maimonides Medical Center, Brooklyn, NY; Long Island Jewish Medical Center, New Hyde Park, NY; Massachusetts General Hospital, Boston; North Shore University Hospital, Manhasset, NY; Upstate Medical Center, Syracuse, NY; and Norris Cotton Cancer Center, Hanover, NH.

Submitted May 19, 1986; accepted December 13, 1986.

Supported in part by Grants CA-02599, CA-33601, and CA-04326 awarded by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services and by a grant from the T.J. Martell Foundation. (See Appendix for additional grant support information.)

Address reprint requests to Harvey D. Preisler, MD, Department of Hematologic Oncology, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

0006-4971/87/6905-0027$3.00/0

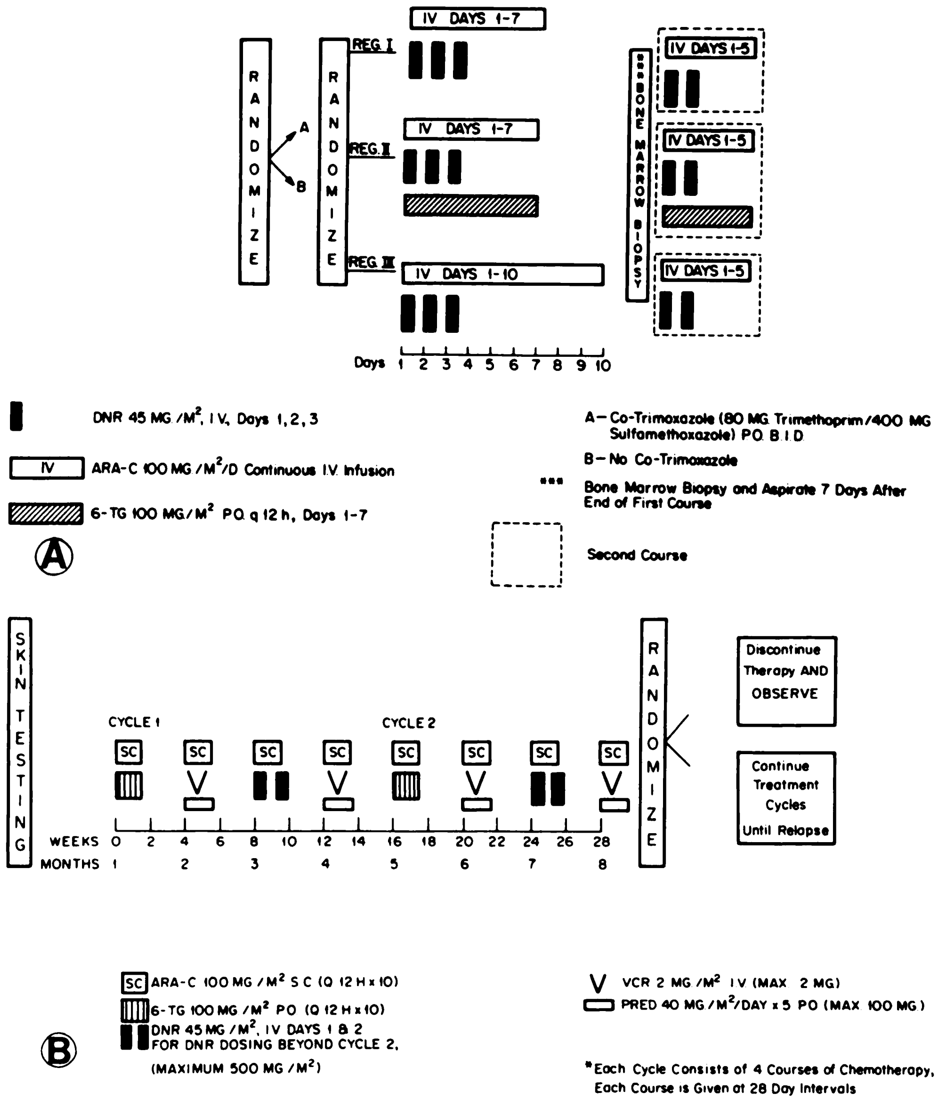

Fig 1. Treatment schema. (A) Remission induction phase. (B) Maintenance phase.

whose intensity was increased either by extending the administration of cytosine arabinoside to ten days ("10 + 3") or by the addition of 6-thioguanine (6-TG; TAD) at 100 mg/m^2 every 12 hours for seven days concurrent with cytosine arabinoside. These two modifications of the 7 + 3 regimen were based upon reports in the literature that the therapeutic efficacy of our standard regimen might be improved by extending cytosine arabinoside administration to ten days[12] or by the addition of 6-TG.[13-15]

A second course of therapy was administered, as indicated in Fig 1A, if the patient's leukemia failed to enter remission. The only exceptions were patients who achieved a partial remission and in whom the severity of toxicity during the first course of therapy was felt to preclude the administration of course 2. Half of the patients on each program were randomized to receive cotrimoxazole, two regular-strength tablets (80 mg trimethoprim and 400 mg sulfamethoxazole), by mouth twice a day starting on the day before initiation of chemotherapy and continuing until remission occurred or until the patient was removed from the study as a treatment failure.

The study was amended in November 1980 so that the DNR dose in all three regimens was reduced to 30 mg/m^2/d for patients over 60 years old. This modification was introduced as a consequence of the previous CALGB protocol in ANLL that suggested that this change would increase the CR rate and reduce the death rate for older patients.[2]

Patients who entered CR or partial remission following the second course of induction therapy advanced to the maintenance phase. The remaining patients were considered to be treatment failures and were removed from the study.

Dose reductions of 50% and/or dose interruptions were permitted for severe gastrointestinal toxicity, hepatic dysfunction, or renal dysfunction. A lumbar puncture was performed on the day prior to the initiation of chemotherapy and every 6 months for 5 years. If any leukemic cells were seen on a cytocentrifuge preparation, the patient received 50 mg of cytosine arabinoside intrathecally every four days until leukemic cells were no longer detectable in the CSF, and this was followed by the same dose of cytosine arabinoside every 4 weeks for 8 months.

Maintenance therapy. As indicated in Fig 1B, maintenance therapy consisted of a series of monthly five-day courses of combination chemotherapy. Each cycle was composed of four such courses. Sequential courses consisted of five days of administration of cytosine arabinoside together with 6-TG (course 1), prednisone/vincristine (courses 2 and 4), or DNR (course 3) administered on a rotating schedule. When a cumulative dose of 500 mg/m^2 of DNR was reached, the third course of each cycle was modified by replacement of DNR with 6-TG, 100 mg/m^2 orally every 12 hours for ten times.

Following two cycles of maintenance therapy (8 months), marrow aspiration and biopsy were performed. Patients who were still in CR at this time were randomized either to stop maintenance chemotherapy immediately or to continue maintenance for an additional seven cycles (for a total duration of maintenance therapy of 3 years) or until the time of relapse if that occurred before the seven cycles were completed.

Bone marrow aspiration was repeated every 4 months until relapse for all patients regardless of their maintenance treatment assignment.

Evaluation of Response

A CR was defined by the criteria previously reported by Rai et al.[1] In brief, a bone marrow aspirate had to contain <5% abnormal cells, with a normal cellularity and normal granulopoiesis, thrombopoiesis, and erythropoiesis. Additional requirements included a peripheral blood count within normal limits and clearing of all signs and symptoms attributable to leukemia.

Relapse was defined as a return of leukemic cells to the marrow in excess of 25%.

Statistical Methods

Patients who were clearly ineligible were excluded from this analysis. Patients who were registered but withdrawn prior to the initiation of protocol therapy and patients with no follow-up data after registration were also excluded. Patients with prior cancer were not eligible for randomization but were nonrandomly assigned to treatment with 7 + 3 without cotrimoxizole and have been excluded from this report. Seven hundred forty-nine patients were registered in the study. Their study status is shown in Table 1. Six hundred sixty-eight (95.8%) of the 697 patients with primary leukemia were eligible and evaluable.

The primary end points of interest for the induction questions were response rates and duration of survival. Analysis of these end points were stratified by age (60 and under *v* over 60). Comparisons of the three induction regimens were also stratified by the randomized assignment of cotrimoxazole, and the evaluations of this antimicrobial agent were stratified by the induction regimen assigned.

For the maintenance phase of the study, the primary end points were time to relapse and survival. Both end points were measured from the date of CR and from the time of maintenance randomization (ie, after two cycles of maintenance). These comparisons were stratified by the induction chemotherapy regimen assigned since the maintenance randomization was stratified in that way.

All *P* values reported are two sided. Survival and response duration curves as well as any rates computed from these curves were calculated by using the life table method (product limit estimator) of Kaplan and Meier.[16] Survival comparisons were made using the Mantel-Haenszel (log rank) test.[17] The chi-square test for contingency tables was used for overall comparisons of response rates across strata.[18]

A number of patients were deemed "not evaluable for response," usually as a result of inadequate documentation of marrow status posttreatment. For purposes of estimating and comparing response rates, a conservative approach was used with respect to these patients. They were assumed to have been treatment failures, ie, they were included in the denominators of the rates, but not in the numerators.

A number of patients entered bone marrow transplantation programs prior to completion of this study. Patients who entered transplantation programs while in their initial remission were considered censored at the date of entry into that program for calculation of the remission duration but continued to be followed for survival.

Toxicity of the treatments under study was assessed by using previously reported CALGB toxicity criteria.[2] Specific comparisons of infection rates between the cotrimoxazole-treated and the control groups were used to determine the efficacy of prophylactic administration of cotrimoxazole.

Table 1. Study Status of Patients in the Study

	With Cotrimoxazole			Without Cotrimoxazole			
	7 + 3	TAD	10 + 3	7 + 3	TAD	10 + 3	Total
Patients entered							749
Prior cancer							52
Patients randomized	106	110	119	116	111	135	697
Ineligible	1	2	2	5	2	5	17
Cancelled	1	1	3	1	0	1	7
No follow-up	2	0	0	1	0	2	5
Cases analyzed	102	107	114	109	109	127	668

RESULTS

Remission Induction Therapy

The Outcome of Remission Induction Therapy

Fifty-six percent of the 668 eligible patients entered CR, 4% achieved a partial remission, 24% expired during therapy, 14% survived but did not enter remission, and 1% were inevaluable because of a lack of definitive marrow studies. The CR rates for 7 + 3, TAD, and 10 + 3 regimens were 52.6%, 56.9%, and 57.3%, respectively (Table 2) ($P = .6$). Fewer patients treated with 10 + 3 required two courses of therapy to enter remission (15% of complete responders) than did patients treated with 7 + 3 (29%) or TAD (28%) ($P = .011$), but the median time to remission was not significantly different for the three regimens (10 + 3, 4.8 weeks; 7 + 3, 4.4 weeks; TAD, 4.1 weeks). The toxicity of the three regimens was identical, with all patients experiencing life-threatening hematopoietic toxicity, and 7% to 11% of patients experiencing severe or life-threatening renal, hepatic, and/or cardiac toxicity.

Three hundred twenty-three patients were randomized to receive cotrimoxazole, and 345 patients were randomized to receive no antimicrobial prophylaxis during remission induction therapy. The CR rate was 56% whether or not the patient received cotrimoxazole. In addition, cotrimoxazole

Table 2. Outcomes of Remission Induction Therapy

	"7 + 3"	TAD	"10 + 3"
Number of patients	211	216	241
CR	111 (53)*	123 (57)	138 (57)
Partial remission†	13 (6)	6 (3)	10 (4)
No response alive†	38 (18)	31 (14)	26 (11)
Expired‡	45 (21)	55 (26)	63 (26)
Not evaluable	4 (2)	1 (0.5)	4 (2)

*Number of patients (%).

†Patients whose leukemia proved to be resistant to the chemotherapy administered.

‡Death during remission induction therapy.

had no effect on patient survival or on the toxicity associated with each of the chemotherapy treatment arms.

Prognostic Factors for the Outcome of Remission Induction Therapy

Table 3 lists the patient characteristics that were evaluated for possible relationship to the outcome of remission induction therapy. Only five of these 20 characteristics were significantly related to treatment outcome, and one was of borderline significance (Table 4). Age was by far the single most important factor, with only 41% of 104 patients >60 years old entering remission as compared with 65% of patients ≤60 years old ($P < .00001$). The next most important factor was serum creatinine levels. Only 36% of patients with a creatinine level of 1.6 to 2.0 mg/dL entered remission as compared with 56% for patients whose creatinine level was <1.6 ($P = .006$). An SGOT level of ≥40 mU/mL was associated with a CR rate of 47% compared with 59% for patients whose SGOT level was <40 mU/mL. A WBC count at diagnosis of >100,000/μL was associated with a CR rate of only 38% as compared with 58% for patients with a count below this value ($P = .041$). The presence of skin or gingival involvement was an unexpectedly good prognostic sign, being associated with a CR rate of 68% as compared with a CR rate of 54% for patients without such extramedullary involvement ($P = .032$).

Forty-three percent of patients presented without fever or infection. These patients tended to have a higher CR rate than the 57% of patients who were febrile and/or had a documented infection at the time of diagnosis (60% *v* 52.6% CR rates respectively, $P = .07$). The presence of severe infection was also of prognostic significance, being associated with a CR rate of only 40% as compared with a CR rate of 57% for patients without severe infection ($P = .057$). The administration of cotrimoxazole had no effect on the outcome of treatment or on the survival of patients whether or not they were afebrile or febrile, infected or not infected at diagnosis. The incidence of severe or life-threatening infection during induction therapy for patients who were afebrile at diagnosis was reduced from 73% to 59% by the administration of cotrimoxazole ($P = .013$), but as noted earlier, this had no effect on treatment outcome. Table 5 provides information regarding the types of infection experienced by patients who received or did not receive cotrimoxazole. Bacterial infections were the predominant cause of first infections. Fungal infections were frequent causes of second infections and were more common in the cotrimoxazole group (50%) than in the control group (29%).

Table 3. Patient Characteristics at Diagnosis Evaluated for Potential Prognostic Significance

Age	Infection
Sex	CNS involvement
Race	Skin or gingival involvement
	Hepatomegaly
WBC count	Splenomegaly
Number of circulating leukemic cells	Lymphadenopathy
Hematocrit	BUN
Hemoglobin level	Creatinine
Platelet count	SGOT
Bleeding	Bilirubin
Temperature	

Table 4. Factors of Prognostic Significance

	Remission Induction Outcome	Remission Duration	Survival
Age	<.00001	.023	<.0001
WBC count	.041	NS	.013
Infection	.057	NS	.008
Skin or gingival involvement	.032	NS	NS
Creatinine	.006	NS	.016
SGOT	.018	NS	.0001
Hemoglobin	NS	.001	.008

Results are *P* values using univariate analysis.
Abbreviation: NS, not significant.

Miscellaneous Observations Regarding the Outcome of Remission Induction Therapy

One year after the study was initiated, the protocol was modified so that patients >60 years of age would receive 30 mg/m²/d of DNR rather than 45 mg/m²/d. One hundred eleven patients in this age group received the higher DNR dosage, whereas 139 patients received the lower dosage. Although the CR rates were not significantly different (39% *v* 43% respectively), fewer patients treated at the lower dosage died during therapy (31% *v* 45% respectively, $P = .028$).

Table 5. Types of Induction Infections

	With Cotrimoxazole (n = 323)		Without Cotrimoxazole (n = 345)	
	Severe* Infection	Life-Threatening Infection†	Severe Infection	Life-Threatening Infection
First induction infection‡				
Bacterial	14	20	14	40
Fungal	6	11	5	9
Viral	3	0	1	1
Multiple	2	3	1	5
FUO	37	5	49	6
Type not reported	54	25	66	13
Second induction infection				
Bacterial	3	20	4	28
Fungal	9	14	6	7
Viral	0	0	1	0
Multiple	0	3	0	3
FUO	4	0	7	1
Type not reported	19	5	23	12

Abbreviation: FUO, fever of undetermined origin.
*Local or visceral infection with systemic signs and/or a fever of 38°C.
†Fulminant local or visceral infection with sepsis, shock, or other system failure.
‡Type of infection documented by culture or by biopsy.

Remission Duration

Figure 2A provides the remission duration curve for all patients who entered CR. The median was 52.4 weeks; 22% of patients were projected to be in remission at 3 years. There was no statistically significant difference in remission duration between patients treated on the three induction arms. The overall remission duration was related to the number of courses necessary to induce a CR. Patients who required a single course of therapy had longer remissions than those who required two courses (median remission durations of 55.9 *v* 45.4 weeks respectively, $P = .02$). Patients who entered partial remission status relapsed at a median of 20.7 weeks, with no patient remaining in this status beyond 100 weeks.

One hundred forty-eight patients relapsed or died before reaching the point of second randomization to stop or to continue maintenance therapy. Of the remaining patients, 151 were randomized, and 73 were not. There were no statistically significant differences in remission duration between patients who were or were not randomized. The median duration of remission for all patients after randomization was 67 weeks, with 38% of patients projected still to be in remission 3 years later (Fig 2b). This figure also provides the remission duration curve for patients randomized to continue or to stop therapy. The curves diverged 3 months after randomization but converged and became persistently superimposable 75 weeks after randomization. The median time to relapse after randomization for patients in whom therapy was discontinued was 45 weeks compared with 71 weeks in patients who continued therapy ($P = .62$). The type of remission induction therapy had no statistically significant effect on the time to relapse for patients randomized to stop or to continue maintenance chemotherapy.

Toxicity Associated With Maintenance Chemotherapy

Toxicity data were available for 329 patients for the first cycle of maintenance therapy and for 220 patients on the second cycle. Seventy-five percent of patients experienced severe or worse hematologic toxicity at some time during cycle 1 with a reduction of the blood counts to life-threatening levels (WBC count reduced to $<1{,}000/\mu L$, granulocyte count to $<500/\mu L$, and/or platelet count to $<25{,}000/\mu L$) occurring in 51% of patients. Sixty-six percent of patients who received cycle 2 of therapy had severe hematologic toxicity, with 31% having life-threatening reductions in blood counts to the levels just described.

Death in remission occurred only during cycles 1 and 2 and was clearly age related, with a 3% death rate in remission for patients <40 years old, 9% for patients 41 to 60 years old, and 14% for patients >60 years old ($P = .03$).

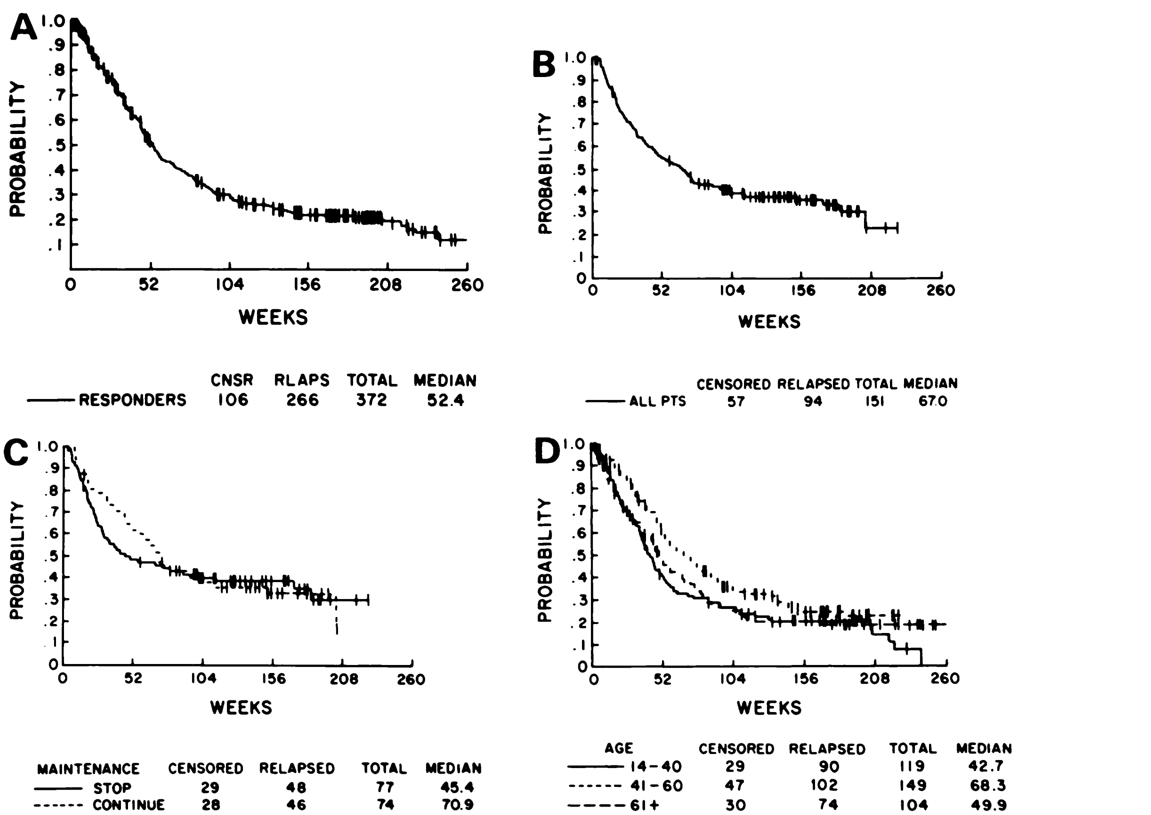

Fig 2. Remission duration. (A) Remission duration curve for all patients whose leukemia entered CR. (B) Remission duration subsequent to randomization to stop or continue maintenance therapy—all patients—and (C) relationship of remission duration to the cessation or continuation of chemotherapy beyond 8 months. (D) Relationship between age and remission duration.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

WHAT WILL YOU BUILD? | **sales@docketalarm.com** | **1-866-77-FASTCASE**

fastcase® Smarter legal research.