# A Comparative Study of Two Different Doses of Cytarabine for Acute Myeloid Leukemia: A Phase III Trial of Cancer and Leukemia Group B

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**Between 1982 and 1986, 326 evaluable patients with acute myeloid leukemia (AML) were randomized to receive cytarabine (Ara-C) at 200 mg/m² (A200) or 100 mg/m² (A100) for induction and maintenance therapy. Cycle 1 of induction therapy consisted of 7 days of continuous intravenous (IV) Ara-C and 3 days of IV daunorubicin (DNR); cycle 2, if needed, consisted of 5 days of Ara-C and 2 days of DNR. Complete responders (CR) then received monthly subcutaneous (SC) Ara-C at the respective doses (A100 or A200) with 6-thioquanine (6TG) at months 1 and 5, with vincristine (VCR) and prednisone at months 2, 4, 6, and 8, and with DNR at months 3 and 7. Complete response rates were 58% (A100) and 64% (A200) (*P* = .29). Median survival was 46 weeks (A100) and 38 weeks (A200) (*P* = .64); 5-year survival was 10% (A200) and 8% (A100). Median time to remission was 6.7 weeks (A200) and 8.1 weeks (A100) (*P* = .18). Median disease-free survival was 41 weeks (A200) and 44 weeks (A100) (*P* = .86). Deaths were attributed to therapy-related toxicities in 21% (A200) and 13% (A100) (*P* = .05). The 5-year survival was 15% for patients with performance status (PS) 0, 8% for PS 1 to 2, and 2% for PS 3 to 4, 18% for patients less than 40 years, 8% for ages 40 to 59, and 3% for age 60 or greater. Stratification of data by age and PS suggested that A200 may improve survival in patients less than 60 years with a good PS 0 (*P* = .05). This trial does not support the superiority of A200 over A100 in the treatment of AML.**



DESPITE IMPROVED survival, the management of acute myeloid leukemia (AML) remains unsatisfactory. Modern chemotherapy regimens typically produce a response rate of approximately 65%, median survival of about 1 year, and long-term survival of 20%.[1,2] However, age is a crucial variable, with younger patients having much better response rates and better survival.[3,4] Prior Cancer and Leukemia Group B (CALGB) studies established the utility of cytarabine (Ara-C) and daunorubicin (DNR) in the management of AML.[5] CALGB 7421 showed that induction therapy with 7 days of Ara-C and 3 days of anthracycline (7 and 3) was superior to 5 days of Ara-C and 2 days of anthracycline (5 and 2).[6] CALGB 7721 demonstrated that DNR was less toxic than doxorubicin (DOX), while comparable in efficacy, and a DNR dose of 30 mg/m² was less toxic than 45 mg/m² for patients over the age of 60.[7] CALGB 7921 showed that 10 days of Ara-C was no better than 7 days of Ara-C, and the addition of a third agent, 6-thioguinine (6TG), provided no advantage over the 7 and 3 two-drug regimen.[8]

In vitro studies with leukemia cells have consistently suggested that higher doses of Ara-C are more cytotoxic.[9] A pilot study suggested that a dose of 200 mg/m² Ara-C might produce a higher response rate than 100 mg/m² Ara-C.[3] In 1982, CALGB embarked on a clinical trial comparing the efficacy of these two different Ara-C doses in AML.

## MATERIALS AND METHODS

*Eligibility.* This study was conducted in CALGB institutions after approval by their Institutional Review Boards, and in accord with assurances filed with, and approved by, the Department of Health and Human Services. Eligible patients had to have a diagnosis of AML by the French-American-British (FAB) classification as it was defined at that time based on morphology and histochemical stains.[9] Patients with a prior history of neoplasia, preleukemia, or myelodysplastic syndrome were eligible if they met FAB criteria of leukemia (>30% blasts). Patients had to have a blood urea nitrogen (BUN) less than or equal to 30 mg/dL and a creatinine less than 2.0 mg/dL.

*Study design.* From November 1982 to February 1986, a prospective randomized trial comparing two different doses of Ara-C in AML was conducted. Induction chemotherapy was followed by maintenance chemotherapy for responders (Fig 1). Patients were stratified by age 60 years, and randomized to receive Ara-C at doses of 100 mg/m² (A100) or 200 mg/m² (A200). After June 24, 1984, patients 60 years or older were no longer randomized, because an interim analysis indicated that the A200 arm could not be superior for this age group. Subsequently, elderly patients were assigned to the A100 arm. DNR was administered at 30 mg/m² for patients 60 years or older, because of enhanced toxicity at 45 mg/m² in older patients.[7] Bone marrow aspirate and biopsy were repeated 1 week after completion of the first induction course. Patients who still had greater than 5% leukemia cells and 25% cellularity were administered a second course of chemotherapy. Patients who were aplastic following the initial induction cycle underwent weekly marrow analysis until persistent leukemia or remission was shown. Those who failed to achieve an M0/M2 marrow after two cycles went off study. Patients with an M0/M1 marrow (0% to 5% myeloblasts, and 0% to 10% myeloblasts plus promyelocytes, and normalization of peripheral blood counts) after induction or an M2 marrow (5% to 25% blasts and 10% to 30% myeloblasts and promyelocytes) with normal peripheral blood

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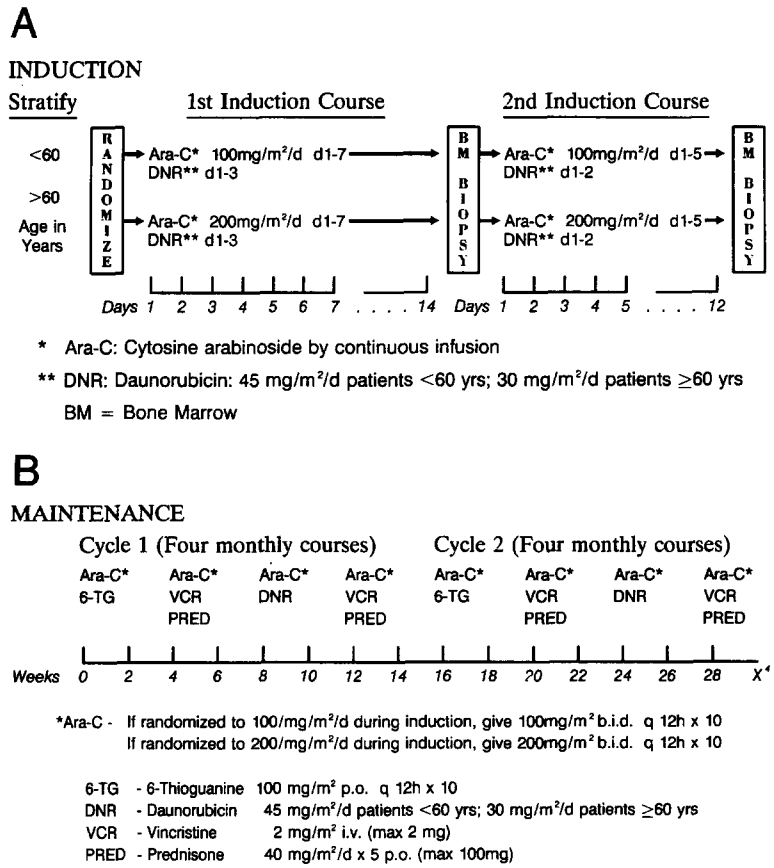


**Fig 1. Treatment schema for 8321: (A) induction and (B) maintenance.**

counts after induction, received eight courses of monthly maintenance chemotherapy (Fig 1).

*Dose modifications.* There were no dose reductions based on blood counts during induction therapy. Platelets were transfused prophylactically for counts less than 20,000/μL. Antibiotics were administered empirically, but not prophylactically. Patients unable to eat because of mouth ulceration and pain subsequently received Ara-C at a 50% dose reduction. Patients with an increase in bilirubin, transaminases, or alkaline phosphatase to twice baseline had 50% dose reductions applied to Ara-C, DNR, and 6TG. During maintenance, doses of vincristine (VCR), 6TG, and DNR were reduced by 50% for bilirubin 3 to 5 mg/dL and withheld for bilirubin greater than 5 mg/dL.

During maintenance, full drug doses were administered for granulocyte counts greater than 2,000/μL and platelets greater than 100,000/μL; therapy was delayed 1 week for lesser counts. If counts recovered, full doses were given; if not, the bone marrow was re-examined. If there was no leukemia, but greater than 50% cellularity, therapy was administered at a 50% dose reduction. If there was no leukemia and less than 50% cellularity, treatment was held until cellularity was greater than 50%, granulocytes greater than 2,000/μL, and platelets greater than 100,000/μL, then therapy was resumed at a 50% dose reduction. If the granulocyte nadir was less than 1,000/μL, platelets less than 30,000/μL, and/or severe infection or hemorrhage occurred, all subsequent doses were reduced by 50%. VCR was reduced by 50% for decreased muscle strength or persistent parasthesias, and withheld in the presence of more severe disability until neurologic symptoms had resolved.

*Central nervous system (CNS) evaluation and treatment.* Lumbar puncture was performed at diagnosis and repeated every 6 months for 5 years. If leukemia was present, intrathecal (IT) treatment with 50 mg Ara-C was administered every 4 days until leukemia cells were absent for three successive treatments. Subsequently, these patients received IT therapy monthly for 8 months. In those patients whose leptomeningeal leukemia persisted after two doses of IT Ara-C, 12 mg of IT methotrexate was administered. If leukemia cells still persisted after two doses of methotrexate, 2,400 cGy craniospinal radiation was administered by external beam, and maintenance chemotherapy was administered with an initial 50% dose reduction.

*Statistical methods.* Patient characteristics were compared using the Wilcoxon test for continuous variables,[11] and appropriate exact tests for unordered categorical data[12] and ordered categorical variables.[13] Key end points for analysis were complete response, survival time, and time to relapse. Patients who achieved M0/M1 with normal peripheral blood counts were considered complete responders (CR), and those who achieved M2 were considered partial responders (PR). Patients who achieved an M0/M1 marrow were considered to have relapsed if a bone marrow subsequently showed 25% or greater blasts and promyelocytes. For patients who reached only M2, relapse was defined by 25% or greater blasts or at least twice the percentage of blasts and promyelocytes than the percentage present at the time the patient started maintenance therapy. Physicians were asked to categorize patients who died during induction therapy into one of three groups: (1) death with residual leukemia; (2) death during marrow aplasia; and (3) death with marrow status indeterminate.

Treatment assignments were determined by a permuted blocks randomization with institutional balancing. Survival curves were calculated by the method of Kaplan and Meier.[14] The log rank test was used for comparison of survival curves.[15] Categorical outcomes

**Table 1. Patient Characteristics for CALGB 8321**

| | Ara-C Dose | | |
|---|---|---|---|
| | 100 mg | 200 mg | *P* Value |
| No. of patients | 160 | 166 | |
| Age (yr) | | | .47 |
| Median | 54 | 51 | |
| Range | 16-81 | 15-83 | |
| <40 | 41 (26) | 53 (32) | |
| 40-59 | 69 (43) | 63 (38) | |
| ≥60 | 50 (31) | 50 (30) | |
| Sex | | | .44 |
| Male | 90 (56) | 86 (52) | |
| Female | 70 (44) | 80 (48) | |
| Histology (FAB) | | | .16 |
| M1 | 36 (22) | 41 (25) | |
| M2 | 35 (22) | 50 (30) | |
| M3 | 11 (7) | 10 (6) | |
| M4 | 68 (42) | 50 (30) | |
| M5 | 8 (5) | 11 (7) | |
| M6 | 1 (1) | 4 (2) | |
| M7 | 1 (1) | 0 (0) | |
| PS | | | .07 |
| 0 | 61 (38) | 46 (28) | |
| 1 | 48 (30) | 56 (34) | |
| 2 | 31 (19) | 40 (24) | |
| 3 | 18 (11) | 21 (13) | |
| 4 | 2 (1) | 3 (2) | |

Percentages in parentheses.

such as response rates were compared using exact tests or 2 × 2 tables.[16] All statistical tests for primary treatment comparisons were stratified by patient age less than 60 or 60 or greater years.

Time to failure was measured from study entry until the first event, including removal from study for failure to respond, death, or relapse. Survival was measured from study entry until death or the date the patient was last known to be alive. Disease-free survival was computed only for patients who achieved a CR and was measured from the date of CR to relapse or death, whichever occurred first. Patients (four in A200, and one in A100) who entered bone marrow transplant programs before reaching an end point in the study were censored from analyses at that time.

Some analyses were made by grouping patients according to performance status (PS). At study entry, patients were categorized as having PS 0 (fully active), PS 1 (restricted in physically strenuous activity, but ambulatory and able to perform light work), PS 2 (ambulatory and capable of all self care, but unable to perform any work activities, up and about >50% of waking hours), PS 3 (capable of only limited self care, sedentary >50% of waking hours), or PS 4 (completely disabled, unable to perform any self care, sedentary).

## RESULTS

There were 345 patients randomized to CALGB 8321; 326 were eligible and evaluable for study end points. There were six ineligible patients in A100 and five in A200; two were in the blast phase of chronic myeloid leukemia, three had acute lymphoid leukemia (ALL), two had biphenotypic leukemia (mixed AML and ALL), one had undifferentiated leukemia, one had an elevated blood urea nitrogen, and one did not have a pretreatment bone marrow. There were four pretreatment cancellations from A200 and 2 from A100; no follow-up data were available for two patients in A100. This left 160 patients in A100 and 166 in A200 for analysis.

The characteristics of eligible patients are summarized in Table 1; their clinical features are summarized in Table 2 by treatment. The treatment groups were well balanced, with the exception that the *P* value associated with PS suggested a possible imbalance for that characteristic. Also, a somewhat greater number of patients with M4 histology were randomized to A100 (42% *v* 30%, $P = .03$). Subsets of patients with M4 (those with marrow eosinophilia) may have a better prognosis.[17] Data forms used in this trial did not identify patients who had preleukemic syndromes. Standard karyotypic analysis was not available on all patients and not a requirement at the time this trial was conducted.

Response rates and death rates following induction therapy are grouped by age for each regimen in Table 3. The CR rate among all patients was 61%. Response rates stratified by age were not different for the two treatment groups ($P = .29$). The difference in CR rate for the two regimens did not differ in older patients ($P = .68$) or for patients less than 60 years of age ($P = .08$). Patients classified as "off-study, no response" or "death with leukemic marrow" in Table 3 could have had more resistant

**Table 2. Clinical Features at Study Entry for Patients Enrolled in CALGB 8321**

| | Ara-C Dose | | |
|---|---|---|---|
| | 100 mg | 200 mg | *P* Value |
| No. of patients | 160 | 166 | |
| Hemoglobin (g/dL) | | | .37 |
| Median | 9.3 | 9.2 | |
| Range | 2.2-16.4 | 3.1-14.1 | |
| Leukocytosis ($10^3$ cells/μL) | | | |
| Median | 14.2 | 17.3 | .74 |
| Range | 0.4-220 | 0.5-600 | |
| Platelets ($10^3$ cells/μL) | | | .48 |
| Median | 59.0 | 51.0 | |
| Range | 5.0-476 | 5.0-591 | |
| Infection | | | .71 |
| None | 93 (58) | 93 (56) | |
| Mild | 30 (19) | 29 (17) | |
| Moderate | 29 (18) | 40 (24) | |
| Severe | 7 (4) | 4 (2) | |
| Life-threatening | 1 (12) | 0 (0) | |
| Hemorrhage | | | .33 |
| None | 99 (62) | 92 (55) | |
| Petechiae/ecchymosis | 41 (26) | 52 (31) | |
| Active–no transfusion | 2 (1) | 8 (5) | |
| Required transfusion | 18 (11) | 14 (8) | |
| Bone marrow cellularity: | | | .70 |
| Hypocellular | 7 (4) | 6 (4) | |
| Normocellular | 3 (2) | 5 (3) | |
| Hypercellular | 82 (51) | 81 (49) | |
| Packed | 65 (41) | 72 (43) | |
| Not reported | 3 (2) | 2 (1) | |
| Extramedullary involvement | 62 (39) | 66 (40) | .91 |
| CNS | 18 (11) | 11 (7) | .17 |

Percentages in parentheses.

**Table 3. Response to Induction Therapy by Regimen and Age**

| | Ara-C Dose | | | |
|---|---|---|---|---|
| | <60 yr | | >60 yr | |
| | 100 mg | 200 mg | 100 mg | 200 mg |
| No. of patients | 110 | 116 | 50 | 50 |
| CR | 70 (64) | 87 (75)* | 22 (44) | 19 (38)† |
| PR | 8 (7) | 5 (4) | 2 (4) | 2 (4) |
| Off study, alive, no response | 15 (14) | 6 (5) | 6 (12) | 6 (12) |
| Died, leukemic marrow | 9 (8) | 11 (9) | 15 (30) | 13 (26) |
| Died, aplastic marrow | 6 (5) | 6 (5) | 4 (8) | 7 (14) |
| Died, marrow status unknown | 2 (2) | 1 (1) | 1 (2) | 3 (6) |

Percentages in parentheses.
*$P$ = .08.
†$P$ = .68.

disease. The distribution of such patients was 36 of 166 (22%) in A200 compared with 45 of 160 (28%) in A100 ($P$ = .22). There was no apparent difference between treatment groups in the proportion of patients dying during induction therapy with a leukemic marrow or aplastic marrow.

Of the 198 patients who achieved CR, 70% achieved CR after one induction course, while 30% required a second. Overall, there was no difference between treatments in the proportion going into CR after one course (39% for A100 *v* 45% for A200, $P$ = .88). There was also no difference between treatments for the 157 patients less than 60 years of age who went into CR after one induction course (74% for A200 *v* 69% for A100, $P$ = .59). Table 4 shows the correlation between certain patient characteristics and achieving CR. Younger age and excellent PS were more likely to be associated with a CR.

There have been 297 deaths, and the remaining 29 patients have been monitored for a median of 5.2 years, with a range of 2.8 to 7.1 years. There were no differences between treatment groups in survival (Fig 2, $P$ = .64), failure-free survival ($P$ = .33), or disease-free survival for patients achieving a CR (Fig 3). There was also no

**Table 4. Number of Patients With CR by Selected Characteristics**

| | CR | *P* Value |
|---|---|---|
| Age (yr) | | |
| <40 | 74/94 (79) | <.0001 |
| 40-59 | 83/132 (63) | |
| ≥60 | 41/100 (41) | |
| FAB | | |
| M1 | 40/77 (52) | .39 |
| M2 | 55/85 (65) | |
| M3 | 13/21 (62) | |
| M4 | 76/118 | |
| M5 | 12/19 (63) | |
| M6 | 2/5 (40) | |
| M7 | 0/1 (0) | |
| PS | | |
| 0 | 77/107 (72) | .01 |
| 1 | 57/104 (55) | |
| 2 | 41/71 (58) | |
| 3 or 4 | 23/44 (52) | |

Percentages in parentheses.

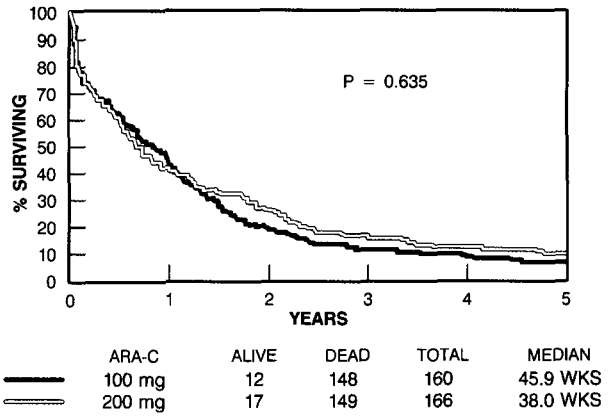


**Fig 2. Overall survival by treatment.**

difference in survival between the two regimens in either age stratum (Fig 4). However, survival curves for three different age groups (Fig 5) and four PS groups (Fig 6) showed striking survival advantages for patients less than 40 years of age and patients with PS 0 at initiation of therapy. There was no difference when survival was examined by FAB histologic type ($P$ = .37). Additional analyses that stratified patients by age and PS suggested that patients less than 60 years who entered with PS 0 had superior survival if treated on A200 ($P$ = .05).

As expected, the major chemotherapy complication observed in this trial was bone marrow suppression associated with infection and/or hemorrhage. However, it is virtually impossible to distinguish between the marrow suppressive effects of leukemia and the marrow suppressive effects of cytotoxic drugs. During induction therapy, there were 78 deaths. As shown in Table 3, 43 of these deaths (62%) were associated with residual leukemia, 23 (29%) were associated with an aplastic marrow, and marrow status was indeterminate in seven (9%). Forty-nine deaths were attributed to induction therapy and an additional six deaths were attributed to maintenance therapy.

The distribution of therapy-related deaths by age group

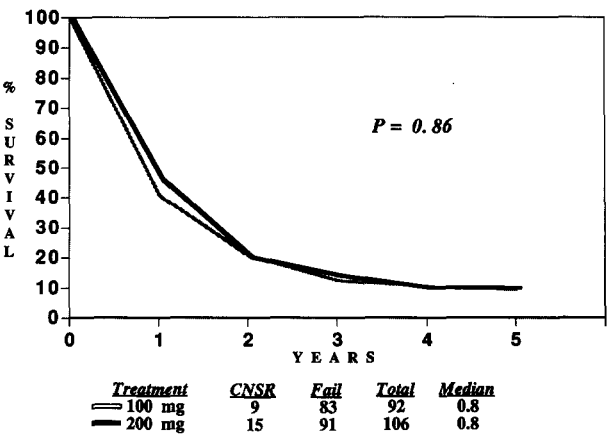


**Fig 3. Disease-free survival for patients who had achieved complete remission. Duration was calculated from the date of achieving complete remission.**

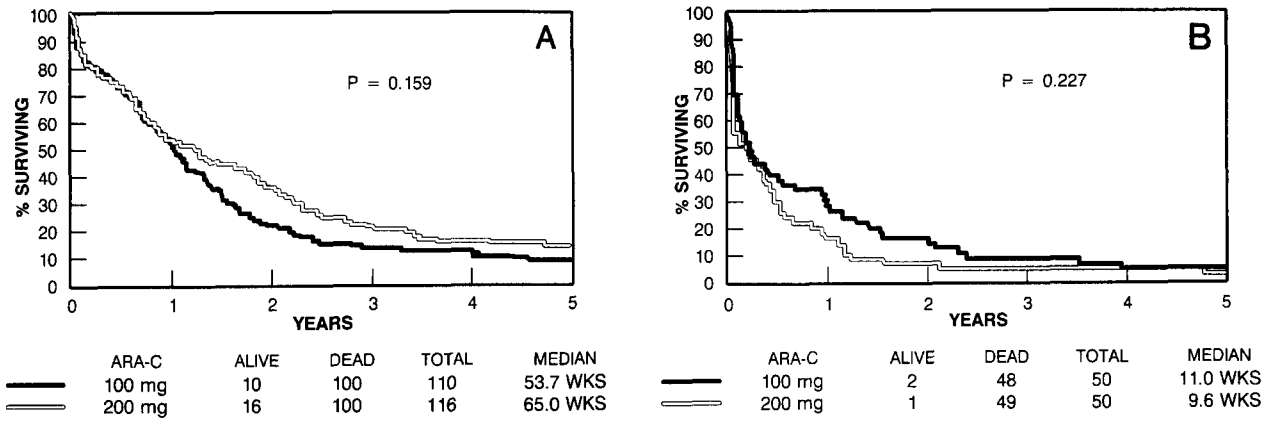


**Fig 4. Survival for patients <60 years (A) and ≥60 years (B).**

and therapy is shown in Table 5. A200 was associated with more deaths attributed to therapy for patients less than 60 years ($P = .04$ during induction, $P = .08$ during maintenance, and $P = .03$ overall). There was no difference between treatments for therapy-related deaths in patients age 60 years or older. For all patients, regardless of age, the therapy-related death rate was 21% for A200 and 13% for A100 ($P = .054$).

During induction therapy, life-threatening or fatal CNS toxicities were seen in six patients in A100 and five in A200 among patients less than 60 years, while for patients 60 years or older, such toxicity was seen in three patients in A200 and one in A100. Life-threatening hepatic injury was seen in two patients less than 60 (both in A200) during induction. In patients 60 or older, life-threatening liver damage was noted in one patient in A100 and five in A200.

Because significant Ara-C levels are measurable in cerebral spinal fluid after intravenous (IV) injection, it had been proposed that higher doses of Ara-C might provide greater protection against CNS relapse. Among CRs, there were four of 72 (6%) who relapsed in the CNS in A100 and three of 106 (3%) in A200 group ($P = .70$).

## DISCUSSION

There has been extensive investigation regarding the dose and schedule of Ara-C delivery for treatment of AML.[5-7,18-20] The current study tested the hypothesis that doubling the dose of Ara-C to 200 mg/m$^2$ might be superior because of the intensification of dose during induction and maintenance. The results of CALGB 8321 provide no evidence that a twofold increase in Ara-C dose is superior to 100 mg/m$^2$ of Ara-C in terms of CR rate, time to CR, overall survival, failure-free survival, duration of relapse-free survival, or frequency of relapse in the CNS. There was still no detectable difference in survival when subsets of patients less than 60 years of age and 60 or greater were analyzed for the effects of therapy, although there may be a higher CR rate in younger patients.

This study confirms previous observations regarding the significance of age and PS in predicting response and survival in AML.[3,4] Younger patients have higher CR rates and longer survival than older age groups. These observations complicate interpretation of data purporting to demonstrate improved survival resulting from bone marrow

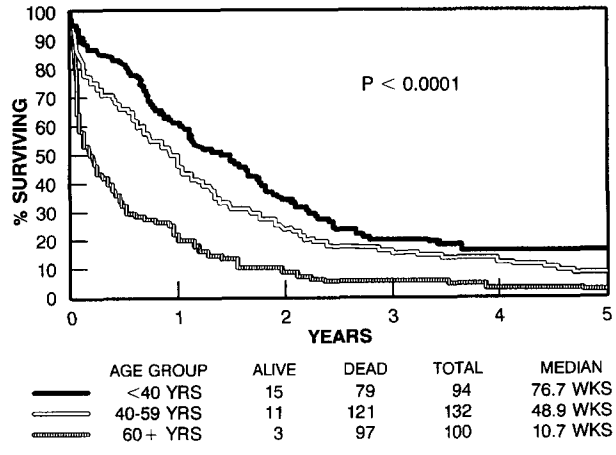


**Fig 5. Survival for three different age groups regardless of therapy.**

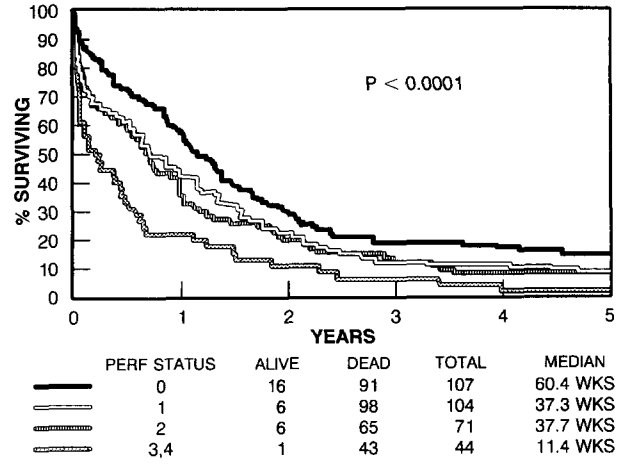


**Fig 6. Survival by performance level regardless of therapy.**

**Table 5. Deaths Attributed to Therapy in CALGB 8321**

| | <60 yr | | ≥60 yr | |
|---|---|---|---|---|
| | A100 | A200 | A100 | A200 |
| Induction | (N = 110) | (N = 116) | (N = 50) | (N = 50) |
| Infection | 6 | 10 | 10 | 9 |
| Hemorrhage | 1 | 3 | 0 | 2 |
| Both | 0 | 2 | 1 | 0 |
| CNS | 0 | 0 | 0 | 1 |
| Cardiopulmonary | 0 | 0 | 1 | 3 |
| Both | 1 | 0 | 0 | 0 |
| Total | 7 (6%) | 15 (13%) | 12 (24%) | 15 (30%) |
| | ($P$ = .04) | | ($P$ = .51) | |
| Maintenance | (N = 67) | (N = 83) | (N = 19) | (N = 15) |
| Infection | 0 | 4 | 0 | 0 |
| Hemorrhage | 0 | 0 | 1 | 0 |
| Both | 0 | 0 | 0 | 1 |
| Total | 0 (0%) | 4 (5%) | 1 (5%) | 1 (7%) |
| | ($P$ = .08) | | ($P$ = .33) | |

transplantation, because that approach is typically restricted to younger patients who have already exhibited a good response to induction chemotherapy.[21] Survival in leukemia is also better for patients who have an excellent PS. It is only when our data are analyzed for groups of patients with a young age and an excellent PS that any survival advantage could be ascertained for either regimen. Patients less than 60 years of age with PS 0 randomized to A200 had a better survival than similar patients randomized to A100.

Higher doses of Ara-C may increase prolonged marrow aplasia, neurologic toxicity,[22] or hepatic toxicity.[23] If such increases in toxicity were offset by an increase in long-term survival, they would be acceptable from a risk/benefit standpoint. Unfortunately, in the setting of leukemia and cytotoxic therapy, it is difficult to clearly distinguish deaths due to leukemia from those due to therapy. However, there were more deaths attributed to toxic effects of therapy in the A200 arm during both induction and maintenance for patients less than 60 years. Our data do not reflect a direct correlation between "aplastic death" and "toxic death."

The long-term survival results of this trial are similar to those seen in CALGB 7921.[8] The overall 5-year survival of only 10% is disappointing and emphasizes the need for continued investigation of therapeutic regimens that may improve long-term survival. Our study failed to show a therapeutic advantage for doubling the dose of Ara-C. However, it did not address the potential for higher Ara-C doses, perhaps given by different schedules, that might produce a higher response rate and a better survival, perhaps with equivalent or even less toxicity. Other studies have suggested that much higher doses of Ara-C may be advantageous when used during induction[18,24] or as an intensification after remission has been achieved.[25,26]

## APPENDIX

### Institutions Participating in the Study (Grant No.)

University of California at San Diego, San Diego, CA, Mark Green (11789); Walter Reed Army Medical Center, Washington, DC, Raymond Weiss (CA-26806); Upstate Medical Center at Syracuse, Syracuse, NY, Arlan Gottlieb (CA-21060); McGill Cancer Center, Montreal, Canada, Bernard Cooper (CA-31809); Maimonides Medical Center, Brooklyn, NY, Samuel Kopel (CA-25119); Long Island Jewish Medical Center, New Hyde Park, NY, Kanti Rai (CA-11028); Massachusetts General Hospital, Boston, MA, Robert W. Carey (CA-12449); Wilmington Medical Center, Wilmington, DE, Irving Berkowitz (CA-37041); Columbia University, New York, NY, Rose Ruth Ellison (CA-12011); Rhode Island Hospital, Providence, RI, Louis Leone (CA-08025); Bowman-Gray School of Medicine, Winston-Salem, NC, Robert Cooper (CA-03927); University of Missouri, Columbia, MO, Michael Perry (CA-12046); Finsen Institute, Copenhagen, Denmark, Nis I. Nissen; New York Hospital–Cornell Medical Center, New York, NY, Richard T. Silver (CA-07968); Dartmouth Medical School–Norris Cotton Cancer Center, Hanover, NH, Gibbons Cornwell (CA-04326); West Virginia University Medical Center, Morgantown, WV, Peter Raich (CA-28562); Mount Sinai Hospital, New York, NY, James F. Holland (CA-04457); Central Massachusetts Oncology Group, Worcester, MA, Mary Costanza (CA-37135); University of Tennessee, Memphis, TN, Alvin M. Mauer (CA-47555).

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