

## A Randomized Study of High-Dose Cytarabine in Induction in Acute Myeloid Leukemia

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**High-dose cytarabine (ara-c) may overcome cytarabine resistance in leukemic blasts. It has been used as a successful salvage and in postremission therapy but not as initial induction treatment. Patients aged 15 to 60 years, presenting with newly diagnosed acute myeloid leukemia (AML) were randomized to receive either high-dose cytarabine, 3 g/m<sup>2</sup> 12 hourly on days 1, 3, 5, and 7 for 8 doses, daunorubicin 50 mg/m<sup>2</sup> days 1 to 3, etoposide 75 mg/m<sup>2</sup> days 1 to 7, (HIDAC-3-7) or standard dose cytarabine 100 mg/m<sup>2</sup> continuous intravenous infusion for 7 days with daunorubicin and etoposide at the same dose and schedule as above (7-3-7). Patients could receive a second or third induction course if complete remission (CR) was not achieved. All patients received the same postinduction consolidation therapy (5-2-5) for 2 courses. Eligible patients had no prior chemotherapy or myelodysplastic disease. Patients have been followed for a median of 4.5 years. Of 301 patients treated, complete response (CR) was achieved in 71% with HIDAC-3-7 and 74% with 7-3-7. For patients in CR, the estimated median remission**

**duration was 45 months with HIDAC-3-7 and 12 months with 7-3-7 ( $P = .0005$  univariate analysis,  $P = .0004$  multivariate analysis). The estimated percentage of patients relapse free 5 years after achieving a CR was 49% on HIDAC-3-7 and 24% on 7-3-7. Patients in CR tended to survive longer with HIDAC-3-7 but there were no overall survival differences between the two arms. HIDAC-3-7 was associated with significantly more toxicity in induction with more leukopenia, thrombocytopenia, nausea, and vomiting and eye toxicity (all  $P < .001$ ) but a similar incidence of severe central nervous system and cerebellar toxicity compared to 7-3-7. The consolidation treatment was the same in both arms but caused significantly more leukopenia and thrombocytopenia in patients previously treated with HIDAC-3-7 induction ( $P < .0001$ ). We conclude that a dose-effect exists for cytarabine in AML and that HIDAC-3-7 prolongs remission duration and disease-free survival and is tolerable when used as initial induction therapy in patients with de novo AML.**

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**T**HE TREATMENT of acute myeloid leukemia (AML) has improved over the last 2 decades with better supportive measures and postinduction bone marrow transplantation (BMT).<sup>1-3</sup> However, with standard induction regimens, approximately 30% of patients still fail to achieve a complete remission and remission duration is often only about 12 months.<sup>1,2,4</sup>

Etoposide is a semisynthetic podophyllotoxin derivative with activity as a single agent and in combination in relapsed patients with AML.<sup>5-9</sup> Etoposide in initial induction chemotherapy was reported to significantly prolong remission duration compared to standard therapy.<sup>9,10</sup> In a recent update, with median follow-up of 7 years, the median remission duration was 18 months for the etoposide combination (7-3-7) and 12 months for standard 7-3 (log rank,  $P = .007$ ). In that trial, a subset of younger patients (aged <55 years) tolerated treatment better and showed a significantly longer survival. Thus, the Australian Leukemia Study Group (ALSG) designed this study to use 7-3-7 as the standard arm.

Cytarabine (ara-C) has been an essential component of combination chemotherapy for induction of AML because Ellison et al<sup>11</sup> first produced long-term survivors in AML. The rationale for using a higher dose of cytarabine is that there appears to be a steep dose response curve for cytarabine in experimental tumor systems.<sup>12,13</sup> Patients whose myeloblasts formed and retained higher levels of ara-C 5'-triphosphate had higher complete remission (CR) rates. Thus, high-dose cytarabine could overcome clinical drug resistance by this and other mechanisms.

Early clinical studies in AML suggested that high-dose cytarabine with amsacrine produced high response rates in refractory and heavily pretreated patients.<sup>14</sup> High-dose cytarabine has been successfully used in a number of combinations in relapsed patients and as postinduction therapy in phase I and II studies.<sup>15-17</sup> Within a large ALSG data base, an analysis of the influence of dose and dose intensity on the duration of remission in AML showed the induction dose of cytarabine and daunorubicin significantly influenced the duration of remission.<sup>18</sup> These studies provide a rationale for this study with an intensified dose of cytarabine in induction chemotherapy for "de novo" patients.

This trial continues the approach within the ALSG of investigating new chemotherapy treatment in initial induction chemotherapy. The rationale is that other curable cancers such as lymphoma and testicular cancer depend on optimal doses of chemotherapy given as early as possible for optimal results. In addition, this study was designed to complement other studies of high-dose cytarabine in postinduction therapy.

### MATERIALS AND METHODS

The protocol was written to conform to the ethics guidelines of the National Health and Medical Research Council of Australia and the Australian Federal Department of Health. The Ethics Committee

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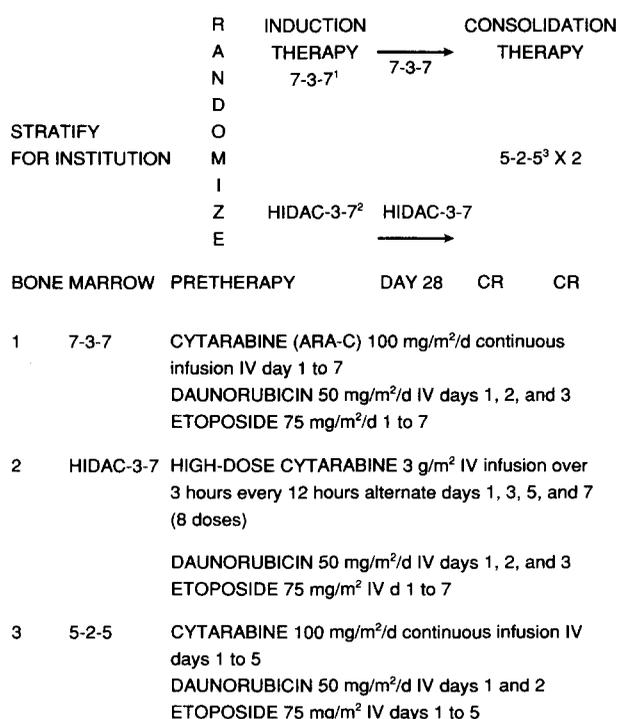


Fig 1. Induction and postinduction treatment schema.

of each participating institution gave approval of the treatment protocol and each patient gave written informed consent before randomization. Patients were entered from 25 institutions in Australia.

**Patient eligibility.** Patients 15 to 60 years old were eligible provided they had a morphologically proven diagnosis of AML, had not previously received chemotherapy, and had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 3. Patients with severe cardiac disease precluding the use of daunorubicin or with previous myeloproliferative disease, myelodysplastic disorder, or other neoplasms were excluded. Diagnostic BM aspirations and biopsies were classified using the French-American-British (FAB) classification<sup>19</sup> and were reviewed by an independent expert morphology panel.

**Treatment plan.** Patients were randomized to receive either cytarabine 100 mg/m<sup>2</sup>/d as a continuous intravenous (IV) infusion for 7 days plus daunorubicin 50 mg/m<sup>2</sup>/d IV for days 1 to 3 plus etoposide 75 mg/m<sup>2</sup>/day IV for days 1 to 7 (7-3-7) or to receive daunorubicin and etoposide as above but with high-dose cytarabine 3 g/m<sup>2</sup>/dose IV infusion over 3 hours twice (BID) on days 1, 3, 5, and 7 for a total of 8 doses per course (HIDAC-3-7, Fig 1). Patients with residual disease with more than 5% blasts at day 28 could receive a second then subsequently a third induction course of the same regimen. Patients with hypocellular or regenerating marrow at day 28 were rebiopsied weekly until their remission status was clear. Patients in CR immediately received two consolidation treatments with standard dose cytarabine, daunorubicin, and etoposide as for induction but for 5, 2, and 5 days, respectively (5-2-5). Maintenance therapy was identical to that used by the Cancer and Acute Leukemia Group B (CALGB)<sup>1</sup> and a previously published study of ALSG.<sup>10</sup> Maintenance therapy was cytarabine 50 mg/m<sup>2</sup> 12 hourly subcutaneously for 5 days, 6-thioguanine 50 mg/m<sup>2</sup> 12 hourly orally for 5 days given every 8 weeks for two years. Vincristine 1 mg/m<sup>2</sup> and prednisolone alternated cycles with daunorubicin until a total dose

of 550 mg/m<sup>2</sup> of daunorubicin was reached. Vincristine was then substituted for daunorubicin.

**Evaluation of response.** CR was defined as ≤5% blasts in a normocellular BM with >1 × 10<sup>9</sup>/L neutrophils and >100 × 10<sup>9</sup>/L platelets in the peripheral blood (PB) and the disappearance of all other signs of leukemia. Relapse was defined as >5% leukemic blasts in BM. BM biopsies were performed at least every 28 days during induction and consolidation courses and every 8 weeks while patients were receiving maintenance treatment. All toxicity was graded using standard World Health Organization (WHO) criteria.<sup>20</sup>

**Statistical methods.** Patients were randomized at the ALSG Trial Center using computer generated randomization charts based on permuted blocks. Separate charts were prepared for each participating center and approximately equal numbers of patients were assigned to the randomization arms within each center. No further stratification was used before randomization. All eligibility criteria were checked by telephone before patients were randomized. Experienced data managers at the Trial Center reviewed all case record forms before entering the data into a computer data base. At the time of planning the trial, the primary criterion for assessing efficacy of treatment was chosen to be the complete response rate. A target accrual of 300 eligible patients was calculated to provide a probability (power) of 0.8 of detecting an increase in the complete response rate from 65% to 80% using a two-tailed test at the *P* = .05 level of significance. Criteria for early stopping were defined in the protocol.

The data were analyzed with a close-out date of August 1, 1994 to prevent bias in the follow-up of patients. The status of all but 11 (4%) patients was known at this date. All data were censored at the close-out date. Remission duration (relapse-free survival) was measured from the date of achieving CR to the date of relapse for patients who relapsed or the earlier of the date of last contact and the date of close-out for patients who did not relapse. Patients who died in CR had their remission duration censored at the date of death. The disease-free interval (disease-free survival) was measured as above but deaths in CR were included as failures and were not censored. A competing risk analysis was used to estimate the cumulative incidences of relapse and death in CR.<sup>21</sup> Overall survival was measured from the date of randomization to the date of death for all patients who died.

Data were analyzed on an intention-to-treat basis using BMDP statistical software versions 1988 and 1990 (University of California, Berkeley).<sup>22</sup> Survival curves were estimated using the Kaplan-Meier product-limit method and compared using the logrank test. Relative rates of relapse and death were estimated using the Cox proportional hazards model adjusting for prognostic factors where appropriate. To determine if patients who were taken off-study to receive BMTs influenced the comparison of HIDAC-3-7 and 7-3-7, all survival analyses were repeated censoring BMT patients' data at the date of their BMT. Complete response rates were compared using Yates' continuity corrected chi-square test. The percentages of patients with grade 3 or 4 toxicities and proven infections were compared using Yates' continuity corrected chi-square test or the Fisher exact test when small numbers were involved. Graded toxicity data were compared using the test for trend for contingency tables and uncensored continuous variables were compared using the Wilcoxon rank sum test. Two-tailed *P* values have been reported throughout the text with no adjustment made for multiple comparisons. Ninety-five percent confidence intervals (CI) have been reported for the main summary statistics.

## RESULTS

**Accrual.** The ALSG entered 309 patients in a 4.5-year period commencing in March 1987. Eight patients (2.6%)

**Table 1. On-study Characteristics for 301 Eligible Patients: 149 on HIDAC-3-7 and 152 on 7-3-7**

		7-3-7	HIDAC-3-7
ECOG PS	0	38%	38%
	1	38%	40%
	2	20%	15%
	3	4%	7%
Sex	Male	52%	48%
	Female	48%	52%
FAB	M0	1%	1%
	M1	16%	17%
	M2	28%	28%
	M3	18%	16%
	M4	27%	23%
	M5	9%	9%
	M6	1%	4%
	M7	0%	2%
	M8	0%	1%
Cytogenetics*	NN	40%	40%
	NA	28%	28%
	AA	31%	33%
	t(8;21)	10%	5%
	inv(16)	5%	8%
	t(15;17)	15%	15%
	-5/5q-	3%	2%
	-7/7q-	7%	5%
	Complex†	6%	3%
Febrile (temperature $\geq 38^{\circ}\text{C}$ )	No	52%	50%
	Yes	48%	50%
DIC	No	77%	76%
	Yes	23%	24%
Age (yr)	Median	39	43
	<30	27%	18%
	30-39	24%	28%
	40-49	24%	21%
	50-60	24%	33%
White blood cell count ( $10^9/\text{L}$ )	Median	9.7	10.9
Peripheral blasts ( $10^9/\text{L}$ )	Median	2.4	3.9
Platelet count ( $10^9/\text{L}$ )	Median	64.5	49
Hemoglobin (g/dL)	Median	9.4	8.8

\* Based on 101 HIDAC-3-7 patients and 102 7-3-7 patients with valid cytogenetics available.

† More than four abnormalities.

were ineligible, of whom 5 did not have AML, 1 had prior treatment, 1 was over 60 years of age, and 1 had inadequate marrow for diagnosis. Of the 301 eligible patients, 152 were randomized to 7-3-7 and 149 to HIDAC-3-7.

**Patient characteristics.** On study characteristics such as ECOG performance status, sex, number of patients febrile, hemoglobin, white blood cell count, and PB blast counts were well balanced between the two arms. However, HIDAC-3-7 patients tended to be older and have a lower platelet count than 7-3-7 patients (Table 1).

**Dose delivery.** On average HIDAC-3-7 patients received 89% of their planned protocol dose of cytarabine in each induction course whereas 7-3-7 patients received 97% of

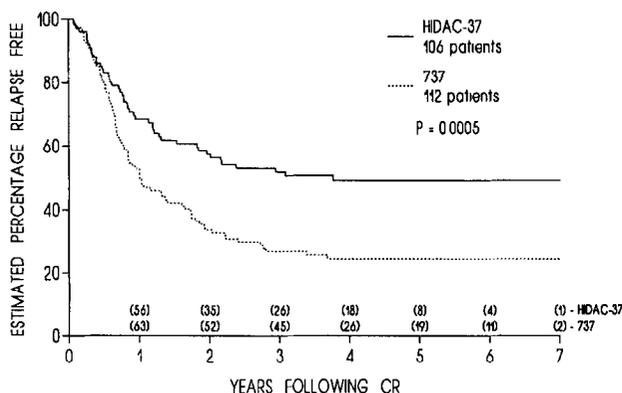
their planned dose ( $P = .0001$ ). More than 90% of the protocol doses of daunorubicin and etoposide were delivered in at least 90% of patients in both study arms. On HIDAC-3-7, 121 (81%) patients received one course of induction, 28 (19%) received two and none received three. On 7-3-7, 93 (61%) patients received one course of induction, 54 (36%) received two, and 5 (3%) received three. The average time between commencement of the first and second induction courses was 36 days for HIDAC-3-7 and 31 days for 7-3-7 ( $P = .15$ ). For HIDAC-3-7 patients there was a significantly longer interval between the start of the last induction course and the start of the first consolidation course compared to 7-3-7 patients (43 days v 37 days respectively,  $P = .004$ ) and between consolidation courses (38 days v 33 days,  $P = .02$ ). There were no significant differences in doses given on either arm during consolidation (5-2-5) therapy.

Fifty-one (34%) of the HIDAC-3-7 patients commenced maintenance and 60 (39%) of the 7-3-7 patients. There was no difference in the number of maintenance courses received (median 4, range 1 to 14) nor in the reasons for ceasing maintenance therapy. Of the 111 patients who commenced maintenance, 18% completed it, 23% were taken off to receive a BMT, 40% relapsed, 12% refused to continue, 7% were taken off because of toxicity and one patient was taken off because of pregnancy.

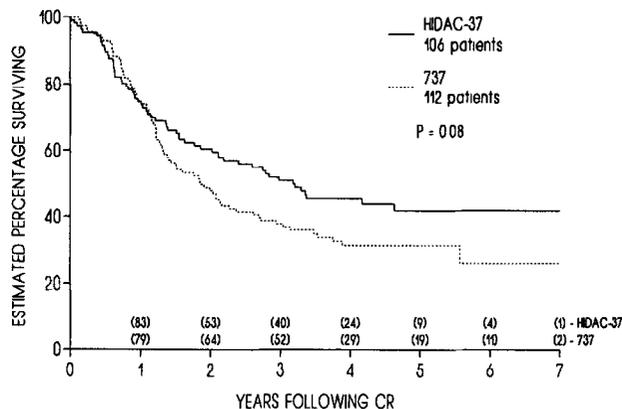
**Complete remission.** Of the 301 eligible patients, CR was achieved in 71% (95% CI:63% to 78%) of patients on the HIDAC-3-7 arm and 74% (95% CI:66% to 81%) on 7-3-7 ( $P = .7$ ). Significantly more patients achieved a complete remission after one induction course on the HIDAC-3-7 arm (60%) than on the 7-3-7 arm (48%,  $P = .04$ ). The median time to CR from the date of randomization was 32 days on HIDAC-3-7 and 35 days on 7-3-7 ( $P = .07$ ). There were no statistically significant differences between the CR rates in the two arms in age subsets divided by decade, but overall CR rates decreased significantly with increasing age ( $P = .0016$ ). Significantly more patients were taken off induction because of toxicity in the HIDAC-3-7 arm (9%) compared with 7-3-7 (1%,  $P = .003$ ).

**Remission duration.** Of 106 patients who achieved CR with HIDAC-3-7, 48 have relapsed and 14 died in CR, whereas of 112 patients who achieved CR with 7-3-7, 80 have relapsed and 7 died in CR. Complete remission duration was significantly prolonged with HIDAC-3-7 compared to 7-3-7 ( $P = .0005$ , Fig 2). The median remission duration for the HIDAC-3-7 arm was 45 months and 12 months for 7-3-7. An estimated 49% (SE 5%) of HIDAC-3-7 patients were relapse free at 5 years compared with 24% (SE 4%) of 7-3-7 patients. The rate of relapse for HIDAC-3-7 patients was 0.53 (95% CI:0.37 to 0.76) relative to 7-3-7 patients ie, HIDAC-3-7 reduced the relapse rate by 47%. A multivariate analysis of the clinical factors that influenced the duration of complete response showed that only peripheral blast (PB) count had a significant influence. When randomization arm was included in a model with PB count, HIDAC-3-7 still significantly prolonged the duration of remission ( $P = .0004$ ).

**Disease-free survival.** Disease-free survival following



**Fig 2. ALSG M4: Duration of response.** Numbers in brackets refer to number of patients at risk at beginning of each period.



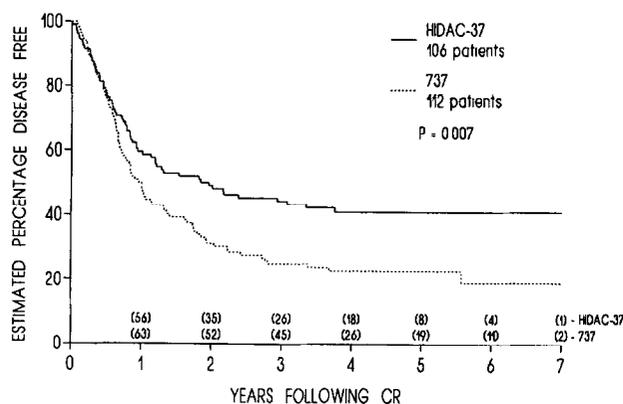
**Fig 4. ALSG M4: Survival after achieving CR.** Numbers in brackets refer to number of patients at risk at beginning of each period.

CR was also significantly prolonged on the HIDAC-3-7 arm ( $P = .007$ , Fig 3). The median disease-free survival was 22 months for HIDAC-3-7 and 12 months for the 7-3-7 patients. An estimated 41% (SE 5%) of HIDAC-3-7 patients were disease free at 5 years after achieving CR, compared with 23% (SE 4%) of 7-3-7 patients. A competing risk analysis showed that 5 years after achieving CR an estimated 46% of HIDAC-3-7 patients will have relapsed and 13% died in CR. For 7-3-7, 72% will have relapsed and 5% died in CR.

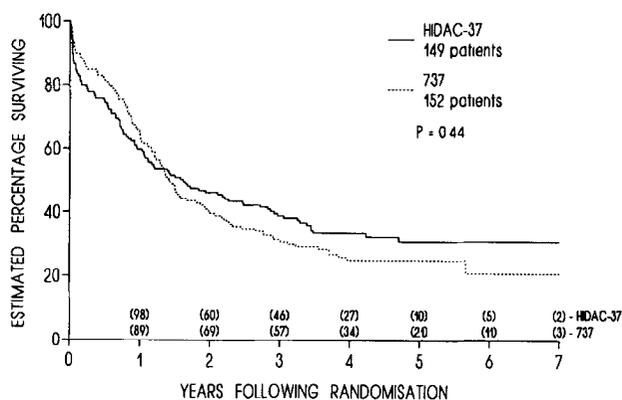
**Survival after CR.** At the time of analysis, 59 of the HIDAC-3-7 patients who achieved CR had died, 14 in CR and 45 following relapse, compared with 76 of the 7-3-7 patients, 7 of whom died in CR and 69 following relapse. Six HIDAC-3-7 and three 7-3-7 patients died in CR following BMT. The remaining causes of death in CR for HIDAC-3-7 patients were hemorrhage (2 patients), infection (3), treatment toxicity (1), liver failure (1) and sepsis, cardiac failure, veno-occlusive disease and acute renal failure (1), whereas for 7-3-7 patients they were hemorrhage (1), respiratory failure (1), hypoxic brain damage (1) and cardiovascular collapse and renal failure (1). Although HIDAC-3-7 in-

creased the duration of survival after CR, the increase was not statistically significant ( $P = .08$ , Fig 4). The estimated median duration of survival following CR was 38 months for the HIDAC-3-7 patients and 22 months for the 7-3-7 patients, with an estimated 42% (SE 5%) and 31% (SE 5%) of patients surviving disease free at 5 years in the HIDAC-3-7 and 7-3-7 arms, respectively. The relative death rate after CR for HIDAC-3-7 patients was 0.74 (95% CI:0.52 to 1.04) compared with 7-3-7 patients.

**Overall survival.** Two hundred and twelve patients died before the close-out date, 100 on HIDAC-3-7 and 112 on 7-3-7. The median follow-up was 4.4 years for HIDAC-3-7 patients and 4.5 years for 7-3-7 patients. On HIDAC-3-7, 18% died during induction compared with 11% of 7-3-7 patients ( $P = .09$ ). The higher initial death rate for HIDAC-3-7 patients was reversed after 12 months (Fig 5). The median survival was 19 months on HIDAC-3-7 and 17 months on 7-3-7. ( $P = .4$ ). The estimated survival 5 years after randomization was 31% (SE 4%) for HIDAC-3-7 and 25% (SE 4%) for 7-3-7. The estimated death rate for HIDAC-3-7 patients relative to 7-3-7 patients was 0.90 (95% CI:0.69%



**Fig 3. ALSG M4: Disease-free survival.** Numbers in brackets refer to number of patients at risk at beginning of each period.



**Fig 5. ALSG M4: Survival.** Numbers in brackets refer to number of patients at risk at beginning of each period.

to 1.18) on univariate analysis and 0.86 (95% CI:0.66 to 1.13) on multivariate analysis. The latter death rate was adjusted for age, sex, and initial white blood cell count that significantly influenced survival. The benefit of the longer remission duration for patients who achieved CR on HIDAC-3-7 was offset by the shorter survival for those who did not achieve CR and in particular by the higher death rate in induction. There was no difference in the survival duration following relapse for the two arms, medians 6.0 and 5.6 months for HIDAC-3-7, and 7-3-7 patients, respectively.

**BMT.** Sixty-two patients, 31 on each arm, received BMTs in CR (23 allogeneic and 39 autologous), one in induction, 36 in consolidation and 25 in maintenance. The median time from CR to transplantation was 5.2 months, 6.7 months for HIDAC-3-7 patients, and 4.1 months for 7-3-7 patients ( $P = .052$ ). When data for BMT patients were censored at the date of transplantation, the relapse and survival advantage associated with HIDAC-3-7 was more pronounced than in the "intention to treat" analysis. For patients who achieved CR, the estimated decrease in the subsequent death rate with HIDAC-3-7 patients relative to 7-3-7 patients was 36% with censoring ( $P = .02$ ) and 26% without censoring ( $P = .08$ ). Adjusting for significant on-study prognostic factors, the estimated decrease in the relapse rate with HIDAC-3-7 was 52% censoring transplant recipients ( $P = .0002$ ) and 47% without censoring ( $P = .0004$ ), whereas the estimated decrease in the overall death rate was 18% with censoring ( $P = .18$ ) and 14% without ( $P = .27$ ).

**Toxicity.** For induction courses, patients on HIDAC-3-7 had a significantly longer duration of leukopenia and thrombocytopenia (Table 2) although severe neutropenic periods ( $<0.5 \times 10^9/L$ ) were similar on both arms. The incidence of microbiologically or clinically proven infection and the number of days febrile or on antibiotics were significantly higher with HIDAC-3-7 compared with 7-3-7. Although both arms received the same consolidation treatment, 5-2-5, patients who received HIDAC-3-7 during induction had significantly longer periods of leukopenia, neutropenia, and thrombocytopenia than 7-3-7 patients. There was a higher incidence of grade 3 or 4 clinical bleeding for HIDAC-3-7 patients (7% v 1%,  $P = .048$ ). Although there were no differences between the arms in the incidence of proven infections in consolidation, HIDAC-3-7 patients had an increased number of days febrile.

During induction therapy, there was significantly more central nervous system (CNS) toxicity on the HIDAC-3-7 arm ( $P = .04$ ). However, there was no increase in severe or life threatening (WHO grades 3 or 4) CNS toxicities ( $P = .4$ ) (Table 3). Cerebellar toxicity was similar between the two arms. During induction, patients on the HIDAC-3-7 arm had significantly more nausea and vomiting, diarrhea, and eye toxicity. These toxicities could generally be successfully managed. Other severe or life threatening (WHO grade 3 or 4) toxicities appeared to occur more frequently with HIDAC-3-7. Three HIDAC-3-7 patients had tumor-lysis syndrome, six patients had gastrointestinal complications and five had acute renal failure. No patient on 7-3-7 had tumor-lysis, two had gastrointestinal complications and three had acute renal

**Table 2. Hematological Toxicity After Induction and Consolidation Courses**

	Course	7-3-7	HIDAC-3-7	P Value
Median days WCC $\leq 1 \times 10^9/L$	Induction 1	15	18	<.0001
	Induction 2	12	18	.015
	Consolidation 1	4	8	<.0001
	Consolidation 2	4	8	<.0001
Median days neutrophils $\leq 0.5 \times 10^9/L$	Induction 1	20	19	.28
	Induction 2	16	17.5	.65
	Consolidation 1	8	9	.056
	Consolidation 2	8	10	.0067
Median days platelets $\leq 50 \times 10^9/L$	Induction 1	18	21	<.0001
	Induction 2	13	20.5	.0018
	Consolidation 1	5	9	<.0001
	Consolidation 2	6	12	<.0001
No. of platelet transfusions	Induction 1	8	9	.044
	Induction 2	5	7.5	.021
	Consolidation 1	1.5	2.5	.0051
	Consolidation 2	1	3	.0001
Infections*	Induction 1	63%	73%	.082
	Induction 2	63%	86%	.053
	Consolidation 1	35%	43%	.27
	Consolidation 2	49%	49%	1.0
No. of days febrile	Induction 1	12	14	.029
	Induction 2	5	10.5	.007
	Consolidation 1	2	3.5	.0043
	Consolidation 2	2	4	.0057
No. of days on antibiotics	Induction 1	20	21	.11
	Induction 2	14	20.5	.0013
	Consolidation 1	5	7	.080
	Consolidation 2	6	8	.045

Abbreviation: WCC, white blood cell count.

\* Clinically or microbiologically proven.

failure. Four patients on HIDAC-3-7 had hyperbilirubinemia or significant elevation of liver enzymes. There were no differences between the two arms in the incidence of nonhematological toxicities in consolidation.

## DISCUSSION

In this study we have intensified induction chemotherapy to optimize initial control of leukemia. We limited our study to patients 60 years of age or less because we were unable to intensify induction in older patients in our previous study.<sup>10</sup> In addition, the CNS toxicity of high-dose cytarabine appears age related.<sup>23</sup> High-dose cytarabine was given every 12 hours, but only on alternate days for 8 doses. This schedule was modified from that successfully given by Mayer et al<sup>16</sup> without major CNS toxicity. In contrast, the South-West Oncology Group (SWOG) study of high-dose cytarabine in induction was associated with unacceptable toxicity using a daily 12 hourly schedule for high-dose cytarabine.<sup>24</sup> Based on intracellular pharmacology lower doses of high-dose cy-

tarabine may be equally effective.<sup>25</sup> Our study has shown that our dose and schedule of high-dose cytarabine can be successfully given in a large cooperative group setting.

In this study, the CR rates were similar for the two treatment arms. HIDAC-3-7 was significantly more successful in inducing complete remission after the first cycle than 7-3-7. The overall CR rate on this study was higher than the CR rate on the previous ALSG study for patients  $\leq 60$  years (72% v 60%). However, the CR rates for the 7-3-7 arm were not significantly different between the two sequential ALSG studies.

Excluding patients who died in induction, 13% of patients who survived induction on HIDAC-3-7, and 17% on 7-3-7, failed to achieve CR. With high response rates on both arms, the duration of remission as measured by the relapse-free survival provides a potentially more sensitive measure of the antileukemic effect of induction therapy. The initial use of high-dose cytarabine dramatically increased the median remission duration from 12 months to 45 months and doubled the relapse-free survival at 5 years from 24% to 59%. This increase in the remission duration was highly significant in a multivariate analysis showing clearly that high-dose cytarabine in induction influenced the quality of the remission. Preliminary results reported in the SWOG trial<sup>24</sup> also suggested that the response rates were similar in the high dose and standard arms but relapse-free survival was prolonged with high-dose cytarabine.

The results of this trial are remarkably similar to those recently reported by Mayer et al,<sup>26</sup> using high-dose cytarabine as postinduction therapy. In that study, patients in remis-

sion received 6 doses per course of high-dose cytarabine, 3 g/m<sup>2</sup>, compared with an intermediate dose of 400 mg/m<sup>2</sup> and standard dose cytarabine of 100 mg/m<sup>2</sup>. Patients on high-dose cytarabine received 4 courses or 24 treatments. Although only 56% of patients were able to complete the 4 courses of high-dose cytarabine, more cytarabine was given in the study by Mayer et al than in our study. In Mayer's study, high-dose cytarabine significantly improved disease-free survival and overall survival when compared with conventional-dose cytarabine. The disease-free survival of patients on high-dose cytarabine was 44% at 4 years for patients aged  $\leq 60$  years, censoring patients who received BMT. In our study, the disease-free survival at 4 years was 41% overall for patients on HIDAC-3-7. Censoring for marrow transplant patients, the disease-free survival was 39% at 4 years. Comparing HIDAC-3-7 and 7-3-7, the hazard ratio for disease-free survival was 0.64. In the study by Mayer et al,<sup>26</sup> high-dose cytarabine postinduction resulted in similar hazard ratio for disease-free survival of 0.67.

High-dose cytarabine prolonged survival in patients who achieved CR but this did not reach statistical significance ( $P = .08$ ). However, the relative death rate of 0.76 for the HIDAC-3-7 patients is identical to the statistically significant age-adjusted hazard ratio for the high-dose cytarabine group reported by Mayer et al.<sup>26</sup>

There was no statistical difference between the arms in overall survival. Possibly, the improvements in relapse-free survival and disease-free survival seen in the HIDAC-3-7 arm were offset by reduced survival among HIDAC-3-7 patients who did not achieve CR. Induction toxicity with an increase in the induction death rate for HIDAC-3-7 patients contributed to this result.

The results of these two studies compare favorably with those of autologous BMT with relapse-free survival rates of 25% to 50% at 3 years.<sup>26</sup> They may compare favorably with 50% relapse-free survival seen with allogeneic transplantation if selection factors such as age, performance status, length of time, after complete remission and tolerance to previous therapy are taken into account.<sup>27,28</sup> Mayer et al<sup>26</sup> reported few relapses after 20 months, but only further follow-up will determine if the remissions noted are as durable as seen with transplantation.

A three-arm postinduction trial by ECOG compared a single course of high-dose cytarabine, 3 g/m<sup>2</sup> for 12 doses plus amsacrine, weekly standard-dose cytarabine plus 6-thioguanine and allogeneic BMT.<sup>29</sup> The event-free survival at 4 years for patients aged less than 60 years in CR who received high-dose cytarabine and amsacrine was 28% (SE 11%). There was no difference in outcome in the ECOG subset of patients aged less than 41 years treated with either high-dose cytarabine amsacrine or allogeneic BMT although only 83 patients were compared. These results with a single course of high-dose cytarabine appear inferior to our results and to those reported by Mayer et al.<sup>26</sup>

Intensification of induction therapy was associated with increased but acceptable toxicity in a group setting. HIDAC-3-7 induction prolonged myelosuppression by approximately 4 days in both the induction and consolidation phase. The

**Table 3. Worst Grade of Toxicity Encountered During Induction Courses Using WHO Toxicity Criteria**

Toxicity	Grade	7-3-7	HIDAC-3-7	P Value*	P Value†
Cerebellum	0	97%	92%		
	1	3%	5%		
	2	1%	0%		
	3	0%	2%		
	4	0%	0%		
Nausea and Vomiting	0	8%	8%		
	1	26%	8%		
	2	34%	30%		
	3	30%	52%		
	4	1%	1%		
Eyes	0	93%	68%		
	1	5%	15%		
	2	1%	11%		
	3	1%	5%		
	4	1%	0%		
Diarrhea	0	85%	77%		
	1	1%	1%		
	2	7%	5%		
	3	5%	6%		
	4	3%	11%		

\* Significance of trend based on chi-square test for contingency tables.

† Significance of grade 3 or 4 toxicities only.

latter occurred without further high-dose cytarabine in the consolidation treatment. The incidence of microbiologically or clinically proven infections was also significantly higher for patients on HIDAC-3-7. However, the use of alternate day dosing is, most likely, responsible for acceptable CNS toxicity and was also used successfully in the study by Mayer et al.<sup>26</sup>

It is clear from a number of studies that the benefits of intensified therapy in AML are confined to younger patients.<sup>10,16,26</sup> In patients receiving the three-drug combination with etoposide (7-3-7) the prolongation of relapse-free survival and survival advantage seen over a standard two-drug therapy was confined to patients aged less than 55 years.<sup>10</sup> Mayer et al<sup>26</sup> stratified their patients according to age, reported no benefit in patients over 60 years of age and could not deliver high-dose cytarabine in that older age group. Our study was age limited but younger patients fared better with higher response rates and lower toxicity. Thus, intensive therapy cannot be generally recommended for older patients.

A more fundamental issue raised by this study and those of postinduction intensification is, when in the chemotherapy cascade should therapy in AML be intensified.<sup>26,29,30</sup> Treatment could be theoretically intensified during the induction phase, immediately after remission, or after 2 to 3 months of preparative regimens as in some transplantation programs. The advantages of giving intensive therapy to patients in remission are that the marrow contains a normal proportion of hematopoietic-cell progenitors and the patients' general condition is better. Thus, intensive treatment is better tolerated and less dangerous during remission than during induction. However, 30% to 40% of patients on standard regimens never have a remission and will never have the chance of benefiting from improved intensified therapies that may develop in the future. Other curable tumors, such as testicular cancer and some lymphomas, appear to benefit from optimal initial treatment. Less high-dose cytarabine may be required when used in one or two courses in induction as in this study compared with the planned 24 doses used in the study by Mayer et al.<sup>26</sup> The disadvantage remains the initial toxicity of intensified induction.

Regardless of its optimal position in the chemotherapy program, it is now clear that a dose-response relationship exists for cytarabine in AML. This has important implications for designing optimal induction and postinduction therapies and preparative regimens for transplantation.

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