A Randomized Investigation of High-Dose Versus Standard-Dose Cytosine Arabinoside With Daunorubicin in Patients With Previously Untreated Acute Myeloid Leukemia: A Southwest Oncology Group Study

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Interest in high-dose cytarabine (HDAC) for both induction and postremission therapy for acute myeloid leukemia (AML) prompted the Southwest Oncology Group (SWOG) to initiate a randomized trial comparing HDAC with standard-dose cytarabine (SDAC) for remission induction of previously untreated AML and to compare high-dose treatment versus conventional doses for consolidation therapy. Patients less than 65 years of age with de novo or secondary AML were randomized for induction between SDAC 200 mg/m^2/d for 7 days by continuous infusion or HDAC at 2 g/m^2 intravenously every 12 hours for 12 doses; both groups received daunorubicin (DNR) at 45 mg/m^2/d intravenously for 3 days. Complete responders to SDAC were randomized to receive either two additional courses of SDAC plus DNR or one course of HDAC plus DNR. Complete responders to HDAC were nonrandomly assigned to receive one additional course of HDAC plus DNR. Of patients randomized between SDAC (n = 493) and HDAC (n = 172) induction, 361 achieved complete remission (CR). The CR rate was slightly poorer with HDAC: 55% versus 58% with SDAC for patients aged less than 50, and 45% (HDAC) versus 53% (SDAC) for patients aged 50 to 64 (age-adjusted one-tailed P = .96). With a median follow-up time of 51 months, survival was not significantly better with HDAC (P = .41); the estimated survival rate at 4 years was 32% (HDAC) versus 22% (SDAC) for those aged less than 50, and 13% (HDAC) versus 11% (SDAC) for those aged 50 to 64. However, relapse-free survival was somewhat better following HDAC induction (P = .049): 33% (HDAC) versus 21% (SDAC) at 4 years for those aged less than 50, and 21% (HDAC) versus 9% (SDAC) for those aged 50 to 64. Induction with HDAC was associated with a significantly increased risk of fatal (P = .0033) and neurologic (P < .0001) toxicity. Among patients who achieved CR with SDAC, survival and disease-free survival (DFS) following consolidation randomization were not significantly better with HDAC compared with SDAC (P = .77 and .46, respectively). Patients who received both HDAC induction and consolidation had the best postremission outcomes; however, the proportion of CR patients who did not go on to protocol consolidation therapy was more than twice as high after HDAC induction compared with SDAC. Induction therapy with HDAC plus DNR was associated with greater toxicity than SDAC plus DNR, but with no improvement in CR rate or survival. Following CR induction with SDAC, consolidation with HDAC increased toxicity but not survival or DFS. In a nonrandomized comparison, patients who received both HDAC induction and consolidation had superior survival and DFS compared with those who received SDAC induction with either SDAC or HDAC consolidation.
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DESPITE ADVANCES in the treatment of acute myeloid leukemia (AML), uncertainty exists about optimal remission and postremission regimens. Induction therapy with 3 days of an anthracycline and 7 days of continuous-infusion cytarabine is generally accepted as the best treatment. For the adult middle-age population (25 to 65 years), many investigators have published reports of between 55% and 85% complete remission (CR) rates with prolonged disease-free survival (DFS) and possible cures in 25% to 30% of the total population studied.[1-5]

High-dose cytarabine (HDAC), alone or in combination with other agents, has been suggested to have utility in inducing remissions in patients with AML, either in relapse or in patients with secondary acute leukemia.[6-9] Whether HDAC offers an advantage over conventional-dose cytarabine for induction in de novo AML patients remains uncertain. CR rates in previously untreated patients with de novo AML using HDAC have been reported to be 50% to 81%.[10-12] The published studies have involved relatively few patients, have included several different additional agents in the regimens, and have largely been uncontrolled, making it impossible to assess accurately the specific contribution of HDAC to remission induction.

The use of HDAC and daunorubicin (DNR) as postremission or consolidation therapy for patients in remission also has been reported in pilot series.[11-18] The Southwest Oncology Group (SWOG) in 1986 initiated a study that asked two questions: (1) is the combination of HDAC plus DNR superior to conventional-dose cytarabine plus daunomycin for remission induction in adults with newly diagnosed AML; and (2) for patients in remission, is the high-dose regimen superior to the conventional-dose regimen for consolidation therapy?

MATERIALS AND METHODS

Patients less than 65 years of age with the diagnosis of AML who had not received prior therapy for leukemia were eligible for this study. Patients with histories of prior myelodysplasia or treatment

Induction **Consolidation**

NOTE

HDAC-2: Ara-C at 2 gm/m²/day (all pts of age 50-64; and pts of age < 50 after December, 1988).
HDAC-3: Ara-C at 3 gm/m²/day (pts of age < 50 until December, 1988).
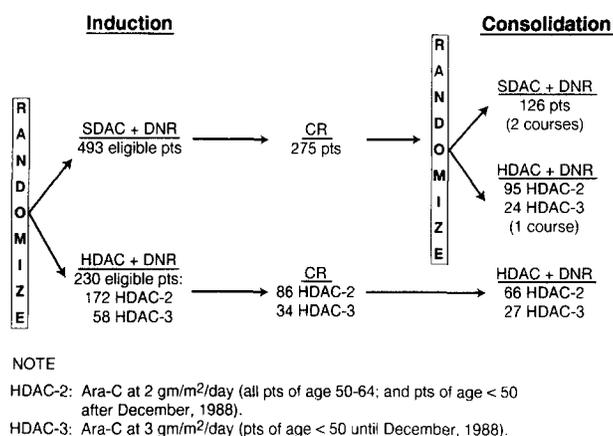
Fig 1. Study schema and flow of patients.

with potentially leukemogenic agents or radiation were eligible, as were patients with de novo AML. The diagnosis of acute leukemia was established on the basis of a bone marrow aspiration and biopsy; the bone marrow biopsy had to demonstrate at least 50% cellularity and an absolute infiltrate of leukemic cells of at least 30% was required. Pathology material for all cases was reviewed by the Leukemia Pathology Committee of the Southwest Oncology Group. Patients with pretreatment bilirubin levels greater than 3.0 mg/dL were excluded. Written informed consent in accordance with institutional and Food and Drug Administration policies was required.

The treatment schema is shown in Fig 1. Patients were randomly assigned to induction treatment with either standard-dose cytarabine (SDAC) plus DNR or HDAC plus DNR. The SDAC + DNR induction regimen consisted of cytarabine 200 mg/m²/d given as a continuous infusion on days 1 to 7, with the addition of bolus DNR at 45 mg/m²/d on days 5 to 7. Patients randomized to induction with HDAC + DNR were treated with cytarabine at 2 g/m² intravenously over 1 hour every 12 hours for 12 doses on days 1 to 6, followed by DNR at the same dose as for induction arm 1 on days 7 to 9. Initially, patients less than 50 years of age received HDAC according to the same schedule, but at 3 g/m², designated HDAC-3. However, about 2 years into the study, in December 1988, the study's Data Monitoring Committee (DMC) determined that this regimen produced too high a rate of neurologic toxicity, with no evidence of improvement in response to treatment. As a result, HDAC was redefined as 2 g/m² for all ages. Patients younger than 50 who received HDAC at 3 g/m² are treated separately in the analyses reported below. No hematopoietic growth factors were given in this study.

Patients who achieved CRs were to be registered for the consolidation portion of the study. Patients who received SDAC + DNR induction were randomized to receive either two additional courses of the SDAC + DNR regimen with DNR omitted on day 5 or one course of HDAC at 2 g/m² for 10 doses on days 1 to 5 followed by bolus DNR at 45 mg/m² days 6 and 7. Patients who had received HDAC + DNR induction were nonrandomly assigned to receive consolidation with HDAC + DNR. Initially, the consolidation dose of HDAC was 3 g/m² for patients younger than 50; however, this was reduced to 2 g/m² in December 1988. In all consolidation arms, DNR was reduced to 30 mg/m² for ages 50 to 64.

Patients who developed neurologic toxicity on HDAC had their medication stopped immediately. The DNR dosage was decreased 50% if the bilirubin level was between 1.5 and 2.9 mg/dL and withheld if the bilirubin level was greater than 3.0 mg/dL. Full doses were given for a bilirubin level less than 1.5 mg/dL. In patients who required a second cycle of induction chemotherapy, identical doses were used as with the first cycle. Patients had to recover from nonhe-

matologic toxicity of grade 2 or higher before they could receive the second cycle.

Postinduction bone marrow samples were obtained on days 15 and 23 in the standard-dose arm, and on day 23 in the high-dose arm. For patients treated with SDAC in whom no change in the cellularity was noted and whose marrow remained A-3 (blasts > 25%), a second cycle of induction therapy was to be initiated immediately. To avoid excessive neurotoxicity in patients who received HDAC, a second cycle of induction chemotherapy did not begin before day 28, even if persistent leukemia was demonstrated on bone marrow examinations. For those patients with reduced cellularity or hypocellular bone marrows, re-treatment required cellularity greater than 30% before either a second induction course or consolidation was permitted to begin. Bone marrow examinations in hypocellular specimens were timed at the discretion of the investigator. Patients were offered alternative therapies off protocol if CR was not achieved after the second cycle of induction chemotherapy. Consolidation therapy was permitted when recovery of the neutrophil count to greater than 1,500/μL and of platelet count to greater than 100,000/μL occurred, but was not permitted if grade 3 or 4 neurologic toxicity occurred during the induction phase. When consolidation treatment was completed, no further therapy was administered and the patients were monitored at monthly intervals for the first 2 years following therapy. Bone marrow examinations were performed every 6 months posttreatment. Following the second year in CR, patients were monitored at 3-month intervals for a minimum of 5 years.

Statistical Considerations

Initial study design. The primary objectives of this study were to compare SDAC + DNR and HDAC + DNR as induction and consolidation therapy with respect to CR rate, DFS, and toxicity. The study plan initially called for 600 eligible patients randomized in a 2:1 ratio between the SDAC + DNR and HDAC + DNR induction regimens. This randomization was stratified by age groups less than 50 and 50 to 64 years. The 2:1 ratio was used to ensure that a sufficient number of patients would achieve CR on SDAC + DNR induction and be available for randomization between the SDAC + DNR and HDAC + DNR consolidation regimens.

In December 1988, the study's DMC determined that induction therapy with HDAC (3 g/m²) + DNR produced too high a rate of neurologic toxicity, with no evidence of improvement in response to treatment. As a result, HDAC was redefined as 2 g/m² for all ages. The study's target sample size was increased to ensure sufficient power for comparisons between HDAC (2 g/m²) + DNR versus SDAC + DNR. In particular, the study was modified to accrue 485 and 188 patients to induction with SDAC + DNR and HDAC, respectively, including those already registered, over a period of 54 months. This would provide 80% power to detect a 60% increase in the odds of CR, the same as originally planned. In addition, this was expected to provide approximately 220 patients randomized between consolidation SDAC + DNR versus HDAC (2 g/m²) + DNR, although in a ratio of 130:90 rather than 110:110, which after 2 years' additional follow-up time would provide 86% power to detect a hazards ratio of 1.5 in the analysis of DFS. In September 1991, near the end of the accrual period, the DMC determined that induction with HDAC (2 g/m²) + DNR was associated with unacceptably high toxicity and no improvement in response. At that point, induction randomization was stopped, and the last 25 patients to enter the study were nonrandomly assigned to induction with SDAC + DNR. However, the consolidation randomization continued for all patients who achieved CR on SDAC + DNR.

Statistical analysis. The primary analyses of the induction portion of the study are based on all eligible patients who were randomized between SDAC + DNR and HDAC (2 g/m²) + DNR. As mentioned earlier, the last 25 patients to enter the study were nonran-

Table 1. Characteristics of 723 Eligible AML Patients by Induction Treatment Arm

Characteristic	SDAC + DNR (N = 493)		HDAC (2 g/m²) + DNR (N = 172)		HDAC (3 g/m²) + DNR (N = 58)	
	Median	Range	Median	Range	Median	Range
Age	45	15-64	50	17-64	32	17-49
Counts						
Marrow blasts (%)	75	0-99	66	0-98	72	3-99
WBC (1,000/µL)	18.0	0.4-416	16.3	0.5-370	14.9	0.8-301
Peripheral blasts (%)	38	0-99	34	0-98	55	0-96
Peripheral blasts (1,000/µL)	5.3	0-378	4.5	0-190	6.2	0-249
Hemoglobin (g/dL)	9.4	4.1-15.0	8.9	5.1-14.3	8.8	5.0-15.4
Platelets (1,000/µL)	54	2-700	50	5-347	63	5-252
	No.	%	No.	%	No.	%
WBC						
≤100,000/µL	431	87	151	88	54	93
≥100,000/µL	62	13	21	12	4	7
Sex						
Female	226	46	72	42	28	48
Male	267	54	100	58	30	52
Race						
White	417	85	152	88	45	78
Black	48	10	17	10	10	17
Other	28	6	3	2	3	5
FAB class (central review)						
M1	103	21	30	17	11	19
M2	186	38	65	38	22	38
M3	60	12	20	12	8	14
M4	61	12	22	13	7	12
M5	46	9	14	8	7	12
M6	9	2	8	5	3	5
M7	5	1	2	1	0	0
M0	10	2	2	1	0	0
Other myeloid	13	3	9	5	0	0

domly assigned to SDAC + DNR and are included in these analyses since the results are essentially unaffected by their inclusion or exclusion. Primary analyses of the consolidation portion of the study are based on the eligible patients who were randomized between SDAC + DNR and HDAC (2 g/m²) + DNR; additional analyses included the patients nonrandomly assigned to HDAC (2 g/m²) + DNR. Patients younger than 50 who received HDAC (3 g/m²) + DNR are described separately. Survival for the induction and consolidation portions of the study was measured from the day of the respective registration until death from any cause, with observation censored at the day of last contact for patients not known to have died. Relapse-free survival (RFS) was measured from the onset of CR until relapse or death from any cause, with observation censored at the day of last contact for patients without report of relapse or death, and DFS was measured from the day of registration for consolidation to the same end point. Rates of toxicity were compared between treatment arms by means of exact tests calculated using the commercially available StatXact-Turbo program (Cytel Software, Cambridge, MA). Distributions of survival, RFS, and DFS were estimated by the method of Kaplan and Meier.[19] Treatment comparisons that involved all ages were adjusted for the stratification by age group. Further analyses of the effects of treatment and other characteristics were based on logistic regression models for rates of CR and toxicities[20] and on proportional hazards regression models for survival, RFS, and DFS.[21] Interim analyses of this study were examined regularly by the study's DMC, which had the authority to terminate the study early if interim analyses showed extreme results concerning toxicity or treatment outcomes. The study was not terminated early,

although it was modified by the DMC as described earlier. Results in this report are based on data available April 17, 1995. Preliminary results were presented in 1992.[22]

RESULTS

Induction

Patients and treatment. Figure 1 is a summary of treatment assignments detailing numbers of eligible patients and results of therapy. From November 1986 through December 1991, 857 patients less than 65 years of age were registered onto this study. Of these, 134 (16%) were ineligible, most frequently due to lack of adequate materials for central pathology review (51 patients) and central review diagnoses other than AML (11 myelodysplasia, 10 ALL, six indeterminate M0/L2, one myelofibrosis, one lymphoma, and three nondiagnostic). Other reasons for ineligibility included insufficient marrow cellularity or leukemic cell infiltration (n = 32), institutional diagnoses other than AML (n = 3), bilirubin level greater than 3.0 mg/dL (n = 2), failure to submit required specimens or data (n = 14), and absence of institutional review board approval (n = 1). The inclusion of ineligible patients did not alter conclusions about remission rates, overall survival, or DFS.

Of 723 eligible patients, 58 less than 50 years of age were randomized to induction with HDAC (3 g/m²) + DNR;

Table 2. Summary of Treatment Assignments and Outcomes for Induction and Consolidation by Age Group

Variable	Age < 50				Age 50-64		
	Induction						
Induction arm (Ara-C dose*)	SDAC + DNR (200 mg/m^2)		HDAC + DNR (2.0 g/m^2)	HDAC + DNR (3.0 g/m^2)	SDAC + DNR (200 mg/m^2)		HDAC + DNR (2.0 g/m^2)
Eligible patients	293		85	58	200		87
No. of CRs	170 (58%)		47 (55%)	34 (59%)	105 (53%)		39 (45%)
4-yr survival‡	22% (17-26%)‡		32% (22-42%)	28% (16-39%)	11% (7-15%)		13% (6-20%)
4-yr RFS‡	21% (15-27%)		33% (19-47%)	29% (14-45%)	9% (3-15%)		21% (8-33%)
	Consolidation						
% of CRs registered and eligible for consolidation	91%		72%	79%	86%		82%
Treatment assignment†	Randomized		Nonrandom		Randomized		Nonrandom
Consolidation arm (Ara-C dose*)	SDAC + DNR (200 mg/m^2)	HDAC + DNR (2.0 g/m^2)	HDAC + DNR (3.0 g/m^2)	HDAC + DNR (2.0 g/m^2)	HDAC + DNR (3.0 g/m^2)	SDAC + DNR (200 mg/m^2)	HDAC + DNR (2.0 g/m^2)	HDAC + DNR (2.0 g/m^2)
Eligible patients	78	53	24	34	27	48	42	32
4-yr survival‡	34% (23-45%)	23% (11-35%)	28% (9-46%)	52% (34-69%)	33% (16-51%)	14% (4-24%)	19% (7-31%)	24% (9-39%)
4-yr DFS‡	24% (15-34%)	14% (4-25%)	20% (4-36%)	34% (18-50%)	26% (9-42%)	4% (0-10%)	17% (5-28%)	25% (10-49%)

Abbreviation: Ara-C, cytarabine.

*The dose of Ara-C in HDAC + DNR for patients of age < 50 was 3.0 g/m^2/d until December 1988, when it was reduced to 2.0 g/m^2/d. The primary comparisons of SDAC + DNR v HDAC + DNR were based on HDAC at 2.0 g/m^2/d.

† Patients who achieved CR with SDAC + DNR induction were randomized between SDAC + DNR and HDAC + DNR consolidation. Those who achieved CR with HDAC + DNR were nonrandomly assigned to HDAC + DNR consolidation. The primary comparisons of consolidation regimens were based on randomized patients.

‡ 95% Confidence interval shown in parentheses.

results for these patients are reported separately later. The primary analysis of the induction portion of the study is based on the remaining 665 patients, of whom 493 and 172 were randomized to SDAC + DNR and HDAC (2 g/m^2) + DNR, respectively.

Characteristics of these 665 patients are summarized in Table 1. The two arms are similar with respect to the characteristics shown in Table 1, with one exception: the SDAC + DNR arm has relatively more patients younger than 50 (59%) than does arm 2 (49%) (Table 2). This is a consequence of the fact that HDAC was redefined as 2 g/m^2 for patients younger than 50 after the study was open for approximately 2 years; patients in this age group randomized to the 3 g/m^2 dose of HDAC before this redefinition are described separately later. Hyperleukocytosis (WBC count > 100,000/ μL) was present in 13% of SDAC + DNR patients and 12% of HDAC (2 g/m^2) + DNR patients. Two patients were classified by central pathology review as having M0/M5 and M0/M7 morphology, respectively, and 20 other patients had AML that could not be subclassified according to French-American-British (FAB) criteria; these 22 patients are identified as "other myeloid" in Table 1.

One patient on the HDAC (2 g/m^2) + DNR arm refused to receive protocol induction therapy, and another 17 (12 SDAC + DNR and five HDAC [2 g/m^2] + DNR) chose to remove themselves from treatment early. Thirty-two patients (13 SDAC + DNR and 19 HDAC [2 g/m^2] + DNR) were removed from induction therapy early because of toxicity, most frequently hemorrhage, hepatotoxicity, or neurotoxicity.

Toxicity. Induction toxicity could not be evaluated for five patients due to major treatment deviations, refusal to receive therapy, early death, or lack of documentation. Fatal toxicity, primarily due to infection or CNS hemorrhage, was significantly more frequent with HDAC (2 g/m^2) + DNR

compared with SDAC + DNR: 14% versus 5% for age less than 50, and 20% versus 12% for age 50 to 64 (age-adjusted two-tailed P = .0033; Table 3). Similar differences were seen for general neurologic toxicities of any grade (P < .0001 result not shown) or grade 3+ (P = .0004).

Treatment outcomes. All 665 eligible patients were evaluated for response to induction chemotherapy, and 361 (54%) achieved CR. As shown in Table 2, CR rates tended to be higher for SDAC + DNR: 58% versus 55% for age less than 50, and 53% versus 45% for age 50 to 64. Thus, there is no evidence for a higher CR rate with the use of HDAC (one-tailed P = .96). Of the 493 SDAC + DNR patients on arm 1, 198 (40%) achieved CR after one course, compared with 71 (41%) of the 172 patients on HDAC (2 g/m^2) + DNR. The second induction course was given to 163 (55%) of the 295 patients who failed to achieve CR with one course on SDAC + DNR, compared with 34 (34%) of the 101 HDAC (2 g^2/m^2) + DNR patients on arm 2. Among patients who received the second course, CR was achieved by 77 (48%) on SDAC + DNR and 15 (44%) on HDAC (2 g/m^2) + DNR.

A total of 82 patients, 52 of 493 (11%) on SDAC + DNR and 30 of 172 (17%) on HDAC (2 g/m^2) + DNR, failed to achieve CR after one course and died before reinduction could be attempted. Thus, there were 117 patients who failed to achieve CR, did not die early, and did not receive a second induction course. The second course was not given to 23 of 37 HDAC (2 g/m^2) + DNR patients (62%) due to toxicity, refusal, or poor medical condition, compared with only 26 of 80 (33%) on SDAC + DNR. In contrast, alternative treatment off protocol was pursued for 20 of 80 (25%) on SDAC + DNR, but only four of 37 (11%) on HDAC (2 g/m^2) + DNR.

Of 665 eligible patients, 548 have died. The remaining 117 have a median follow-up time of 55 months. Overall

Table 3. Frequencies of Selected Induction Toxicities by Age and Treatment

	Age < 50									Age 50-64					
Induction arm (Ara-C dose*)	SDAC + DNR (200 mg/m^2)			HDAC + DNR (2.0 g/m^2)			HDAC + DNR (3.0 g/m^2)			SDAC + DNR (200 mg/m^2)			HDAC + DNR (2.0 gm/m^2)		
No. of evaluated patients	292			84			58			198			86		
Toxicity grade†	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5
Hepatic	16	1	0	5	4	0	5	0	0	11	3	0	6	2	0
Neurologic	5	0	0	6	0	1	9	0	0	0	1	0	4	0	0
Mucositis/ulcers/stomatitis	8	1	0	3	0	0	4	0	0	11	0	0	1	0	0
Nausea/vomiting/anorexia	12	1	0	3	0	0	3	0	0	4	0	0	4	0	0
Infection	2	9	9	1	1	9	0	3	5	1	8	18	2	2	14
Any nonhematologic	34	15	11	18	4	11	15	4	6	22	13	21	16	5	16
Fatal hemorrhage	—	—	6	—	—	2	—	—	0	—	—	3	—	—	1
Total fatal	—	—	16	—	—	12	—	—	6	—	—	23	—	—	17

* See Table 2 (†).

† Grade 5 = fatal. In general terms, grade 4 = life-threatening and grade 3 = severe. The table shows the numbers of patients with toxicities of each grade during the first or second induction attempt.
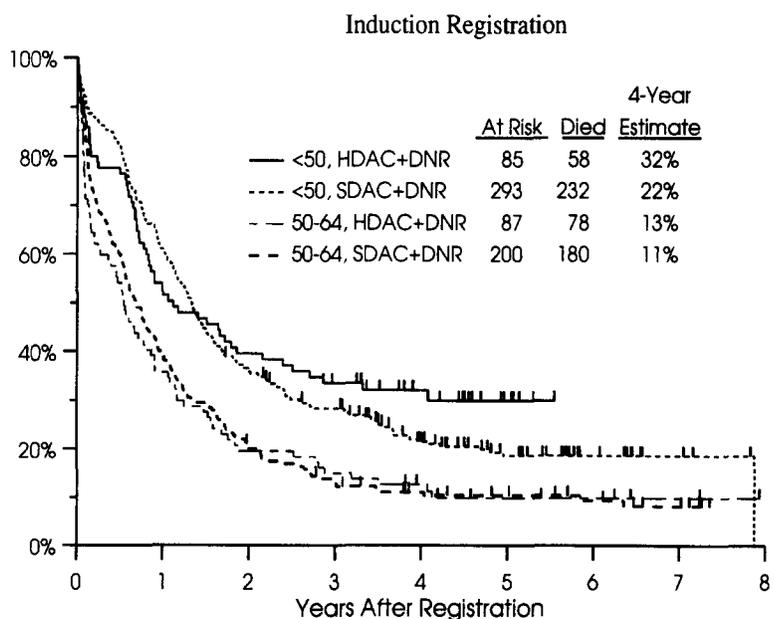
survival was not significantly better with HDAC (2 g/m^2) + DNR (P = .41 based on proportional hazards regression stratified by age groups < 50 and 50 to 64; Fig 2). The estimated probabilities of survival at 4 years for patients less than 50 are 22% (95% confidence interval, 17% to 26%) and 32% (22% to 42%) for SDAC + DNR and HDAC (2 g/m^2) + DNR, respectively. The corresponding estimates for ages 50 to 64 are 11% (7% to 15%) and 13% (6% to 20%).

Of 361 eligible patients who achieved CR, 269 have relapsed and 25 others have died without relapse. Considering all 361 patients, RFS was marginally significantly better following HDAC (2 g/m^2) + DNR induction (P = .049; Fig 3). The estimated probabilities of remaining alive without report of relapse at 4 years for patients less than 50 are 21% (15% to 27%) for SDAC + DNR and 33% (19% to 47%) for HDAC (2 g/m^2) + DNR. The corresponding estimates

for ages 50 to 64 are 9% (3% to 15%) and 21% (8% to 33%), respectively.

Consolidation

Patients and treatment. Of 361 eligible patients who achieved CR with either SDAC + DNR or HDAC (2 g/m^2) + DNR, 48 were not registered for the consolidation portion of the study due to induction toxicity or poor medical condition (n = 24), early relapse or death (n = 7), intention to pursue bone marrow transplantation (n = 6), refusal by the patient or investigator (n = 6), or protocol error (n = 5). Two other patients who were registered were ineligible for the consolidation: one did not meet the criteria for CR until after registration, and another had active infection when registered. Thus, 311 patients were registered and eligible for the study consolidation (Fig 1). Sixty-six of these 311 pa-

Induction Registration

	At Risk	Died	4-Year Estimate
—— <50, HDAC+DNR	85	58	32%
---- <50, SDAC+DNR	293	232	22%
– — 50-64, HDAC+DNR	87	78	13%
– – 50-64, SDAC+DNR	200	180	11%

Fig 2. Overall survival by age and treatment arm.

Induction Registration

	At Risk	Relapsed or Died	4-Year Estimate
—— <50, HDAC+DNR	47	31	33%
···· <50, SDAC+DNR	170	136	21%
— — 50-64, HDAC+DNR	39	31	21%
– – 50-64, SDAC+DNR	105	96	9%

Years After Complete Response

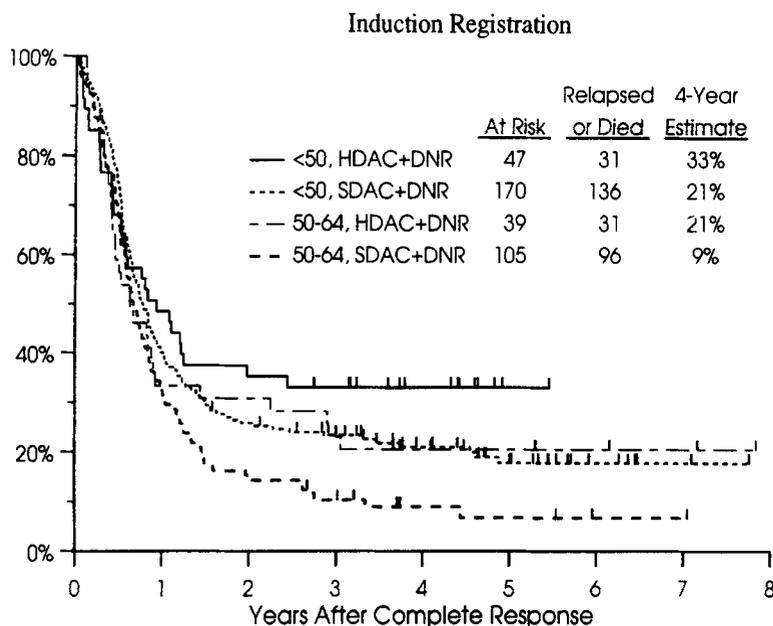**Fig 3. RFS by age and treatment arm.**
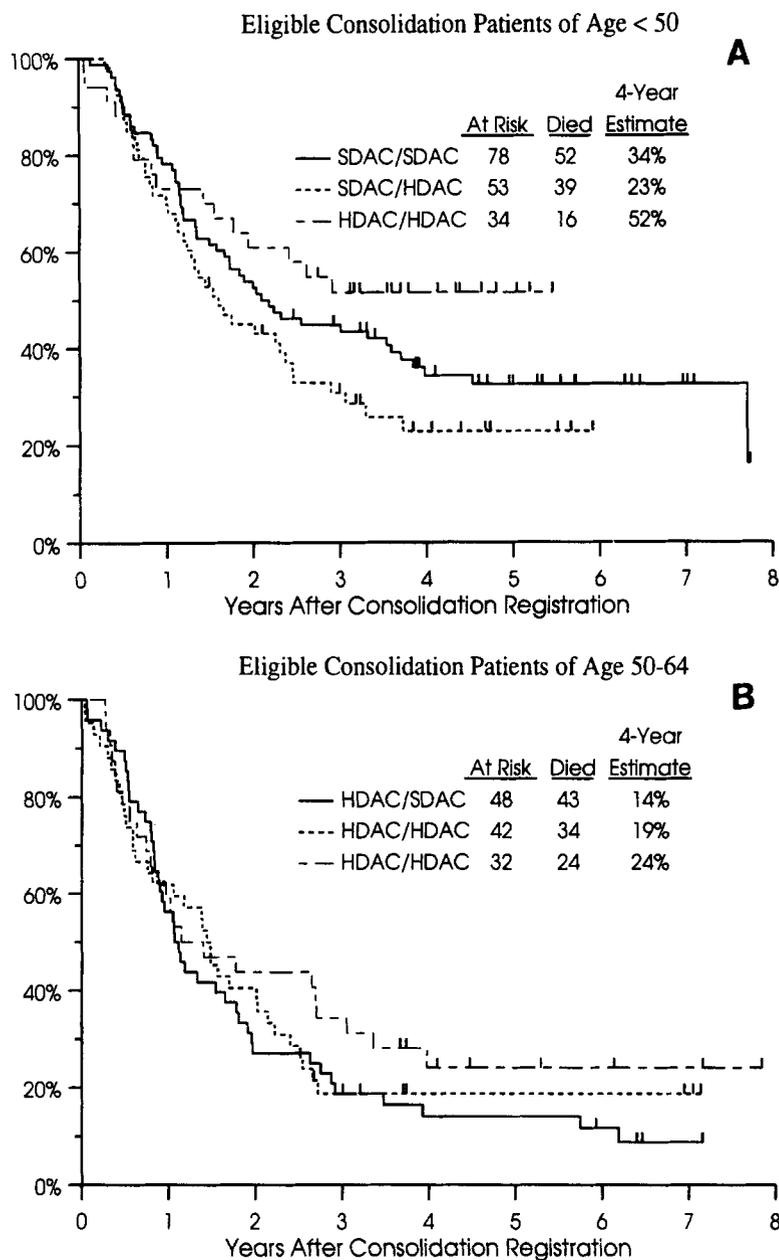
tients received induction with HDAC (2 g/m^2) + DNR and were, therefore, assigned to consolidation with HDAC (2 g/m^2) + DNR (Table 2). Among the 245 patients who received SDAC + DNR induction were 24 patients less than 50 years of age who were randomized early in the study to receive consolidation with HDAC (3 g/m^2) + DNR. These 24 patients are excluded from the comparison of consolidation regimens, and are included in the separate description of results with HDAC (3 g/m^2) + DNR. Of the remaining patients, 126 and 95 were randomized between consolidation with SDAC + DNR and HDAC (2 g/m^2) + DNR, respectively. The primary comparisons of the two consolidation regimens are based on these 221 randomized patients, although results with the 66 nonrandomized patients are also mentioned. Overall, 245 (89%) of 275 patients who achieved CR on SDAC + DNR were registered and eligible for the consolidation portion of the study, compared with 66 (77%) of 86 patients on HDAC (2 g/m^2) + DNR. This suggests that comparisons between consolidation arms may be subject to bias arising from unrecognized factors that influenced decisions to proceed with consolidation.

Toxicity. Consolidation toxicity could not be evaluated for seven of 221 randomized patients: three refused to receive SDAC + DNR and a fourth was not treated due to hepatitis; three others were treated using nonprotocol drugs. There were four consolidation deaths among the 214 evaluated randomized patients, two in each treatment arm, and all in patients of age 50 to 64 (P = .99). Three of these deaths were due to infection and the fourth was due to a probable pulmonary embolism. General neurologic toxicity of grade 3+ was somewhat more frequent with HDAC (2 g/m^2) + DNR than with SDAC + DNR, but the difference was not statistically significant (P = .079). Consolidation toxicity was evaluated for 65 of the 66 patients who were nonrandomly assigned to consolidation with HDAC (2 g/m^2) + DNR consolidation following HDAC (2 g/m^2) + DNR induction. Two of these patients died of infection, combined

with gastrointestinal hemorrhage in one case. Eleven had neurologic toxicities, including six of grade 3+.

Survival and DFS. Among 221 eligible patients who achieved CR on the induction regimen of SDAC + DNR and were randomized between consolidation with SDAC + DNR or HDAC (2 g/m^2) + DNR, 168 have died. Estimates of survival probabilities are shown in Fig 4 and Table 2. Overall survival from the day of consolidation randomization was not significantly longer with HDAC (2 g/m^2) + DNR (one-tailed P = .77). Regarding DFS, 175 patients relapsed and 11 died without relapse. DFS from the day of randomization was not significantly longer with HDAC (2 g/m^2) + DNR (P = .46; Fig 5 and Table 2). Thus, there was no evidence that consolidation with HDAC (2 g/m^2) + DNR improved outcomes relative to SDAC + DNR consolidation, among patients who achieved CR with SDAC + DNR induction.

Additional analyses including the 66 patients nonrandomly assigned to HDAC (2 g/m^2) + DNR were also performed. Forty of these patients have died, and for the analysis of DFS there were 42 relapses and four deaths without relapse. There was no significant heterogeneity among the three combinations of induction and consolidation regimens with respect to either survival (P = .099; Fig 4) or DFS (P = .13; Fig 5). Figures 4 and 5 suggest that consolidation patients who received HDAC + DNR induction fared somewhat better than those who received SDAC + DNR induction (one-tailed P = .021 for survival and .021 for DFS). The significance of these differences must be viewed with caution, since this consolidation treatment assignment was not randomized and may have been subject to selection bias. As shown in Table 2, 23% (20/86) of the patients who achieved CR with HDAC induction did not receive or were not eligible for consolidation on study, compared with only 11% (30/275) of the SDAC induction patients. Such a differential in drop-out rates might result in the selection of patients with better prognosis following HDAC induction. However, if such bias is present, it is unlikely to explain
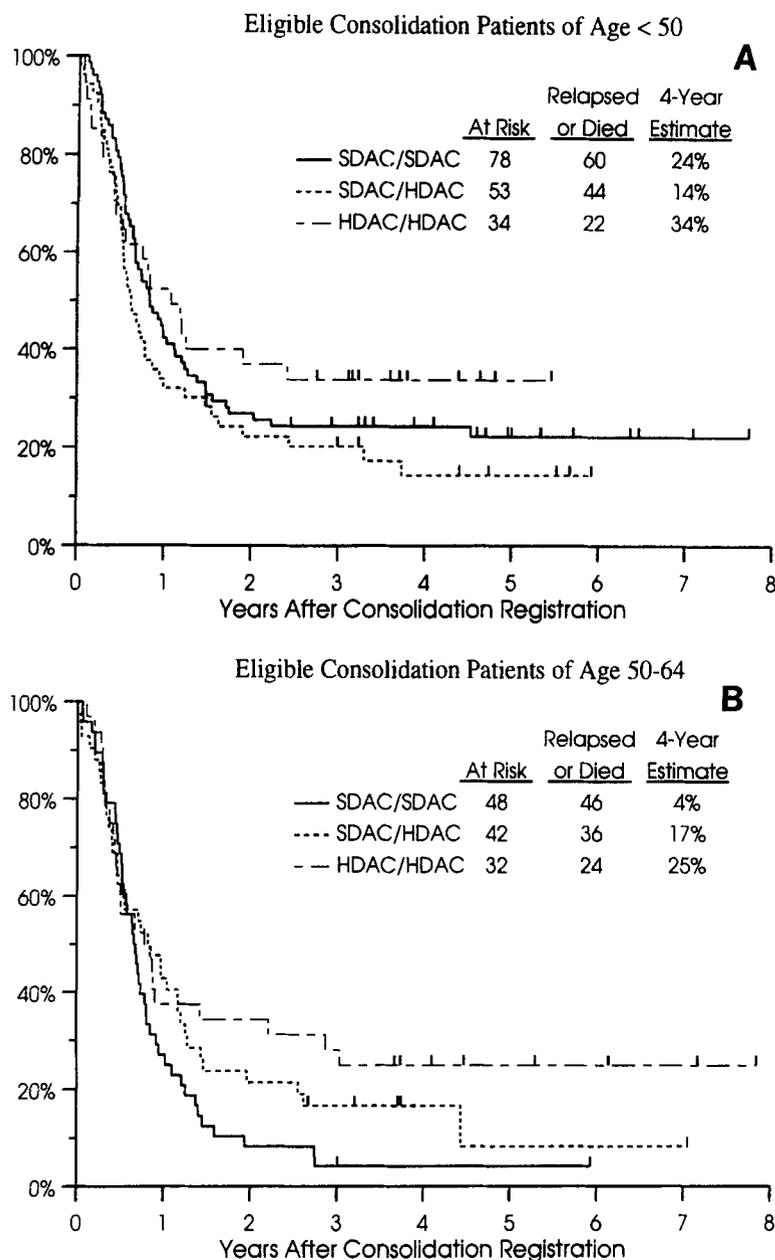
Eligible Consolidation Patients of Age < 50 **A**

	At Risk	Died	4-Year Estimate
—— SDAC/SDAC	78	52	34%
···· SDAC/HDAC	53	39	23%
– – HDAC/HDAC	34	16	52%

Years After Consolidation Registration

Eligible Consolidation Patients of Age 50-64 **B**

	At Risk	Died	4-Year Estimate
—— HDAC/SDAC	48	43	14%
···· HDAC/HDAC	42	34	19%
– – HDAC/HDAC	32	24	24%

Years After Consolidation Registration

Fig 4. Overall survival by induction consolidation. (A) Eligible consolidation patients less than 50 years of age. (B) Eligible consolidation patients 50 to 64 years of age.

completely the better consolidation outcome with HDAC/HDAC. This is because the analyses of RFS (based on all patients who achieved CR) and DFS (based on the subset of patients who received consolidation on study) show treatment effects of similar magnitude: the age-adjusted estimated hazard ratios are 0.79 (95% confidence interval, 0.60 to 1.05) for HDAC (2 g/m^2) + DNR compared with SDAC + DNR in the analysis of RFS (Fig 4), and 0.72 (0.52 to 1.00) for HDAC/HDAC compared with SDAC/SDAC and SDAC/HDAC combined.

HDAC (3 g/m^2) + DNR

As noted earlier, 58 eligible patients younger than 50 received induction with HDAC (3 g/m^2) + DNR. These 58 patients had demographic and disease characteristics similar

to those of the 378 patients less than 50 years of age who received SDAC + DNR or HDAC (2 g/m^2) + DNR induction (results not shown). Twenty-seven of the 58 patients went on to receive consolidation with HDAC (3 g/m^2) + DNR, along with another 24 patients who achieved CR with SDAC + DNR induction and were then randomized to HDAC (3 g/m^2) + DNR. Patients who received HDAC 3 g/m^2 experienced higher rates of neurologic toxicities than patients of the same age who received the lower doses of cytarabine. General neurologic toxicities of any grade occurred in 4%, 21%, and 26% of patients with cytarabine doses of 200 mg/m^2, 2 g/m^2, and 3 g/m^2, respectively, and grade 3 or higher neurologic toxicities occurred in 2%, 8%, and 16%, respectively. The corresponding toxicity rates during consolidation were 4%, 6%, and 29% for neurologic

Eligible Consolidation Patients of Age < 50

A

	At Risk	Relapsed or Died	4-Year Estimate
—— SDAC/SDAC	78	60	24%
---- SDAC/HDAC	53	44	14%
– – HDAC/HDAC	34	22	34%

Years After Consolidation Registration

Eligible Consolidation Patients of Age 50-64

B

	At Risk	Relapsed or Died	4-Year Estimate
—— SDAC/SDAC	48	46	4%
---- SDAC/HDAC	42	36	17%
– – HDAC/HDAC	32	24	25%

Years After Consolidation Registration

Fig 5. DFS by induction consolidation. (A) Eligible consolidation patients less than 50 years of age. (B) Eligible consolidation patients 50 to 64 years of age.

toxicity of any grade, and 0%, 2%, and 16% for grade 3+. Fatal toxicities were registered in 5%, 14%, and 10%, respectively, during induction, and 0%, 2%, and 4%, respectively, during consolidation.

Treatment outcomes among patients who received induction with HDAC (3 g/m^2) + DNR were similar to those among patients who received lower doses of cytarabine. CR rates were 170 of 293 (58%), 47 of 85 (55%), and 34 of 58 (59%) for patients younger than 50 who received cytarabine at 200 mg/m^2, 2 g/m^2, and 3 g/m^2, respectively. The estimated probabilities of survival at 4 years were 22% (95% confidence interval, 17% to 26%), 32% (22% to 42%), and 28% (16% to 39%), respectively. Among patients less than 50 years of age who achieved CR, the estimated probabilities of remaining alive without report of relapse at 4 years were

21% (15% to 27%), 33% (19% to 47%), and 29% (14% to 45%).

The estimated probability of survival 4 years after entering the consolidation portion of the study was 31% (95% confidence interval, 18% to 44%) for the 51 patients who received consolidation with HDAC (3 g/m^2) + DNR, compared with 34% (23% to 45%) and 34% (23% to 44%) for patients who received cytarabine at 200 mg/m^2 and 2 g/m^2, respectively. The estimated DFS at 4 years was 24% (15% to 34%), 22% (12% to 31%), and 23% (12% to 35%) for cytarabine at 200 mg/m^2, 2 g/m^2, and 3 g/m^2, respectively.

A separate analysis for CR, RFS, DFS, and overall survival pooling 2 g/m^2 and 3 g/m^2, compared with 3 g excluded, changes P values slightly, but none of the preceding conclusion are altered.

DISCUSSION

The "community standard" for the initial treatment of AML was established nearly 20 years ago with a combination of 5 to 10 days of SDAC at 100 to 200 mg/m²/d plus 3 days of anthracyclines, either doxorubicin or DNR.[23-27] High doses of cytarabine have been evaluated for induction therapy in AML since the earliest report in 1979 of its clinical utility.[28] Uncontrolled studies have been reported using doses of 1.5 to 3.0 g/m² every 12 hours for 4 to 6 days, with CR rates as high as 90%.[6-8,10] For example, Mitus et al recently published a study in which 3 days or six doses of HDAC were added to a standard "3 + 7" regimen. Using this treatment, CR was achieved in 84 of 94 patients (89%).[29] The small size and uncontrolled nature of these studies leaves some doubt about their significance.

The Australian Leukemia Study Group reported no change in CR rate, but an improved remission duration (36.9 v 12.7 months) in a randomized trial of 302 patients.[30] Patients received either HDAC at 3 g/m² every 12 hours for eight doses, plus DNR at 50 mg/m² on days 1 to 3, and etoposide (VP-16) at 75 mg/m² on days 1 to 7, or a SDAC regimen of 100 mg/m²/d for 7 consecutive days, with identical doses of DNR and VP-16. Because identical doses were used in both arms for postinduction consolidation for two courses, it could reasonably be stated that HDAC had a role in this study for prolonging remission duration. This study and the current report represent the only randomized trials to date to compare SDAC and HDAC induction in previously untreated patients with AML. These two studies are in agreement that the CR rate with HDAC is not higher than with SDAC. The Australian study noted significantly longer DFS for those induced with HDAC, and in the current trial the trend was similar (P = .049).

Attention also has been focused on postremission therapies. The initial results of uncontrolled trials involving the use of HDAC after CR reported that between 30% and 65% of patients treated with HDAC consolidation were predicted to remain in remission 2 years after the initial diagnosis.[11,13,31-33] These initial results, while encouraging, represent the evaluations of relatively small numbers of patients whose median age was between 36 and 46 years, and with relatively short follow-up time. Wolff et al reported that 49% of 87 patients who received one to three courses of HDAC plus DNR in a limited institutional trial were projected to remain disease-free after 5 years with a median follow-up duration at that time of 3.5 years.[15] Randomized trials were obviously needed to confirm these results and have been performed and reported in preliminary fashion by the SWOG, the Eastern Cooperative Oncology Group (ECOG), and the Cancer and Leukemia Group B (CALGB).

ECOG randomized 143 patients who had achieved CR with DNR, cytarabine, and 6-thioguanine (6-TG) (DAT) therapy to receive 24 months of low-dose maintenance therapy using 6-TG and cytarabine, or one course of HDAC at 3 g/m² over 1 hour every 12 hours for 6 days plus amsacrine.[14] Although a higher toxic death rate was seen with the intensive therapy, with a median follow-up duration of 4 years, the likelihood of remaining disease-free in patients less than 60 years of age was 28% for those who received a single

course of intensification versus 15% for those who received 2 years of maintenance therapy (P = .047).

CALGB, in a larger trial, randomized 596 patients who had responded to a standard "3 + 7" regimen to receive four courses of single-agent cytarabine in one of three different dose schedules: HDAC at 3 g/m² in a 3-hour infusion for six doses, intermediate-dose cytarabine at 400 mg/m²/d for 5 days by continuous infusion, or lower-dose cytarabine at 100 mg/m²/d for 5 days by continuous infusion.[4] With a median follow-up time of 37 months, the estimated probabilities of continuous CR after 4 years for the 467 patients less than 61 years of age were 44%, 29%, and 24% for the three treatments, respectively (P = .002). These investigators concluded that the data support the concept of a dose-response effect in AML patients less than 60 years of age.

The Leukemia Group of the Swiss Society for Cancer reported preliminary results of a 288-patient study in 1993.[34] After induction therapy with SDAC, DNR, amsacrine, and VP-16, 137 patients were randomized to receive either SDAC at 100 mg/m²/d × 7, continuous infusion, or HDAC at 3 g/m² every 12 hours for 12 doses plus DNR. With a median follow-up time of 3.4 years, there was no significant difference in the durations of unmaintained first continuous remission (P = .58). These investigators also reported a greater toxicity in the high-dose arm.

When considering the ECOG, SWOG, CALGB, and Swiss studies, it would seem that some form of intensive consolidation is superior to only low-dose maintenance, that single-dose intensification may only provide marginal benefit over conventional consolidation doses (from SWOG and the Swiss), and that multiple cycles may be needed to derive maximum benefit from more intensive cytarabine therapy.

Additionally, dose-intensity treatments may be more or less valuable in subgroups of AML. CALGB reported that there was marked improvement in CR duration in those patients with inv (16) or the t(8;21) translocation.[5] We have previously reported in this SWOG trial that CD34 correlates negatively overall with CR rate (36% CR rate for CD34+ patients v 62% CR rate for CD34-, P = .0057).[35] Notably, however, in CD34+ patients, the CR rate was improved with HDAC. Since CD34 positivity correlated with MDR-1 positivity, the possibility exists that HDAC may be particularly valuable in MDR-1–positive leukemias, a group predicted to derive less benefit from the anthracycline component of their chemotherapy regimen.

Our conclusions from the current clinical trial reported are that patients who receive HDAC at 2 g/m² plus DNR as induction therapy do not do significantly better than those who receive SDAC at 200 mg/m² plus DNR with respect to CR rate, but experienced significantly greater risk of fatal toxicities and general neurologic toxicities. Among the patients whose consolidation therapy was randomly assigned, those who received HDAC did not have significantly improved survival or DFS, both measured from the time of randomization, although they did experience a significantly greater incidence of general neurologic toxicities. The sample sizes in the study's randomized comparisons were large enough that we can confidently reject the alternative hypothesis that HDAC is associated with a 60% increase in the odds of CR and a hazards ratio of 1.5 in the analysis of

DFS. While we cannot rule out the possibility of smaller beneficial effects, this study provides no evidence that the CR rate is improved by the use of a single course of HDAC during induction; or that DFS in patients who achieve CR with SDAC and DNR is improved by the use of HDAC during consolidation. It is of interest that patients who received both HDAC induction and consolidation, particularly if younger, had somewhat superior survival and DFS compared with those who received SDAC induction followed by SDAC or HDAC consolidation. We cannot exclude a contribution to this effect from selection bias, since fewer HDAC patients who achieved CR went on to receive consolidation on study.

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A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study

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