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ORIGINAL REPORT

Prospective Randomized Comparison of Idarubicin and High-Dose Daunorubicin in Induction Chemotherapy for Newly Diagnosed Acute Myeloid Leukemia

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ABSTRACT

Purpose

We compared two induction regimens, idarubicin (12 mg/m^2/d for 3 days) versus high-dose daunorubicin (90 mg/m^2/d for 3 days), in young adults with newly diagnosed acute myeloid leukemia (AML).

Patients and Methods

A total of 299 patients (149 randomly assigned to cytarabine plus idarubicin [AI] and 150 assigned to cytarabine plus high-dose daunorubicin [AD]) were analyzed. All patients received cytarabine (200 mg/m^2/d for 7 days).

Results

Complete remission (CR) was induced in 232 patients (77.6%), with no difference in CR rates between the AI and AD arms (80.5% *v* 74.7%, respectively; $P = .224$). At a median follow-up time of 34.9 months, survival and relapse rates did not differ between the AI and AD arms (4-year overall survival, 51.1% *v* 54.7%, respectively; $P = .756$; cumulative incidence of relapse, 35.2% *v* 25.1%, respectively; $P = .194$; event-free survival, 45.5% *v* 50.8%, respectively; $P = .772$). Toxicity profiles were also similar in the two arms. Interestingly, overall and event-free survival times of patients with *FLT3* internal tandem duplication (ITD) mutation were significantly different (AI *v* AD: median overall survival, 15.5 months *v* not reached, respectively; $P = .030$; event-free survival, 11.9 months *v* not reached, respectively; $P = .028$).

Conclusion

This phase III trial comparing idarubicin with high-dose daunorubicin did not find significant differences in CR rates, relapse, and survival. Significant interaction between the treatment arm and the *FLT3*-ITD mutation was found, and high-dose daunorubicin was more effective than idarubicin in patients with *FLT3*-ITD mutation.

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INTRODUCTION

Induction chemotherapy for acute myeloid leukemia (AML) has been largely standardized over the past three decades. In the 1980s, a series of randomized trials established the so-called 7+3 regimen comprising 7 days of cytarabine (100 to 200 mg/m^2/d as continuous intravenous infusion) and 3 days of daunorubicin (45 mg/m^2/d) as a standard induction therapy for AML.[1-3] The early 1990s saw the publication of the results of several well-conducted randomized trials comparing daunorubicin with idarubicin, a newly introduced anthracycline agent.[4-7] The studies compared daunorubicin at a dose of 45 to 50 mg/m^2/d with idarubicin at 12 to 13 mg/m^2/d, with three of the four trials showing a superior complete remission (CR) rate with idarubicin compared with daunorubicin, particularly in younger patients. However, it was unclear whether any observed improvement with idarubicin over daunorubicin represented an inherent biologic advantage of idarubicin. During the consolidation phase of the studies, when patients received cytarabine and 2 days of either idarubicin or daunorubicin at the same doses as induction therapy, idarubicin showed significantly greater myelosuppression,

ASSOCIATED CONTENT

Appendix
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suggesting that the two drugs were not compared at equivalent doses. In 2009, the results of two randomized trials (one for younger patients [Eastern Cooperative Oncology Group E1900 trial] and the other for elderly patients) investigating the effects of anthracycline dose intensification in AML showed that induction therapy using a high daily dose of daunorubicin (90 mg/m^2/d for 3 days) improved both the CR rate and survival duration compared with the standard daunorubicin dose (45 mg/m^2/d for 3 days).[8,9] During a similar period to the previously mentioned studies, we also conducted a randomized trial comparing two different doses of daunorubicin (90 mg/m^2/d for 3 days *v* 45 mg/m^2/d for 3 days) in younger patients with AML and confirmed superior outcomes with high-dose daunorubicin over standard-dose daunorubicin.[10]

Accordingly, a high daily dose of daunorubicin (90 mg/m^2/d for 3 days) should be the future standard of care for induction in patients with AML, but it remains unclear whether high-dose daunorubicin is superior to idarubicin (12 mg/m^2/d for 3 days). Thus, we performed another randomized trial comparing the two induction regimens—idarubicin vs high-dose daunorubicin—in young adults with AML. Here, we present the final results of the study.

PATIENTS AND METHODS

Patient Population

All patients had been cytologically confirmed to have AML; the level of myeloblasts in bone marrow exceeded 20%. Patients with acute promyelocytic leukemia or chronic myeloid leukemia in the blastic phase were not included. No patients had been previously treated, and all patients were age 15 to 65 years.

The study was approved by the institutional review board of each participating institute. All patients provided informed consent in accordance with the Declaration of Helsinki before random assignment. We randomly assigned patients to cytarabine plus idarubicin (AI arm) or to cytarabine plus high-dose daunorubicin (AD arm). The study was registered at ClinicalTrials.gov as NCT01145846.

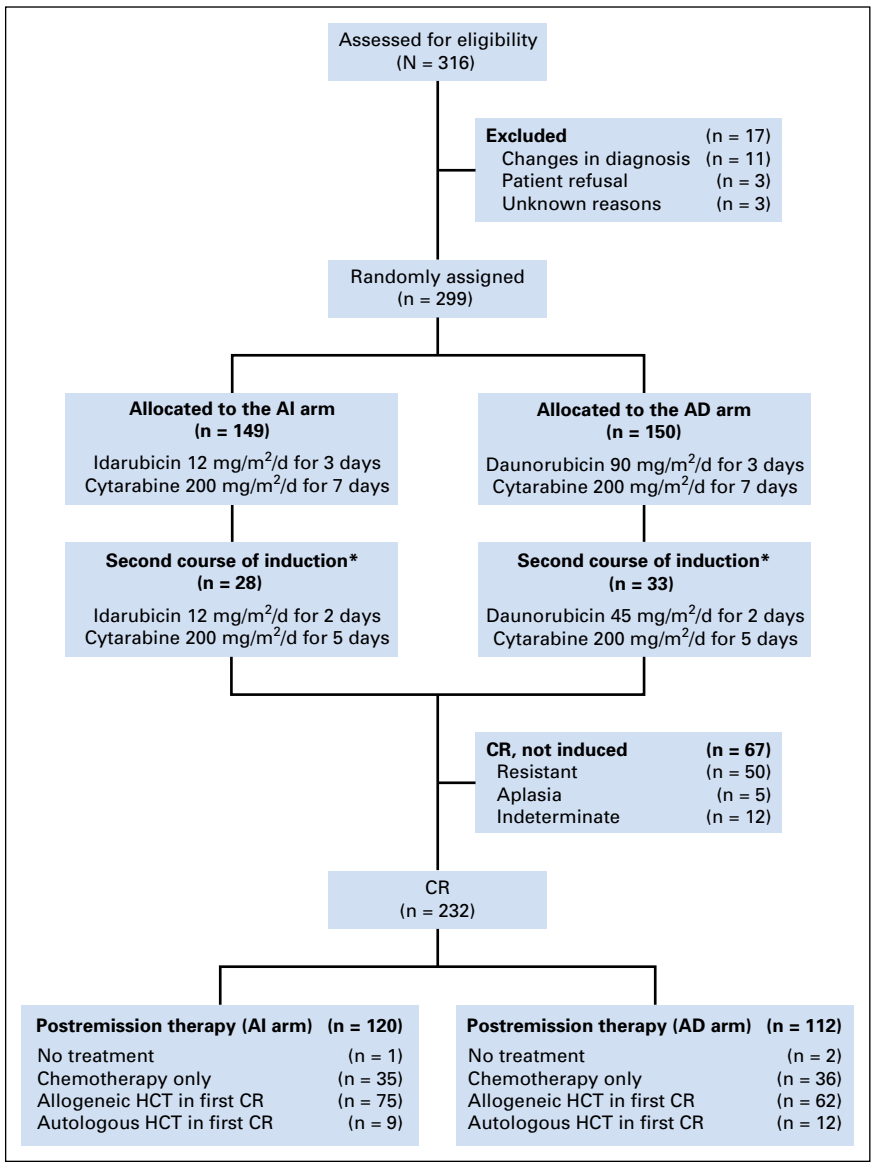

Fig 1. CONSORT flow diagram. (*) If patients showed persistent leukemia at the interim bone marrow examination (usually 14 days after induction chemotherapy), a second course of induction therapy was given. AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; CR, complete remission; HCT, hematopoietic cell transplantation.

Treatment

Patients randomly assigned to the AI arm received idarubicin 12 mg/m^2/d for 3 consecutive days; patients randomly assigned to the AD arm received daunorubicin 90 mg/m^2/d for 3 consecutive days. All patients also received cytarabine 200 mg/m^2/d by continuous intravenous infusion for 7 consecutive days. Interim bone marrow examination was usually performed 14 days after commencement of the first session of induction chemotherapy to permit physicians to decide about the need for a second round of therapy. For patients showing persistent leukemia after initial induction chemotherapy, the second course of induction chemotherapy consisted of cytarabine 200 mg/m^2/d given by continuous intravenous infusion for 5 days and idarubicin 12 mg/m^2/d (AI arm) or daunorubicin 45 mg/m^2/d (AD arm) for 2 days. Patients who did not achieve CR after the second course of induction chemotherapy were eliminated from the study, although their survival data were obtained.

Patients in either group who attained CR received four courses of consolidation chemotherapy. High-dose cytarabine (cytarabine 3 g/m^2 every 12 hours on days 1, 3, and 5, to constitute a total of six doses per course) was given in patients with good- or intermediate-risk cytogenetics, whereas cytarabine (1 g/m^2 for 6 days) plus etoposide (150 mg/m^2 for 3 days) was administered to those with high-risk cytogenetics. During the first period of CR, allogeneic hematopoietic cell transplantation (HCT) was performed in patients with intermediate- or poor-risk cytogenetics and for whom appropriate donors were available, and autologous HCT was performed in patients with good-risk cytogenetics, as determined by the attending physicians. Generally, the patients underwent HCT after two courses of consolidation chemotherapy.

Evaluation

Standard cytogenetic techniques were used to karyotype leukemic cells at diagnosis. Patients were classified into three risk groups according to karyotype.[11] Good-risk status was defined by the presence of abnormalities in core-binding factors [ie, t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22)]. Poor-risk status was defined by the presence of inv (3)(q21q26.2), t(3;3)(q21;q26.2), t(6;9)(p23;q34), 11q23 abnormalities except for t(9;11)(p22;q23), −5, del(5q), −7, or 17p abnormalities or the presence of a complex karyotype (with three or more abnormalities). Patients with poor-risk status were divided into two groups according to the presence of a monosomal karyotype, which was defined as two or more monosomies or a single monosomy in the presence of structural abnormalities.[12] The presence of a normal karyotype or any other cytogenetic abnormality, including t(9;11)(p22;q23), was considered to indicate intermediate-risk status. Molecular studies such as *FLT3* internal tandem

Table 1. Characteristics of Eligible Patients According to Treatment Group

Characteristic	No. of Patients (%)			*P*
	All Patients (n = 299)	AI Arm (n = 149)	AD Arm (n = 150)	
Sex				.326
Male	163 (54.5)	77 (51.7)	86 (57.3)	
Female	136 (45.5)	72 (48.3)	64 (42.7)	
Age, years				
Median	49	49	48.5	.449
Range	15-65	15-65	15-65	
< 40	88 (29.4)	42 (28.2)	46 (30.7)	.813
40-49	70 (23.4)	37 (24.8)	33 (22.0)	
≥ 50	141 (47.2)	70 (47.0)	71 (47.3)	
Leukemia				.035
De novo	275 (92.0)	142 (95.3)	133 (88.7)	
Secondary	24 (8.0)	7 (4.7)	17 (11.3)	
Karnofsky performance score				.601
≥ 90	156 (52.2)	80 (53.7)	76 (50.7)	
< 90	143 (47.8)	69 (46.3)	74 (49.3)	
Hemoglobin, g/dL*				.475
< 8.0	114 (38.3)	60 (40.3)	54 (36.2)	
≥ 8.0	184 (61.7)	89 (59.7)	95 (63.8)	
WBC at diagnosis				.095
< 50,000/μL	229 (76.6)	108 (72.5)	121 (80.7)	
≥ 50,000/μL	70 (23.5)	41 (27.5)	29 (19.3)	
Uric acid, mg/dL†				.277
< 7.0	227 (84.4)	109 (82.0)	118 (86.8)	
≥ 7.0	42 (15.6)	24 (18.0)	18 (13.2)	
LDH‡				.699
Normal	85 (29.3)	41 (28.3)	44 (30.3)	
Elevated	205 (70.7)	104 (71.7)	101 (69.7)	
Cytogenetic risk group§				.004
Good	62 (21.1)	27 (18.6)	35 (23.5)	
Intermediate	170 (57.8)	97 (66.9)	73 (49.0)	
Poor	62 (21.1)	21 (14.5)	41 (27.5)	
FLT3-ITD‖				.116
Absence	211 (82.7)	102 (79.1)	109 (86.5)	
Presence	44 (17.3)	27 (20.9)	17 (13.5)	

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; ITD, internal tandem duplication; LDH, lactate dehydrogenase.
*Data on one patient were missing.
†Data on 30 patients were missing.
‡Data on nine patients were missing.
§Data on five patients were missing.
‖Data on 44 patients were missing.

duplication (ITD) were not protocol mandated but performed as institutional policy.

CR was defined according to the following standard criteria: < 5% blasts in bone marrow, hematologic recovery measured as an absolute neutrophil count ≥ 1,000/μL and a platelet count ≥ 100,000/μL, and absence of blasts with Auer rods or extramedullary leukemic involvement.[13] The causes of CR induction failure were divided into the following three categories, which are defined elsewhere[13]: treatment failure, complications of aplasia, and an indeterminate cause.

Relapse after CR was defined as reappearance of leukemic blasts in the peripheral blood; ≥ 5% blasts in the bone marrow not attributable to any other cause, such as bone marrow regeneration after consolidation therapy; or the appearance of extramedullary leukemic involvement. Adverse events were graded using the Common Toxicity Criteria for Adverse Events, version 4.02.[14]

Statistical Analysis

The main objective of this phase III randomized, unblinded study was to assess the noninferiority of the AD regimen versus the AI regimen, and the sample size was calculated based on the CR rate. We assumed a 70% CR rate after induction chemotherapy because previous reports have shown CR rates of 65% to 75% with the AI regimen. Sample sizes of 142 patients in each arm would achieve 80% power to detect a noninferiority margin ratio in the group proportions of 0.8. The reference group (AI arm) proportion was 0.7. The test static used was the one-sided score test.[15] The significance level of the test was targeted at $P = .0250$. Considering a dropout rate of 10%, we planned to enroll 158 patients in each arm.

The end points were the CR rate, overall survival (OS), cumulative incidence of relapse (CIR), and event-free survival (EFS). The survivals were calculated for all patients from the date of study entry to the date of death from any cause (OS) or to the date of induction therapy failure, relapse, or death from any cause (EFS). CIR was calculated only for patients who achieved CR from the date of achievement of CR until the date of relapse. Death in remission was counted as a competing cause of failure.

The χ^2 test was used to compare categorical variables, and the Mann-Whitney *U* test or *t* test was used to compare continuous variables. Survival was estimated using the Kaplan-Meier method, and differences in survival were compared using the log-rank test. CIR was estimated using the method of Gray, and differences between groups were analyzed using a test developed by Gray. Multivariable analysis was performed using stepwise multiple logistic regression for CR achievement, the Cox proportional hazards model for survival, and the Fine and Gray method for CIR. Analyses were performed using SPSS software version 21 (IBM, Armonk, NY) and R software (The R Foundation, www.r-project.org).

RESULTS

Patient Characteristics

Between May 2010 and March 2014, 316 patients from eight Korean institutes were registered onto this study. Seventeen patients were excluded, and the remaining 299 patients were analyzed. After random assignment, 149 patients received AI and 150 patients received AD for induction of CR (Fig 1). The distribution of eligible patients was well balanced between the two treatment groups except proportion of secondary leukemia and each cytogenetic risk group. The AD arm had a significantly higher proportion of patients with secondary leukemia and also had more patients with both good- and poor-risk cytogenetic features (Table 1).

Treatment Data

After receiving only one course of induction chemotherapy, 69.2% of patients attained CR (71.1% with AI *v* 66.7% with AD; Table 2). A second course of induction chemotherapy was administered to 61 patients, of whom 26 patients attained CR. Thus, 232 patients (77.6%) achieved CR using either one or two courses of induction chemotherapy. The CR rates did not significantly differ between the AI and AD arms (80.5% *v* 74.7%, respectively; $P = .224$). The main reason for treatment failure in either arm was the presence of resistant disease. Most patients received postremission therapy. Allogeneic HCT was performed in 137 patients (59.1%) and autologous HCT in 21 patients (9.1%). The proportion of patients receiving postremission therapy and its nature were similar between the two arms (Table 2).

Table 2. Induction Chemotherapy, Response, and Postremission Therapy

Response and Postremission Therapy	All Patients (N = 299)	AI Arm (n = 149)	AD Arm (n = 150)	*P*
Interim BM study after induction, No. (%)				.250
Blasts < 5%	223 (74.6)	114 (76.5)	109 (72.7)	
Blasts ≥ 5%	60 (20.1)	25 (16.8)	35 (23.3)	
Unknown	16 (5.4)	10 (6.7)	6 (4.0)	
CR with 1 course of induction, No. (%)	207 (69.2)	106 (71.1)	100 (66.7)	.403
CR after 2 courses of induction, No./total No. (%)	26/61 (42.6)	14/28 (50.0)	12/33 (36.4)	.283
Interval between first and second course, days, median (range)	26.0 (14-144)	26.5 (14-85)	25.0 (14-144)	.891
Overall CR, No. (%)	232 (77.6)	120 (80.5)	112 (74.7)	.224
Reason for treatment failure, No.				.085
Resistant	50	22	28	
Aplasia	5	0	5	
Indeterminate	12	7	5	
Postremission therapy, No. (%)				
No treatment	3 (1.3)	1 (0.8)	2 (1.8)	.629
Chemotherapy only	71 (30.6)	35 (29.2)	36 (32.1)	
Allogeneic HCT	137 (59.1)	75 (62.5)	62 (55.4)	
Autologous HCT	21 (9.1)	9 (7.5)	12 (10.7)	

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; BM, bone marrow; CR, complete remission; HCT, hematopoietic cell transplantation.

Infection was the most common severe adverse event (grade ≥ 3 as rated by Common Terminology Criteria for Adverse Events v4.02) during induction therapy. The frequency of severe adverse events was similar in the AI and AD arms (Appendix Table A1, online only). Time to platelet recovery was shorter in the AD arm than in the AI arm (median, 24 *v* 26 days, respectively; $P = .006$; Appendix Table A1).

Survival Data

The median follow-up duration for surviving patients was 34.9 months (range, 2.8 to 60.7 months). During this time, 67 patients did not achieve CR, 64 patients experienced relapse after CR, 18 patients died without evidence of relapse, and 120 patients died of any cause. The 4-year probabilities of OS, CIR, and EFS were 52.8%, 30.4%, and 48.2%, respectively. Survival did not significantly differ between the AI and AD arms (4-year OS, 51.1% *v* 54.7%, respectively; $P = .756$; CIR, 35.2% *v* 25.1%, respectively; $P = .194$; EFS, 45.5% *v* 50.8%, respectively; $P = .772$; Fig 2).

Prognostic Factors

The prognostic value of several variables, including treatment group, was assessed by univariable (Appendix Table A2, online only) and multivariable (Table 3) analyses. Multivariable analysis showed that cytogenetic risk group (for CR rate, OS, CIR, and EFS), HCT comorbidity index (for CR rate), age (for OS and EFS), WBC at diagnosis (for OS, CIR, and EFS), and secondary leukemia (for CR rate, OS, and EFS) were independent prognostic factors for clinical outcomes.

Interaction Between the Treatment Arm and Other Prognostic Factors

We investigated whether the effect of the treatment arm was the same across all prognostic factors. A univariable Cox proportional hazards model was used to evaluate the effects of anthracycline type (idarubicin *v* high-dose daunorubicin) on OS in each prognostic group. All hazard ratios were for patients receiving high-dose daunorubicin versus those receiving idarubicin (Fig 3). We also performed subgroup analysis in several important prognostic groups for CR rate, OS, CIR, and EFS (Appendix Table A3, online only).

Interestingly, we found that the interaction between the treatment arm and the *FLT3*-ITD mutation was significant, despite the similar distribution of patient characteristics in the two treatment groups (Appendix Table A4, online only). In patients with the *FLT3*-ITD mutation, the AD arm (n = 17), compared with the AI arm (n = 27), showed higher OS (median, not reached *v* 15.5 months, respectively; $P = .030$) and EFS (median, not

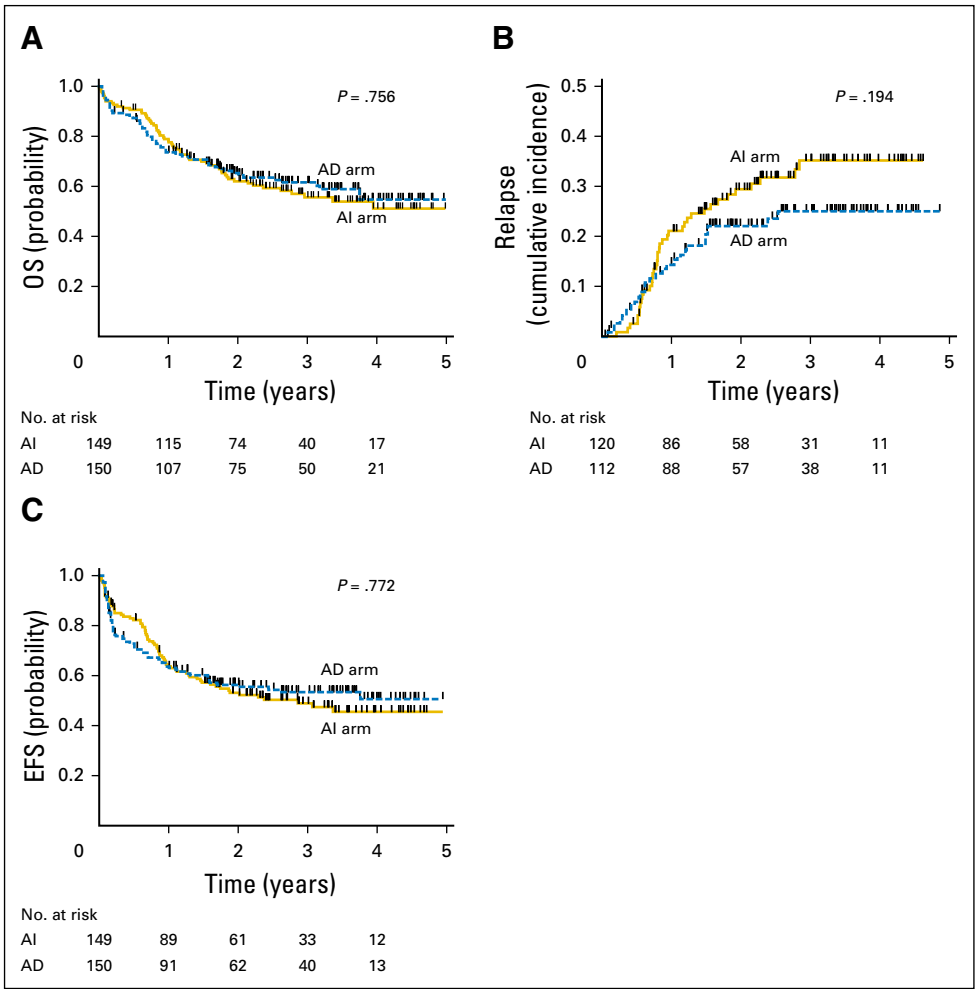

Fig 2. Survival differences between the cytarabine plus idarubicin (AI) and cytarabine plus high-dose daunorubicin (AD) arms. (A) Overall survival (OS). (B) Cumulative incidence of relapse. (C) Event-free survival (EFS).

Table 3. Multivariable Analysis of Prognostic Factors for Induction of Complete Remission, Survival Probabilities, and Cumulative Incidence of Relapse

Variable	Hazard Ratio	95% CI	*P*
Complete remission rate			
Treatment arm			.983
AI	1		
AD	1.007	0.510 to 1.989	
Leukemia			< .001
De novo	1		
Secondary	0.042	0.013 to 0.142	
HCT-CI			.044
0	1		
≥ 1	0.501	0.255 to 0.982	
Cytogenetic risk group			
Good	1		< .001
Intermediate	0.371	0.105 to 1.308	.123
Poor, MK negative	0.093	0.024 to 0.354	< .001
Poor, MK positive	0.048	0.010 to 0.226	< .001
Overall survival			
Treatment arm			< .001
AI	1		
AD	0.961	0.672 to 1.460	.961
Age, years			
< 40	1		< .001
40-49	1.842	0.976 to 3.479	.060
≥ 50	2.968	1.730 to 5.092	< .001
Leukemia			< .001
De novo	1		
Secondary	3.058	1.832 to 5.104	
WBC at diagnosis			< .001
< 50,000/μL	1		
≥ 50,000/μL	2.242	1.481 to 3.393	
Cytogenetic risk group			
Good	1		< .001
Intermediate	3.376	1.446 to 7.885	.005
Poor, MK negative	5.790	2.342 to 14.314	< .001
Poor, MK positive	12.054	4.468 to 32.519	< .001
Cumulative incidence of relapse			
Treatment arm			.330
AI	1		
AD	0.771	0.455 to 1.310	
WBC/μL at diagnosis			.005
< 50,000	1		
≥ 50,000	2.235	1.282 to 3.900	
Cytogenetic risk group			
Good	1		< .001
Intermediate	1.994	0.940 to 4.230	.072
Poor, MK negative	3.117	1.188 to 8.180	.021
Poor, MK positive	19.653	6.994 to 55.220	< .001
Event-free survival			
Treatment arm			.734
AI	1		
AD	0.940	0.660 to 1.340	
Age, years			
< 40	1		.002
40-49	1.063	0.611 to 1.851	.828
≥ 50	2.119	1.351 to 3.324	.001
Leukemia			< .001
De novo	1		
Secondary	4.696	2.776 to 7.946	
WBC/μL at diagnosis			< .001
< 50,000	1		
≥ 50,000	2.031	1.386 to 2.976	
Cytogenetic risk group			
Good	1		< .001
Intermediate	2.075	1.115 to 3.862	.021
Poor, MK negative	4.601	2.305 to 9.184	< .001
Poor, MK positive	7.266	3.184 to 16.5846	< .001

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; HCT-CI, hematopoietic cell transplantation comorbidity index; MK, monosomal karyotype.

Subgroup	No. of Patients (AI/AD)	4-Year OS Probability (%) AI	AD	Hazard Ratio (95% CI)	P
All patients	149/150	51.1	54.7	0.945 (0.660 to 1.352)	.756
Sex					
Male	77/86	47.9	46.2	0.945 (0.642 to 1.609)	.945
Female	72/64	55.2	65.9	0.827 (0.463 to 1.475)	.519
Age, years					
< 40	42/46	77.3	77.4	0.769 (0.296 to 1.999)	.591
40-49	37/33	56.4	62.4	1.068 (0.494 to 2.311)	.867
≥ 50	70/71	31.3	34.9	0.992 (0.634 to 1.551)	.972
Leukemia					
De novo	142/133	53.0	64.5	0.743 (0.498 to 1.109)	.146
Secondary	7/17	0	0	2.124 (0.697 to 6.470)	.185
HCT-CI score					
0	90/104	55.5	59.3	0.943 (0.588 to 1.512)	.943
> 0	59/46	46.1	46.3	1.006 (0.579 to 1.747)	.984
Karnofsky performance score					
≥ 90	80/76	63.3	68.4	0.782 (0.432 to 1.413)	.415
< 90	69/74	39.7	42.4	1.026 (0.652 to 1.615)	.910
White blood cells					
< 50,000/μL	108/121	52.4	58.1	0.918 (0.595 to 1.417)	.700
≥ 50,000/μL	41/29	44.9	37.9	1.273 (0.668 to 2.427)	.463
LDH					
Normal	41/44	61.4	55.7	1.563 (0.752 to 3.248)	.231
Elevated	104/101	48.5	55.3	0.769 (0.500 to 1.180)	.229
Cytogenetic risk group					
Good	27/35	85.2	90.7	0.352 (0.065 to 1.925)	.229
Intermediate	97/73	53.1	49.0	1.089 (0.681 to 1.741)	.723
Poor, MK negative	12/31	25.0	40.8	0.994 (0.411 to 2.403)	.989
Poor, MK positive	9/10	0	24.0	1.095 (0.381 to 3.148)	.866
FLT3-ITD					
Absence	102/109	57.5	55.2	1.130 (0.718 to 1.780)	.597
Presence	27/17	30.8	61.9	0.345 (0.126 to 0.946)	.039

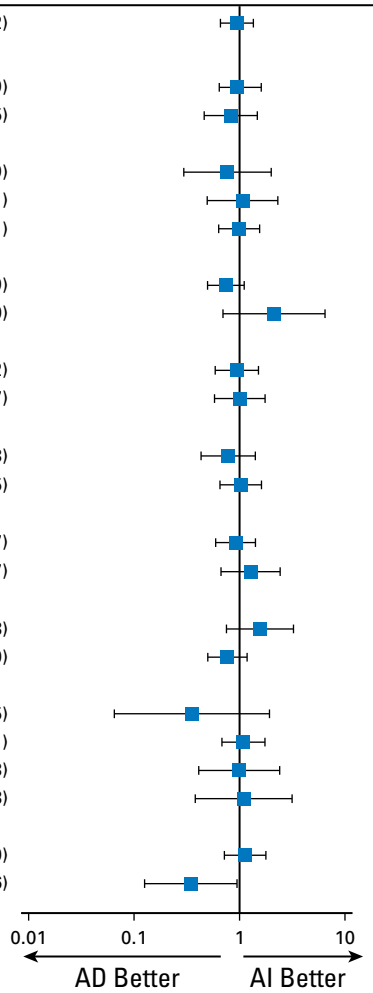

Fig 3. Interaction between the treatment arm and other prognostic factors for overall survival (OS). A univariable Cox proportional hazards model was used to estimate hazard ratios and the significance of the comparison for OS. The horizontal lines represent 95% CIs for the ratios. All hazard ratios are for patients receiving cytarabine plus high-dose daunorubicin (AD) compared with those receiving cytarabine plus idarubicin (AI). HCT-CI, hematopoietic cell transplantation comorbidity index; ITD, internal tandem duplication; LDH, lactated dehydrogenase; MK, monosomal karyotype.

reached *v* 11.9 months, respectively; $P = .028$; Fig 4); however, the CR rate (88.2% *v* 74.1%, respectively; $P = .257$) and CIR (4-year probability, 23.1% *v* 30.0%, respectively; $P = .387$) were not significantly different (Appendix Table A5, online only). Multivariable analysis confirmed higher OS and EFS in the AD arm than in the AI arm (Appendix Table A6, online only). There were no significant differences in clinical outcomes between the two arms in patients without the *FLT3*-ITD mutation.

DISCUSSION

The results of this phase III trial comparing idarubicin (12 mg/m^2/d for 3 days) with high-dose daunorubicin (90 mg/m^2/d for 3 days) did not show significant differences in CR rates and survival between the two arms. Although there were differences in patient characteristics regarding secondary leukemia and cytogenetic risk group between the two arms (more patients with secondary leukemia, good cytogenetic risk, and poor cytogenetic risk in the AD arm), multivariable and subgroup analysis showed that the imbalances did not have significant impact on the outcomes. Adverse events during induction therapy were also similar between the two arms, although platelet recovery after induction therapy was faster in the AD arm than in the AI arm.

In the randomized French Acute Leukemia Association (ALFA) 9801 trial, high-dose daunorubicin (80 mg/m^2/d for 3 days) or idarubicin (12 mg/m^2/d for 4 days [IDA4]) was compared with standard-dose idarubicin (12 mg/m^2/d for 3 days [IDA3]) for remission induction in older patients with AML (age 50 to 70 years). CR rates were significantly different among the three arms (IDA3, IDA4, and daunorubicin: 83%, 78%, and 70%, respectively; $P = .04$), but no significant differences were observed in relapse incidence, EFS, or OS.[16] The Japan Adult Leukemia Study Group conducted a randomized trial for induction therapy of young adults (age 15 to 64 years) with AML, and the patients were randomly assigned to receive either daunorubicin (50 mg/m^2/d

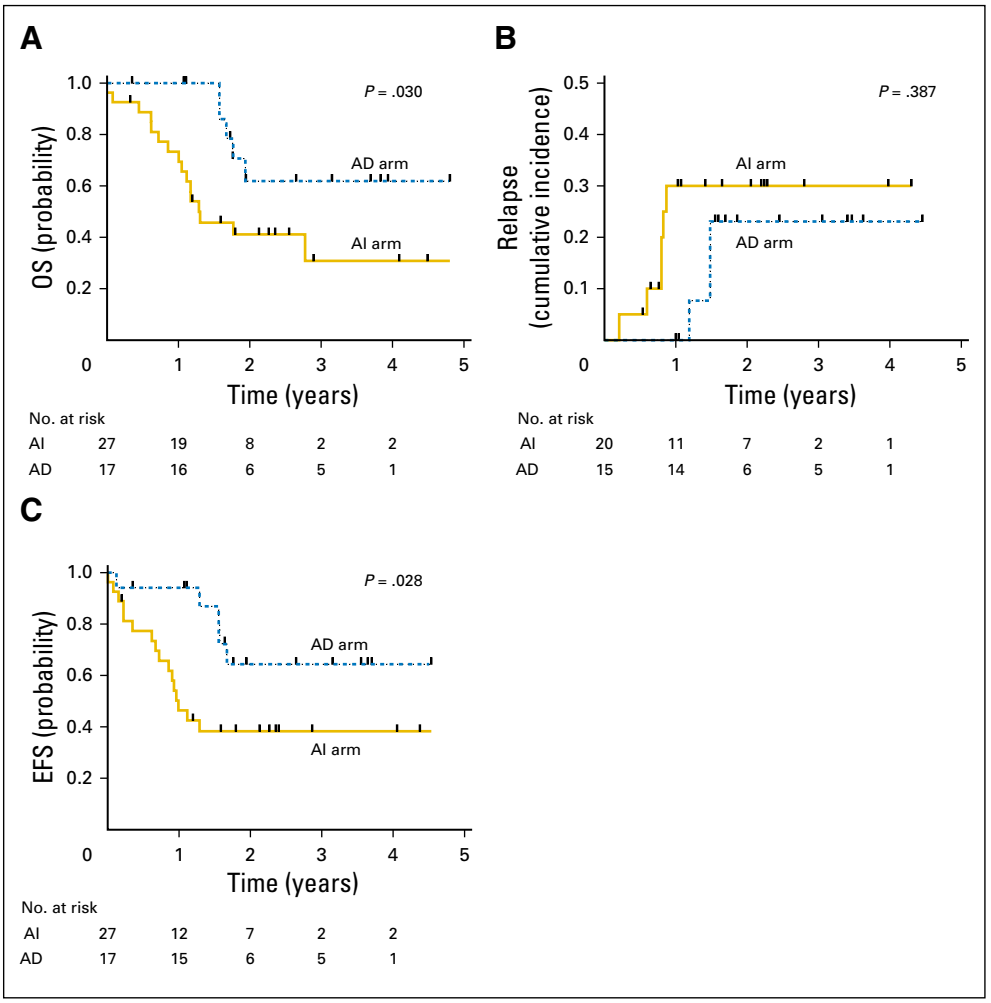

Fig 4. Survival differences between the cytarabine plus idarubicin (AI) and cytarabine plus high-dose daunorubicin (AD) arms in patients with the *FLT3*-internal tandem duplication mutation. (A) Overall survival (OS). (B) Cumulative incidence of relapse. (C) Event-free survival (EFS).

for 5 days) or idarubicin (12 mg/m^2/d for 3 days) in combination with cytarabine. CR rates and survival were similar between the two arms.[17] In a randomized trial (Groupe Ouest-Est d'Etude des Leucémies Aiguës et Autres Maladies du Sang [GOELAMS] LAM-2001), two remission induction regimens comprising idarubicin (8 mg/m^2/d for 5 days) or daunorubicin (60 mg/m^2/d for 3 days) in combination with cytarabine showed similar OS and leukemia-free survival.[18] For induction therapy of pediatric patients with AML (< 18 years old), liposomal daunorubicin (80 mg/m^2/d for 3 days) was compared with idarubicin (12 mg/m^2/d for 3 days); each drug was combined with cytarabine and etoposide. Five-year results were similar in the two treatment arms in terms of OS, EFS, and CIR.[19] A meta-analysis of anthracyclines during induction therapy in younger patients with AML (< 60 years old) showed that idarubicin was superior to daunorubicin when the daunorubicin-to-idarubicin dose ratio was less than 5 (risk ratio, 0.65; 95% CI, 0.66 to 0.99; $P = .04$), whereas the two agents were comparable with a daunorubicin-to-idarubicin dose ratio ≥ 5 (risk ratio, 1.03; 95% CI, 0.91 to 1.16; $P = .63$).[20] Although idarubicin at a dose of 12 to 13 mg/m^2/d for 3 days seemed to be superior to daunorubicin at a dose of 45 to 50 mg/m^2/d for 3 days in several randomized trials,[4-7] our study and other recent randomized trials showed that daunorubicin at a dose range of 60 to 90 mg/m^2/d for 3 days seems to be comparable to idarubicin at a dose of 12 mg/m^2/d for 3 days as induction therapy for younger patients with AML.

We found significant interaction between the treatment arm and the *FLT3*-ITD mutation. Patients with *FLT3*-ITD mutations in the AD arm showed higher OS and EFS than those in the AI arm. Recently, long-term follow-up results of the E1900 trial found more beneficial effects from high-dose daunorubicin (90 mg/m^2/d) than standard-dose daunorubicin (45 mg/m^2/d) among patients with the *FLT3*-ITD mutation in terms of CR rate (70% *v* 48%, respectively; $P = .008$), OS (4-year probability, 28% *v* 17%, respectively; $P = .008$), and EFS (23% *v* 8%, respectively; $P = .009$); the CIR at 4 years was 61% *v* 70%, respectively ($P = .24$).[21] In the United Kingdom National Cancer Research Institute (UK NCRI) AML17 trial comparing daunorubicin 90 mg/m^2 versus 60 mg/m^2, outcomes with 90 mg were not significantly better in patients with the *FLT3*-ITD mutation after 12 months (hazard ratio, 0.74; 95% CI, 0.47 to 1.17; $P = .20$).[22] In a recent update of the UK NCRI AML17 trial, 3-year OS was significantly higher with 90 mg compared with 60 mg (54% *v* 34%, respectively; $P = .03$).[23] The E1900 and UK NCRI AML17 trials suggested that patients with the *FLT3*-ITD mutation might benefit from daunorubicin dose intensification in induction therapy. In contrast, there have been no data supporting that idarubicin dose intensification is beneficial to patients with *FLT3*-ITD mutations. Our trial suggests that higher doses of daunorubicin are better than idarubicin in this population, although this finding should be confirmed in a larger randomized study. Our finding might also be

important to develop optimal combination strategies of cytotoxic agents plus FLT3 inhibitors.

In summary, the results of this phase III trial comparing idarubicin (12 mg/m^2/d for 3 days) with high-dose daunorubicin (90 mg/m^2/d for 3 days) did not show significant differences between the two arms in terms of CR rates and survival. Significant interaction between the treatment arm and the *FLT3*-ITD mutation was found, and high-dose daunorubicin was more effective than idarubicin in patients with the *FLT*-ITD mutation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Adverse Events (grade ≥ 3 by NCI CTCAE v4.02) and Hematologic Recovery During and After Induction Therapy

Adverse Event	All Patients (N = 299)	AI Arm (n = 149)	AD Arm (n = 150)	*P*
Adverse events (grade ≥ 3 by NCI CTCAE v4.02), No. (%)				
Bleeding	4 (1.3)	1 (0.7)	3 (2.0)	.317
Cardiac	5 (1.7)	3 (2.0)	2 (1.3)	.647
Ophthalmologic	1 (0.3)	1 (0.7)	0	.315
General	10 (3.3)	6 (4.0)	4 (2.7)	.513
GI	49 (16.4)	23 (15.4)	26 (17.3)	.658
Hepatobiliary	4 (1.3)	2 (1.3)	2 (1.3)	.995
Infection	227 (75.9)	111 (74.5)	116 (77.3)	.566
Metabolism	18 (6.0)	9 (6.0)	9 (6.0)	.988
Neurologic	3 (1.0)	2 (1.3)	1 (0.7)	.558
Renal	1 (0.3)	1 (0.7)	0	.315
Respiratory	8 (2.6)	4 (2.6)	4 (2.6)	.955
Dermatologic	20 (6.6)	9 (6.0)	11 (7.2)	.666
Hematologic recovery				
Time to recovery, days, median (95% CI)				
ANC > 500/μL	25 (24.4 to 25.6)	26 (24.8 to 27.2)	24 (23.0 to 25.0)	.105
PLT > 20,000/μL	25 (24.2 to 25.8)	26 (24.9 to 27.1)	24 (23.0 to 25.0)	.006
Transfusion requirements, units, median (range)				
RBC	8 (0-43)	9 (0-29)	8 (0-43)	.189
PLT	60 (0-879)	66 (0-879)	54 (0-590)	.396

Abbreviations: AD, cytarabine plus daunorubicin; AI, cytarabine plus idarubicin; ANC, absolute neutrophil count; NCI CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; PLT, platelets.

Table A2. Univariable Analysis of Prognostic Factors for the Induction of CR, Survival Probabilities, and CIR

Variable	CR Rate (%)	*P*	Probabilities at 4 Years					
			OS (%)	*P*	CIR (%)	*P*	EFS (%)	*P*
Treatment arm		.224		.756		.194		.772
AI	80.5		51.1		35.2		45.5	
AD	74.7		54.7		25.1		50.8	
Sex		.071		.112		.294		.075
Male	73.6		46.8		33.5		43.0	
Female	82.4		60.3		26.7		54.6	
Age, years		< .001		< .001		.314		< .001
< 40	86.4		76.8		25.0		64.4	
40-49	87.1		58.8		26.3		54.9	
≥ 50	67.4		33.2		38.3		34.1	
Leukemia		< .001		< .001		.297		< .001
De novo	82.9		58.5		30.0		53.2	
Secondary	16.7		0		50.0		0	
HCT-CI score		.030		.055		.327		.080
0	81.4		57.2		28.0		50.0	
≥ 1	70.5		46.2		35.1		43.5	
Karnofsky performance score		< .001		< .001		.025		< .001
≥ 90	85.9		65.5		25.4		58.3	
< 90	68.5		41.0		37.6		38.2	
Hemoglobin, g/dL		.857		.658		.341		.696
< 8.0	78.1		57.7		34.5		47.7	
≥ 8.0	77.2		49.5		27.9		48.2	
WBC/μL		.918		.002		.008		.004
< 50,000	77.7		55.5		26.8		51.9	
≥ 50,000	77.1		42.2		42.0		35.4	
Uric acid, mg/dL		.503		.921		.114		.483
< 7.0	76.2		51.7		30.4		47.7	
≥ 7.0	81.0		52.6		42.1		43.1	
LDH		.222		.258		.089		.487
Normal	72.9		58.0		21.6		55.0	
Elevated	79.5		51.5		33.5		46.3	
Cytogenetic risk group		< .001		< .001		< .001		< .001
Good	95.2		88.3		16.1		78.2	
Intermediate	80.6		50.9		30.6		47.5	
Poor, MK negative	60.5		39.4		40.0		29.9	
Poor, MK positive	36.8		10.5		100.0		0	
FLT3-ITD		.690		.074		.901		.690
Absence	76.8		56.2		27.2		49.6	
Presence	79.5		43.2		31.3		48.3	

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; CIR, cumulative incidence of relapse; CR, complete remission; EFS, event-free survival; HCT-CI, hematopoietic cell transplantation comorbidity index; ITD, internal tandem duplication; LDH, lactate dehydrogenase; MK, monosomal karyotype; OS, overall survival.

Table A3. Subgroup Analysis According to Several Variables and Type of Postremission Therapy to Evaluate the Effects of Anthracycline Type (idarubicin *v* daunorubicin) on Clinical Outcomes

Variable	CR Rate (%)	*P*	Probabilities at 4 Years					
			OS (%)	*P*	CIR (%)	*P*	EFS (%)	*P*
All patients (N = 299)	77.6		52.8		30.4		48.2	
Cytogenetic good-risk group		.043		.208		.288		.587
AI (n = 27)	88.9		85.2		13.5		73.2	
AD (n = 35)	100.0		90.7		17.4		82.7	
Cytogenetic intermediate-risk group		.134		.723		.342		.944
AI (n = 97)	84.5		53.1		33.8		46.7	
AD (n = 73)	75.3		49.0		25.8		48.6	
Cytogenetic poor-risk and MK-negative group		.859		.989		.021		.533
AI (n = 12)	58.3		25.0		57.1		14.1	
AD (n = 31)	61.3		40.8		23.5		36.3	
Cytogenetic poor-risk and MK-positive group		.515		.866		.151		.267
AI (n = 9)	44.4		0		100.0		0	
AD (n = 10)	30.0		24.0		100.0		0	
De novo leukemia		.931		.144		.170		.153
AI (n = 142)	83.1		53.0		34.8		47.5	
AD (n = 133)	82.7		64.5		24.4		59.5	
Secondary leukemia		.315		.176		.083		.192
AI (n = 7)	28.6		0		33.3		0	
AD (n = 17)	11.8		0		0		0	
FLT3-ITD negative		.126		.596		.218		.610
AI (n = 102)	81.4		57.5		37.2		49.3	
AD (n = 109)	72.5		55.2		25.0		49.8	
FLT3-ITD positive		.257		.030		.387		.028
AI (n = 27)	74.1		30.8		30.0		38.3	
AD (n = 17)	88.2		61.9		23.1		64.4	
Chemotherapy only*				.167		.532		.708
AI (n = 35)			56.4		48.6		48.5	
AD (n = 36)			63.6		42.5		52.7	
Allogeneic HCT*				.111		.166		.037
AI (n = 75)			61.9		32.0		52.6	
AD (n = 62)			75.7		18.6		74.2	
Autologous HCT*				.414		.889		.889
AI (n = 9)			100		11.1		88.9	
AD (n = 12)			83.3		8.3		91.7	

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; CIR, cumulative incidence of relapse; CR, complete remission; EFS, event-free survival; HCT, hematopoietic cell transplantation; ITD, internal tandem duplication; MK, monosomal karyotype; OS, overall survival.
*Type of postremission therapy in patients who achieved CR.

Table A4. Characteristics of Patients and Postremission Therapy in Patients With *FLT3*-ITD Mutation

Characteristic	No. of Patients (%)			*P*
	All Patients (N = 44)	AI Arm (n = 27)	AD Arm (n = 17)	
Sex				.548
Male	26 (59.1)	15 (55.6)	11 (64.7)	
Female	18 (40.9)	12 (44.4)	6 (35.3)	
Age, years				.131
< 40	9 (20.5)	3 (11.1)	6 (35.3)	
40-49	12 (27.3)	9 (33.3)	3 (17.6)	
≥ 50	23 (52.3)	15 (55.6)	8 (47.1)	
Leukemia				.422
De novo	43 (97.7)	26 (96.3)	17 (100)	
Secondary	1 (2.3)	1 (3.7)	0	
Karnofsky performance score				.651
≥ 90	24 (54.5)	14 (51.9)	10 (58.8)	
< 90	20 (45.5)	13 (48.1)	7 (41.2)	
Hemoglobin, g/dL				.160
< 8.0	16 (36.4)	12 (44.4)	4 (23.5)	
≥ 8.0	28 (63.6)	15 (55.6)	13 (76.5)	
WBC/μL at diagnosis				.694
< 50,000	30 (68.2)	19 (70.4)	11 (64.7)	
≥ 50,000	14 (31.8)	8 (29.6)	6 (35.3)	
Uric acid, mg/dL				.973
< 7.0	33 (76.7)	20 (76.9)	13 (76.5)	
≥ 7.0	10 (23.3)	6 (23.1)	4 (23.5)	
Not tested	1	1	0	
LDH				.381
Normal	8 (18.2)	6 (22.2)	2 (11.8)	
Elevated	36 (81.8)	21 (77.8)	15 (88.2)	
Cytogenetic risk group				.322
Good	4 (9.8)	1 (4.2)	3 (17.6)	
Intermediate	28 (68.3)	18 (75.0)	10 (58.8)	
Poor	9 (22.0)	5 (20.8)	4 (23.5)	
Unknown	3	3	0	
Postremission therapy				
Chemotherapy only	3	3	0	
Allogeneic HCT	31	16	15	
Autologous HCT	1	1	0	

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI; cytarabine plus idarubicin; HCT, hematopoietic cell transplantation; ITD, internal tandem duplication; LDH, lactate dehydrogenase.

Table A5. Univariable Analysis of Prognostic Factors for the Induction of CR, Survival Probabilities, and Cumulative Incidence of Relapse in Patients With *FLT3*-ITD Mutation

	CR		OS		4-Year CIR		EFS	
Variable	Rate (%)	*P*	Median (months)	*P*	Rate (%)	*P*	Median (months)	*P*
Treatment arm		.257		.030		.387		.028
AI	74.1		15.5		30.0		11.9	
AD	88.2		NR		23.1		NR	
Sex		.604		.562		.385		.766
Male	76.9		21.1		22.4		18.9	
Female	83.3		33.3		34.1		NR	
Age, years		.226		.039		.185		.059
< 40	88.9		NR		0		NR	
40-49	91.7		21.2		37.9		18.9	
≥ 50	69.6		18.9		32.6		15.5	
Leukemia		.046		.828		—		.756
De novo	81.4		23.2		27.2		20.1	
Secondary	0		—		—		—	
HCT-CI score		.078		.844		.523		.645
0	88.5		23.2		22.8		NR	
≥ 1	66.7		21.1		35.2		20.1	
Karnofsky performance score		.003		.275		.502		.180
≥ 90	95.8		NR		22.7		NR	
< 90	60.0		18.9		35.4		15.5	
Hemoglobin, g/dL		.572		.740		.996		.304
< 8.0	75.0		23.2		26.2		11.9	
≥ 8.0	82.1		NR		27.2		NR	
WBC/μL		.913		.006		.072		.021
< 50,000	80.0		NR		17.4		NR	
≥ 50,000	78.6		15.6		49.1		11.1	
Uric acid, mg/dL		.421		.504		.381		.712
< 7.0	81.8		21.2		32.3		18.9	
≥ 7.0	70.0		NR		14.3		NR	
LDH		.537		.518		.084		.512
Normal	87.5		NR		0		NR	
Elevated	77.8		21.2		34.6		18.9	
Cytogenetic risk group		.020		.503		.431		.405
Good	100.0		NR		0 (2 years)		NR	
Intermediate	89.3		21.1		32.5		20.1	
Poor, MK negative	42.9		NR		0		NR	
Poor, MK positive	50.0		—		—		—	

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; CIR, cumulative incidence of relapse; CR, complete remission; EFS, event-free survival; HCT-CI, hematopoietic cell transplantation comorbidity index; ITD, internal tandem duplication; LDH, lactate dehydrogenase; MK, monosomal karyotype; NR, not reached; OS, overall survival.

Table A6. Multivariable Analysis of Prognostic Factors for Induction of Complete Remission and Survival Probabilities in Patients With *FLT3*-ITD Mutation

Variable	Hazard Ratio	95% CI	*P*
Complete remission rate			
Treatment arm			.300
AI	1		
AD	2.680	0.416 to 17.259	
Karnofsky performance score			.015
≥ 90	1		
< 90	0.065	0.007 to 0.591	
Overall survival			
Treatment arm			.022
AI	1		
AD	0.306	0.111 to 0.844	
WBC/μL at diagnosis			.005
< 50,000	1		
≥ 50,000	3.580	1.484 to 8.638	
Event to free survival			
Treatment arm			.014
AI	1		
AD	0.276	0.098 to 0.774	
WBC/μL at diagnosis			.008
< 50,000	1		
≥ 50,000	3.336	1.3724 to 8.112	

Abbreviations: AD, cytarabine plus high-dose daunorubicin; AI, cytarabine plus idarubicin; ITD, internal tandem duplication.