VOLUME 32 · NUMBER 3 · JANUARY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High-Dose Cytarabine in Induction Treatment Improves the Outcome of Adult Patients Younger Than Age 46 Years With Acute Myeloid Leukemia: Results of the EORTC-GIMEMA AML-12 Trial

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Published online ahead of print at www.jco.org on December 2, 2013.

Written on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) and Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) Leukemia Groups.

Supported by the European Organisation for Research and Treatment of Cancer (EORTC) Charitable Trust.

Presented at the 53rd American Society of Hematology Annual Meeting and Exposition, San Diego, CA, December 10-13, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00004128.

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0732-183X/14/3203w-219w/$20.00

DOI: 10.1200/JCO.2013.51.8571

ABSTRACT

Purpose
Cytarabine plays a pivotal role in the treatment of patients with acute myeloid leukemia (AML). Most centers use 7 to 10 days of cytarabine at a daily dose of 100 to 200 mg/m^2 for remission induction. Consensus has not been reached on the benefit of higher dosages of cytarabine.

Patients and Methods
The European Organisation for Research and Treatment of Cancer (EORTC) and Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) Leukemia Groups conducted a randomized trial (AML-12; Combination Chemotherapy, Stem Cell Transplant and Interleukin-2 in Treating Patients With Acute Myeloid Leukemia) in 1,942 newly diagnosed patients with AML, age 15 to 60 years, comparing remission induction treatment containing daunorubicin, etoposide, and either standard-dose (SD) cytarabine (100 mg/m^2 per day by continuous infusion for 10 days) or high-dose (HD) cytarabine (3,000 mg/m^2 every 12 hours by 3-hour infusion on days 1, 3, 5, and 7). Patients in complete remission (CR) received a single consolidation cycle containing daunorubicin and intermediate-dose cytarabine (500 mg/m^2 every 12 hours for 6 days). Subsequently, a stem-cell transplantation was planned. The primary end point was survival.

Results
At a median follow-up of 6 years, overall survival was 38.7% for patients randomly assigned to SD cytarabine and 42.5% for those randomly assigned to HD cytarabine (log-rank test $P = .06$; multivariable analysis $P = .009$). For patients younger than age 46 years, survival was 43.3% and 51.9%, respectively ($P = .009$; multivariable analysis $P = .003$), and for patients age 46 to 60 years, survival was 33.9% and 32.9%, respectively ($P = .91$). CR rates were 72.0% and 78.7%, respectively ($P < .001$) and were 75.6% and 82.4% for patients younger than age 46 years ($P = .01$) and 68.3% and 74.8% for patients age 46 years and older ($P = .03$). Patients of all ages with very-bad-risk cytogenetic abnormalities and/or FLT3-ITD (internal tandem duplication) mutation, or with secondary AML benefitted from HD cytarabine.

Conclusion
HD cytarabine produces higher remission and survival rates than SD cytarabine, especially in patients younger than age 46 years.

J Clin Oncol 32:219-228. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Cytarabine plays an important role in the treatment of patients with acute myeloid leukemia (AML). Administration at a daily dose of 100 to 200 mg/m^2 for 7 to 10 days in combination with 3 days of an anthracycline is the most commonly used remission induction regimen. This schedule results in complete remission (CR) rates of 60% to 80% depending on age and cytogenetic and molecular features of the acute leukemia.[1,2] Higher doses of cytarabine (2,000 to 6,000 mg/m^2 per day for eight to twelve doses) for induction of remission and/or in consolidation have been tested in various AML trials.[3-17] Thus far, four

randomized trials have been reported that evaluated increased dosages of cytarabine as part of the induction regimen of previously untreated patients.[14-17] Despite these experiences, definite conclusions on the value of high-dose (HD) cytarabine remain hard to draw. Possible reasons are insufficient numbers of patients per trial or more intensive induction strategies in the control arm.[13] On the basis of the encouraging results of the Australian Leukemia Study Group reported by Bishop et al,[14] the Leukemia Groups of the European Organisation for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) conducted a large randomized trial (AML-12; Combination Chemotherapy, Stem Cell Transplant and Interleukin-2 in Treating Patients With Acute Myeloid Leukemia) to compare HD cytarabine versus standard-dose (SD) cytarabine in the induction regimen. In both arms, patients who achieved CR after one or two induction courses received a single consolidation course containing intermediate-dose cytarabine and allogeneic or autologous stem-cell transplantation (SCT).

PATIENTS AND METHODS

Eligibility

Untreated patients with de novo or secondary AML age 15 to 60 years were eligible. Main inclusion criteria were morphologically confirmed AML with bone marrow containing 30% or more blasts; a WHO performance status of 3 or less; no evidence of severe concurrent cardiac, pulmonary, neurologic, or metabolic disorders or uncontrolled infections; and adequate liver and renal function tests. Secondary AML was defined as AML following hematologic or

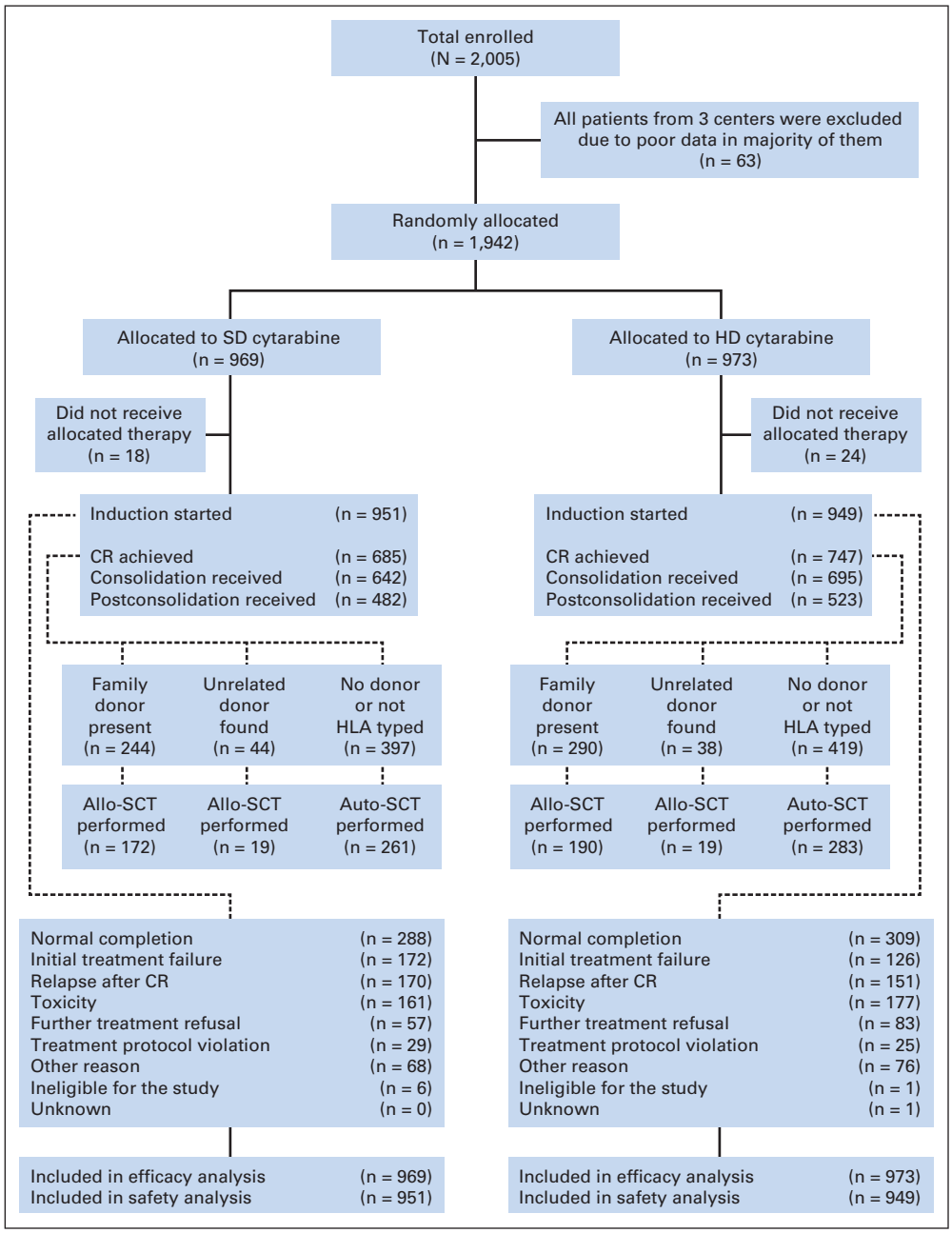

Fig 1. Disposition of patients in each arm. Allo-SCT; allogeneic stem-cell transplantation; auto-SCT, autologous SCT; CR, complete remission; HD, high dose; SD, standard dose.

nonhematologic malignancies or after exposure to chemotherapy or radiation. Patients with promyelocytic leukemia, AML after myelodysplastic syndrome of more than 6 months duration, or AML/blast crisis after chronic myeloproliferative disease or during concomitant other progressive malignant disease were excluded (Fig 1).

The study was approved by the internal review boards of EORTC and GIMEMA and the ethical committee of each participating institution and was conducted in accordance with the Declaration of Helsinki. All patients signed the informed consent form.

Study Design

The study aimed to compare efficacy and toxicity of an induction regimen that contained HD cytarabine versus SD cytarabine. Primary end point was overall survival (OS). Secondary end points were CR rate, disease-free survival (DFS), toxicity, and rate of autologous or allogeneic SCT in each arm. Patients who fulfilled the eligibility criteria were randomly assigned to the standard or experimental arm at the EORTC Headquarters in Brussels, Belgium. At random assignment, patients were stratified according to center, age (15 to 45 years *v* 46 to 60 years), WHO performance status (grade 0 to 1 *v* grade 2 *v* grade 3), and total leukocyte count (< 25 *v* 25 to 99.9 *v* $\geq 100 \times 10^9$/L) by using a minimization technique (Fig 2).

The basis for our standard remission induction regimen was the standard arm of the EORTC-GIMEMA Study AML-10 (Daunorubicin Versus Mitoxantrone Versus Idarubicin As Induction and Consolidation Chemotherapy for Adults With Acute Myeloid Leukemia: The EORTC and GIMEMA Groups Study AML-10),[2] which included daunorubicin, etoposide, and 10 days of cytarabine. At that time, the standard arm in the AML-10 trial showed the lowest toxicity with equal efficacy compared with the experimental arms. Furthermore, this schedule had important similarities with the standard arm of the Australian trial.[14] In the experimental arm, 4 days of HD cytarabine replaced the 10 days of SD cytarabine similar to the experimental arm of the Australian trial. Thus, remission induction consisted of daunorubicin (50 mg/m^2 per day as a 5-minute intravenous [IV] infusion on days 1, 3, and 5) and etoposide (50 mg/m^2 per day by 1-hour IV infusion on days 1 through 5) in both arms, in combination with either 10 days of cytarabine (100 mg/m^2 per day as continuous IV infusion) in the standard arm (SD cytarabine) or cytarabine (3,000 mg/m^2 every 12 hours as a 3-hour IV infusion on days 1, 3, 5, and 7) in the experimental arm (HD cytarabine). Assessment of response was planned by day 31 of induction. Criteria for response and relapse followed the Report of the National Cancer Institute-Sponsored Workshop.[18] In case of partial remission, a second identical induction course was given. Once CR with or without full hematologic recovery was achieved, a single consolidation course identical with the consolidation course of EORTC-GIMEMA AML-10,[2] consisting of intermediate-dose cytarabine (500 mg/m^2 every 12 hours as a 2-hour IV infusion on days 1 through 6) plus daunorubicin (50 mg/m^2 per day as a 5-minute infusion on days 4 through 6) was administered. In some centers, allogeneic SCT (allo-SCT) was strongly recommended after consolidation for patients younger than age 50 years or up to age 60 years with an HLA-compatible family donor, or for patients without a family donor who had AML with chromosome abnormalities involving 3q, 5, t(6;9), t(9;22), 7, or 11q23 complex abnormalities, or for those with a matched unrelated donor who needed a second remission induction course. All patients not eligible for allo-SCT were planned for autologous SCT. Mobilization and collection of autologous stem cells of those patients was scheduled during the recovery phase of consolidation. Lenograstim (150 μg/m^2 per day) was given by daily subcutaneous injections from day 20 of consolidation until completion of the blood stem-cell harvest. All CR patients without a suitable stem-cell donor were eligible for a second random assignment involving 5 days of low-dose subcutaneous interleukin-2 as monthly courses for a year or until relapse. Results of the second random assignment are not within the scope of this report.

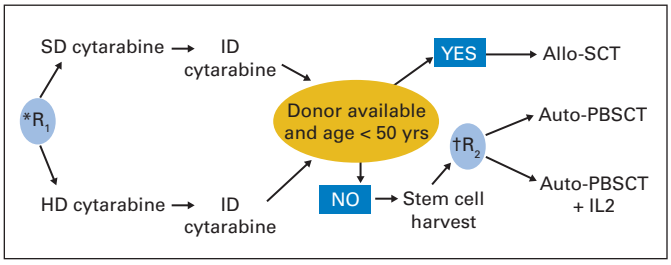

Fig 2. Trial design of the European Organisation for Research and Treatment of Cancer/Gruppo Italiano Malattie Ematologiche dell' Adulto (EORTC-GIMEMA) AML-12 trial. Treatment schedules are as follows: standard-dose (SD) cytarabine induction: daunorubicin (50 mg/m^2 per day as a 5-minute intravenous [IV] infusion on days 1, 3, and 5) plus etoposide (50 mg/m^2 per day by 1-hour IV infusion on days 1 through 5) plus10 days of cytarabine (100 mg/m^2 per day as continuous IV infusion); high-dose (HD) cytarabine induction: daunorubicin (50 mg/m^2 per day as a 5-minute IV infusion on days 1, 3, and 5) plus etoposide (50 mg/m^2 per day by 1-hour IV infusion on days 1 through 5) plus cytarabine (3,000 mg/m^2 every 12 hours as a 3-hour IV infusion on days 1, 3, 5, and 7); intermediate-dose (ID) cytarabine consolidation: cytarabine (500 mg/m^2 every 12 hours as a 2-hour IV infusion on days 1 through 6) plus daunorubicin (50 mg/m^2 per day as a 5-minute infusion on days 4 through 6). Allo-SCT, allogeneic stem-cell transplantation; auto-PBSCT, autologous peripheral blood SCT; IL-2, interleukin-2 (4×10^6 IU/m^2 subcutaneous injection on day $1 + 8 \times 10^6$ IU/m^2 subcutaneous injections on days 2 through 5, every 4 weeks, for 1 year). (*) R_1, first randomization; (†) R_2, second randomization.

End Points

OS was defined as the time interval from random assignment until death, whatever the cause. Follow-up of patients still alive was censored at the moment of last visit or contact. DFS was defined as the time from CR until the first relapse or death as a result of any cause. For patients still alive in first CR, DFS was censored on the date of last visit or contact. Because allo-SCT was integrated into the treatment scheme, follow-up of patients was not censored at the date of allo-SCT. Event-free survival (EFS) for patients in CR was defined as DFS, whereas for patients who did not reach CR, EFS was set as being an event at time zero. The duration of hematologic recovery was defined as the time from the first day of the chemotherapy course until neutrophil level was more than 0.5×10^9/L or platelet level was more than 10×10^9/L or more than 100×10^9/L; patients without recovery were censored at day 99. Toxicity was evaluated according to Common Toxicity Criteria version 2.0.

Statistical Analysis

The study was powered to detect an 8% treatment difference (from 35% to 43%) in the 5-year OS rate, corresponding to a hazard ratio (HR) of 0.80 (two-sided α, 5%; power, 95%) and a treatment-age (15 to 45 *v* 46 to 60 years) interaction with an 80% power. A total of 2,000 randomly assigned patients was required to follow 1,100 of them until death.

Time-to-event outcomes were computed by using the Kaplan-Meier technique and were compared by using the two-tailed log-rank test.[19] Cumulative incidence of relapse and of the incidence of death in CR were estimated by using competing risk methods.[19] Forest plot technique was used to obtain treatment HR estimate, along with its 95% or 99% CI, and to perform subgroup analyses. The Cox proportional hazards model stratified by cytogenetic-molecular features was used to adjust the treatment comparison by initial patient-disease features. Fisher's exact test and linear logistic regression model were used to compare the CR rates after induction.

All efficacy analyses were performed according to the intention-to-treat principle (all patients randomly assigned were included, except for all patients [n = 63] from three centers with extremely poor data reporting). To avoid selection bias, analysis of the impact of allo-SCT on the outcome was performed according to the availability of a donor, and treatment comparison regarding DFS was performed separately in patients with and without a donor. Data for patients who started the protocol treatment were used for response rate, EFS, and adverse event comparison, and data for patients who reached CR were used for DFS and time-to-recovery comparisons. SAS 9.3 software (SAS Institute, Cary, NC) was used for the statistical analyses.

RESULTS

Patients

Between September 1999 and January 2008, 1,942 patients were randomly assigned: 872 from 22 EORTC and 1,070 from 42 GIMEMA

Table 1. Baseline Characteristics of all Patients, Patients Age 15-45 Years, and Patients Age 46-60 Years, by Randomized Treatment Arm

Characteristic	All Patients				Patients Age 15-45 Years				Patients Age 46-60 Years			
	SD Cytarabine (n = 969)		HD Cytarabine (n = 973)		SD Cytarabine (n = 490)		HD Cytarabine (n = 490)		SD Cytarabine (n = 479)		HD Cytarabine (n = 483)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Male sex	504	52	508	52.2	244	49.8	252	51.4	260	54.3	256	53.6
Age, years												
Median	45		45		36		34		54		53	
Range	15-60		15-60		15-45		15-45		46-60		46-60	
WHO performance status 0-1	871	89.9	872	89.6	438	89.4	454	92.7	433	90.4	418	86.5
Type of leukemia												
De novo AML	906	93.5	919	94.5	466	95.1	470	95.9	440	91.9	449	93
Secondary AML	58	6	47	4.8	22	4.5	17	3.5	36	7.5	30	6.2
WBCs at diagnosis $\times 10^9$/L												
< 25	566	58.4	574	59	270	55.1	282	57.6	296	61.8	292	60.5
25-99.9	287	29.6	283	29.1	147	30	149	30.4	140	29.2	134	28.5
≥ 100	116	12	116	11.9	73	14.9	59	12	43	9	57	11.8
Median	16.3		14.8		18.6		17.1		14		13.8	
Range	0.3-393		0.3-358		0.5-393		0.3-358		0.3-269		0.3-351	
FLT3-ITD mutation												
Negative	487	50.3	469	48.2	252	51.4	244	49.8	235	49.1	225	46.6
Positive	126	13.0	137	14.1	68	13.9	68	13.9	58	12.1	69	14.3
Not done	356	36.7	367	37.7	170	34.7	178	36.3	186	38.8	189	39.1
Cytogenetics/FLT3-ITD*												
Good risk	97	10	93	9.6	70	14.3	65	13.3	27	5.6	28	5.8
Intermediate risk	287	29.6	260	26.7	140	28.6	119	24.3	147	30.7	141	29.2
Bad risk	107	11	94	9.7	61	12.4	61	12.4	64	13.4	74	15.3
Very bad risk/FLT3-ITD	223	23	256	26.3	106	21.6	101	20.6	95	19.8	114	23.6
Unknown risk	255	26.3	270	27.7	109	22.2	144	29.4	146	30.5	126	26.1
Donor availability in CR patients only	685		747		366		399		319		348	
No donor present	330		338		182		187		148		151	
Family donor present	244		290		137		157		107		133	
Unrelated donor present	44		38		31		29		13		9	
No HLA typing	67		81		16		26		51		55	

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; HD, high dose; ITD, internal tandem duplication; SD, standard dose.
*Good risk includes the abnormalities inv(16) and t(8;21). Intermediate risk includes normal karyotypes and those with −Y only, without FLT3-ITD mutation. Very bad risk/FLT3-ITD includes presence of −5/5q− and −7/7q−, complex abnormalities, 3q, t(6;9), t(9;22), and 11q23, and all patients with an FLT3-ITD mutation. Other abnormalities were pooled into a separate "bad risk" cytogenetic risk group. Patients with unknown, not done, or unsuccessful cytogenetic tests were grouped together as "unknown risk."

centers. Their median age was 45 years (range, 15 to 60 years). As induction, 969 patients were randomly assigned to receive the SD cytarabine and 973 to receive the HD cytarabine regimen. The two treatment arms were matched with respect to baseline characteristics (Table 1). Fifty-three randomly assigned patients were ineligible—25 (2.6%) in the SD cytarabine and 28 (2.9%) in the HD cytarabine arm—but they were included in the main intention-to-treat analysis. Reasons for ineligibility were wrong diagnosis (acute lymphoblastic leukemia, chronic myeloblastic leukemia, acute promyelocytic leukemia, or myelodysplastic syndrome in 40 patients and other reasons in 13 patients.

Treatment Phases and Outcomes

A total of 1,900 patients started induction treatment: 951 in the SD cytarabine and 949 in the HD cytarabine arm (Fig 1). Reasons for not starting induction were refusal (n = 4), death before treatment (n = 10), ineligibility (n = 21), and other (n = 7). Details regarding treatment phases and outcomes in both randomly assigned arms are shown in Table 2. A significantly higher percentage of patients receiving HD cytarabine achieved CR ($P = .009$). The death rate after one or two induction courses was similar in both arms. Among 1,432 patients who achieved CR, consolidation course was administered to 1,337 patients: 93.7% in the SD cytarabine arm and 93.0% in the HD cytarabine arm. Reasons for not receiving consolidation were death before treatment (n = 7), no longer in CR (n = 14), persisting infection (n = 34), persisting organ failure (n = 7), neurologic toxicity (n = 7), and other (n = 26).

At a median follow-up of 6 years, 1,091 patients had died: 568 (59.7%) in the SD cytarabine arm and 523 (55.2%) in the HD cytarabine arm. The OS rate at 6 years was 40.6% for all patients: 38.7% in the SD cytarabine arm and 42.5% in the HD cytarabine arm (HR, 0.89; $P = .06$). Comparison of treatment outcome stratified for cytogenetic features and adjusted for several other risk factors was significant in favor of HD cytarabine (HR, 0.86; $P = .009$; Fig 3A).

Subgroup Analysis

Planned subgroup analyses according to age group were performed for different end points (Tables 2 and 3, Fig 3B and Fig 4). Both

Table 2. Phases of Treatment and Outcomes, Overall and by Age Group, by Randomized Treatment Arm

	All Patients				Patients Age 15-45 Years				Patients Age 46-60 Years			
	SD Cytarabine		HD Cytarabine		SD Cytarabine		HD Cytarabine		SD Cytarabine		HD Cytarabine	
Induction Treatment	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Patients who started induction	951	100	949	100	484	100	484	100	467	100	465	100
CR after one course	649	68.2	715	75.3	351	72.5	380	78.5	298	63.8	335	72
CR after one or two courses	685	72	747	78.7	366	75.6	399	82.4	319	68.3	348	74.8
Resistant disease	180	18.9	126	13.3	78	16.1	50	10.3	96	20.6	70	15.1
Death during induction phase	86	9	74	7.8	34	7.0	27	5.5	52	11.1	47	10.1
Consolidation treatment (eligible)	685	100	747	100	366	100	399	100	319	100	348	100
Patients who started consolidation	642	93.7	695	93	346	94.5	372	93.2	296	92.8	323	92.8
Postconsolidation treatment	482	75.1	523	75.5	268	77.5	288	77.4	214	72.3	235	72.7
Autologous SCT	261		283		135		149		126		134	
Intensive chemotherapy	30		31		13		18		17		13	
Allogeneic SCT (related donor)	172		190		108		104		64		86	
Allogeneic SCT (unrelated donor)	19		19		12		17		7		2	
Outcome from first CR												
Still alive in first CR	292	42.6	339	45.4	172	47.0	214	53.6	120	37.6	125	35.9
Relapse	321	46.9	315	42.2	164	44.8	157	39.3	157	49.2	158	45.4
Death in first CR	72	10.5	93	12.4	30	8.2	28	7.0	42	13.2	65	18.7
DFS rate at 6 years		41.6		44.7		46.4		52.8		35.8		35.5
HR	0.93		95% CI, 0.81 to 1.06		0.83		99% CI, 0.64 to 1.08		1.03		99% CI, 0.80 to 1.33	
Log rank *P*	0.27				0.07				0.73			
HR*	0.88		95% CI, 0.77 to 1.01		0.79		99% CI, 0.60 to 1.03		0.99		99% CI, 0.77 to 1.27	
Wald *P**	0.08				0.02				0.89			
Relapse incidence at 6 years		47.9		43.0		45.3		40.3		51.1		46.0
Death in CR incidence at 6 years		10.5		12.4		8.3		7.0		13.1		18.5

Abbreviations: CR, complete remission; DFS, disease-free survival; HD, high dose; HR, hazard ratio; ITD, internal tandem duplication; SCT, stem-cell transplantation; SD, standard dose.

*Cox model stratified by cytogenetics/FLT3-ITD, and adjusted by age (when all patients were analyzed).

age ($P = .06$) and disease type (de novo *v* secondary AML $P = .05$) had an impact on treatment comparison regarding survival (Fig 4). For patients age 15 to 45 years, HD cytarabine significantly improved the CR rate (82.4% *v* 75.6%; $P = .01$), the 6-year EFS rate (43.6% *v* 35.1%; $P = .003$), and the 6-year OS rate (51.9% *v* 43.3%; $P = .009$); in older patients, only the CR rate was higher in the HD cytarabine arm. In the younger age group, HD cytarabine increased the 6-year DFS rate compared with SD cytarabine (52.8% *v* 46.4%; $P = .07$) by decreasing the relapse incidence by 5% (40.3% *v* 45.3%) and without increasing the incidence of death in CR (Table 2). In contrast, in the older age group, the decrease of 5.1% (46.0% *v* 51.1%) in relapse incidence was counterbalanced by an increase of 4.6% (18.5% *v* 13.1%) in the incidence of death in CR (Table 2). Furthermore, in the younger age group, HD cytarabine improved OS more in patients with secondary AML (HR, 0.23; $P = .005$) than in patients with de novo AML (HR, 0.83; $P = .04$).

Interestingly, improvement of the CR rate in patients with secondary AML was detected both in younger (odds ratio, 5.99) and in older patients (odds ratio, 3.75), as was the OS in patients with very-bad-risk cytogenetic abnormalities and/or FLT3-ITD (internal tandem duplication) mutation both in younger (HR, 0.70; $P = .02$) and older patients (HR, 0.80, $P = .14$). These findings were confirmed by multivariable analyses (Table 3), and also when eligible patients who started the allocated treatment were considered (data not shown).

DFS According to Donor Availability and Age Group

In the younger age group, availability of a family donor did improve the outcome in both randomly assigned arms. In the SD cytarabine arm, the 6-year DFS rate was 57.4% for patients with a donor and 39.5% for patients without a donor; in the HD cytarabine arm, the 6-year DFS rates were 62.6% and 46.4%, respectively. The estimated treatment HR was 0.84 in patients with a donor and 0.83 in patients without a donor.

For the older age group, the 6-year DFS was approximately 35% in patients with or without a family donor, whether they received HD or SD cytarabine. The estimated treatment HR was close to 1 in each group. Adding patients with unrelated donors to the group of patients with related donors did not significantly alter the treatment comparisons (data not shown).

Adverse Events

Grade 3 and 4 nonhematologic toxicities of the induction courses were not different in the two randomly assigned arms except for conjunctivitis grade 2 to 3 toxicity, which occurred more frequently in the HD cytarabine arm than in the SD cytarabine arm (12.4% *v* 0.5%). Grade 3 and 4 infectious complications were reported in 67.6% of patients receiving SD cytarabine and in 66.2% of those receiving HD cytarabine. In the two age groups (15 to 45 and 46 to 60 years), adverse event profiles in the two randomly assigned arms were remarkably similar. Median time to neutrophil recovery ($> 0.5 \times 10^9$/L) after the

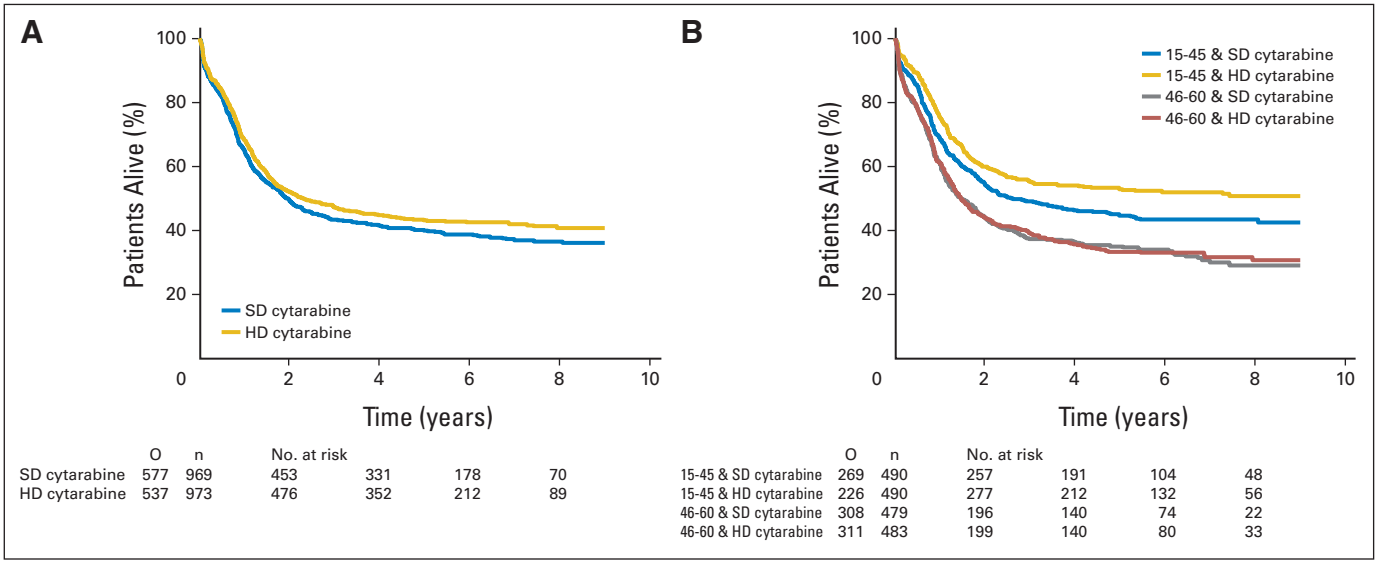

Fig 3. (A) Overall survival according to randomized arm. High-dose (HD) cytarabine versus standard-dose (SD) cytarabine hazard ratio, 0.89 (95% CI, 0.79 to 1.00; $P = .06$). Hazard ratio stratified for cytogenetics and adjusted by age, disease type, WBCs at diagnosis, performance status was 0.86 (95% CI, 0.76 to 0.96; $P = .009$). (B) Overall survival according to age and randomization arm. O, observed No. of deaths.

start of first induction course was 27 days in the SD cytarabine arm *v* 25 days in the HD cytarabine arm. Median times to platelet recovery ($> 100 \times 10^9$/L) were 29 days in the SD cytarabine arm and 27 days in the HD cytarabine arm.

After the consolidation course, grade 3 to 4 nonhematologic toxicities were similar in both arms. Median time to neutrophil recovery ($> 0.5 \times 10^9$/L) was 22 days in both arms. Median time to platelet recovery in the SD *v* HD cytarabine arms was 20 *v* 22 days to reach 10×10^9/L platelets and 31 *v* 38 days to reach 100×10^9/L platelets.

DISCUSSION

This study demonstrates that at a median follow-up of 6 years in patients age 15 to 60 years with untreated AML, induction of remission using HD cytarabine in combination with daunorubicin and etoposide is associated with higher CR rate and survival chance than using the same regimen with SD cytarabine and without significant increase in toxicity. Survival advantage is significant for patients younger than age 46 years and for patients with secondary AML or with AML associated with very-bad-risk cytogenetic abnormalities or FLT3-ITD mutation.

Our results differ from previously published randomized trials on HD cytarabine in the induction regimen.[14-17] Main differences are the number of induction cycles and the total doses of cytarabine administered before establishing treatment response and the number of patients per randomized arm (for details, see Appendix Table A1, online only). We were impressed by the results of the Australian Leukemia Study Group,[14] which randomized remission induction with SD cytarabine and HD cytarabine, both combined with daunorubicin and etoposide, followed (in the case of CR) by two mild consolidation courses and 2 years of maintenance therapy. CR rates were 74% in the SD cytarabine arm and 71% in the HD cytarabine arm. Toxicity was significantly higher after HD cytarabine, and 18% of patients in the HD cytarabine arm died during induction compared with 11% in the SD cytarabine arm ($P = .09$). For patients receiving HD cytarabine, significantly longer duration of remission, DFS, and survival for CR patients was reported. OS was not statistically different between the two arms. The relatively low number of patients included in the trial prevented further long-term analysis. We hypothesized that improvement in supportive care during induction together with availability of more intensive postremission strategies might decrease induction death and relapse rates. Furthermore, the inclusion of a larger number of patients would allow proper evaluation of a potential therapeutic advantage of HD cytarabine in induction therapy. On the basis of these arguments, we designed a large phase III study using both arms of the Australian protocol as well as the control arm of our most recent EORTC-GIMEMA AML-10 study.

In this study, stratification for age (15 to 45 and 46 to 60 years) at registration allowed profound statistical analysis in the two subgroups. In patients younger than age 46, the beneficial effect of HD cytarabine induction was consistently and significantly observed in terms of CR rate, EFS, and OS; in patients age 46 to 60 years, the positive effect of the increase in CR rate was counterbalanced by an increase in death in CR, translating into a small improvement in OS. Younger patients were expected to fare better with intensive chemotherapy and transplantation than older patients.[1,2] However, more intensive treatment and higher remission rates are usually not translated into longer survival. An age effect on survival was not reported by the Australian Leukemia Study Group.[15] Only the HOVON-SAKK (Cytarabine Dose for Acute Myeloid Leukemia) study[17] showed a trend in survival improvement in favor of HD cytarabine in patients younger than 36 years: 52% 5-year OS in the HD cytarabine arm and 42% in the intermediate-dose cytarabine arm (HR, 0.73, $P = .14$). Although the HOVON-SAKK study did not show major differences between the intermediate-dose and HD cytarabine arms, it remains an unanswered question whether a comparison between SD cytarabine and

Table 3. CR Rate, EFS, and OS by Randomized Treatment Group According to Age

Variable	CR Rate							EFS at 6 Years					OS at 6 Years				
	SD	%	HD	%	OR	99% CI	*P*	SD	HD	HR	99% CI	*P*	SD	HD	HR	99% CI	*P*
Age 15-45 years (n = 968)	366/484	75.6	399/484	82.4	1.51	1.00 to 2.26	.01	35.1	43.6	0.79	0.64 to 0.98	.003	43.3	51.9	0.79	0.63 to 1.00	.009
Type of leukemia							.05*					.01*					.02*
De novo AML (n = 927)	353/461	76.6	383/466	82.2	1.41	0.93 to 2.14	.04	35.7	42.5	0.81	0.65 to 1.02	.02	44.1	51.3	0.83	0.65 to 1.05	.04
Secondary AML (n = 39)	13/22	59.1	16/17	94.1	5.99	0.91 to 39.3	.03	24.6	76.5	0.23	0.07 to 0.79	.002	28.7	76.5	0.23	0.08 to 0.89	.005
Cytogenetics/FLT3-ITD†							> .10*					> .10*					> .10*
Good risk (n = 133)	64/69	92.7	56/64	87.5	0.55	0.12 to 2.48	.39	66.1	71.2	0.82	0.37 to 1.84	.53	73.9	80.9	0.70	0.28 to 1.77	.32
Intermediate risk (n = 257)	115/138	83.3	105/119	88.2	1.49	0.59 to 3.71	.29	42.8	57.8	0.63	0.40 to 1.00	.01	54.1	63.4	0.76	0.46 to 1.25	.16
Bad risk (n = 89)	38/50	76	31/39	79.5	1.22	0.33 to 4.52	.80	31.0	35.5	0.98	0.49 to 1.97	.94	42.1	36.6	1.15	0.56 to 2.35	.62
Very bad risk/FLT3-ITD (n = 243)	77/120	64.2	91/123	74	1.58	0.77 to 3.23	.13	16.7	20.3	0.81	0.54 to 1.20	.17	20.0	30.6	0.70	0.47 to 1.04	.02
Unknown risk (n = 246)	72/107	67.3	116/139	83.5	2.44	1.12 to 5.32	.004	27.7	41.1	0.64	0.41 to 1.00	.01	36.4	51.1	0.71	0.45 to 1.11	.05
Multivariable analysis‡					1.58	1.03 to 2.41	.006			0.74	0.60 to 0.92	< .001			0.76	0.60 to 0.96	.003
Age 46-60 years (n = 932)	319/467	68.3	348/465	74.8	1.38	0.95 to 2.01	.03	24.5	26.6	0.93	0.77 to 1.14	.34	33.9	32.9	0.99	0.81 to 1.22	.91
Type of leukemia							.05*					> .10*					> .10*
De novo AML (n = 869)	301/433	69.5	324/436	74.3	1.27	0.86 to 1.87	.13	24.8	26.6	0.94	0.76 to 1.16	.44	34.5	32.6	1.01	0.82 to 1.25	.90
Secondary AML (n = 63)	18/34	52.9	24/29	82.8	3.75	0.95 to 14.74	.002	20.59	26.6	0.79	0.34 to 1.69	.38	28.6	37.0	0.82	0.37 to 1.78	.50
Cytogenetics/FLT3-ITD†							> .10*					> .10*					> .10*
Good (n = 55)	22/27	81.5	23/28	82.1	1.04	0.18 to 6.22	1.00	51.6	42.2	1.20	0.45 to 3.21	.64	59.0	51.3	1.05	0.37 to 2.95	.91
Intermediate (n = 277)	105/143	73.4	108/134	80.6	1.50	0.72 to 3.11	.20	32.5	38.2	0.85	0.57 to 1.28	.31	43.7	43.8	0.96	0.63 to 1.45	.80
Bad (n = 109)	38/56	67.9	36/53	67.9	1.00	0.35 to 2.87	1.00	20.2	18.9	1.06	0.58 to 1.91	.81	31.8	32.5	1.01	0.56 to 1.85	.96
Very bad/FLT3-ITD (n = 229)	55/99	55.6	91/130	70	1.86	0.91 to 3.80	.03	10.3	15.2	0.73	0.48 to 1.10	.05	14.1	20.1	0.80	0.55 to 1.17	.14
Unknown (n = 262)	99/142	69.7	90/120	75	1.30	0.64 to 2.65	.41	22.4	25.8	0.97	0.66 to 1.43	.84	34.1	30.3	1.06	0.72 to 1.56	.70
Multivariable analysis‡					1.44	0.98 to 2.12	.014			0.88	0.72 to 1.07	.09			0.94	0.76 to 1.16	.42

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; EFS, event-free survival; HD, high dose; HR, hazard ratio; ITD, internal tandem duplication; OR, odds ratio; OS, overall survival; SD, standard dose.

*Test for heterogeneity.

†Good risk includes the abnormalities inv(16) and t(8;21). Intermediate risk includes normal karyotypes and those with −Y only, without FLT3-ITD mutation. Very bad risk/FLT3-ITD includes presence of −5/5q−, −7/7q−, complex abnormalities, 3q, t(6;9), t(9;22), 11q23, and all patients with an FLT3-ITD mutation. Other abnormalities were pooled into a separate "bad risk" cytogenetic risk group. Ptients with unknown, not done, or unsuccessful cytogenetic tests were grouped together as "unknown risk."

‡Treatment comparison adjusted by type of leukemia, WBCs at diagnosis, and WHO performance status and Leukemia Group by using a logistic model or a Cox model stratified by cytogenetics/FLT3-ITD risk group.

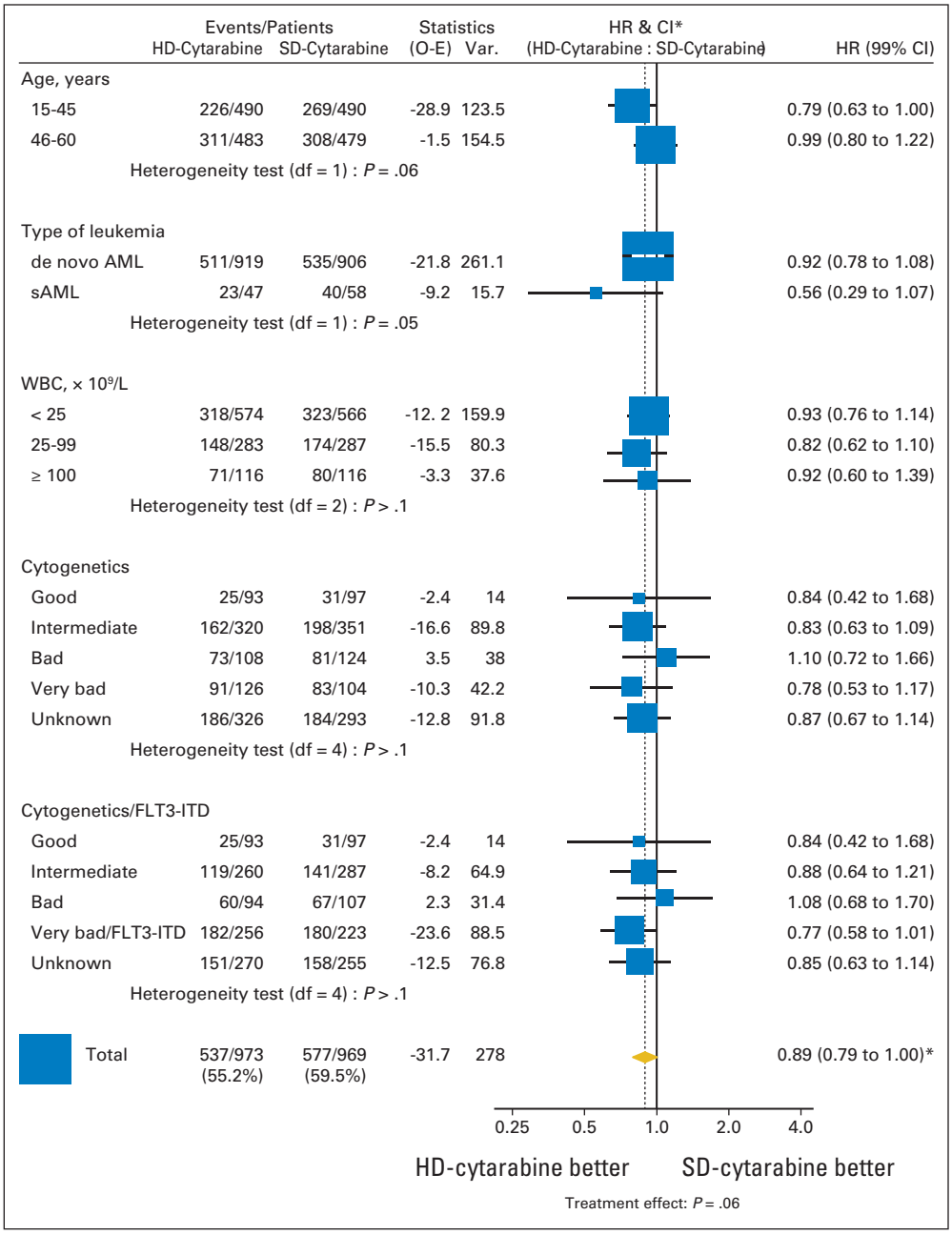

Fig 4. Subgroup analyses of overall survival for high-dose (HD) cytarabine versus standard-dose (SD) cytarabine in the intention-to-treat population. (*) 95%CI for totals and subtotals; 99% CI elsewhere. AML, acute myeloid leukemia; HR, hazard ratio; ITD, internal tandem duplication; O-E, observed-expected; sAML, secondary acute myeloid leukemia; Var., variance.

intermediate-dose cytarabine in induction would have led to the same results as shown with HD cytarabine in our study.

In contrast to the significantly increased toxicity observed in earlier trials,[14,15,17] except for significant conjunctivitis, we report that HD cytarabine, in the way it was administered as it was in our study, was not associated with higher toxicity including death during induction. As mentioned, this could reflect the inclusion of strict supportive guidelines in the treatment protocol. Longer duration of platelet recovery was documented only after the consolidation course. This finding has also been reported in the Australian Study,[14] the EORTC-GIMEMA AML-10 trial[2] and the HOVON-SAKK trial,[17] and may be as a result of increased stem-cell toxicity.

In the younger age group, donor versus no-donor analysis showed that availability of a donor improved the chances to remain alive in first CR equally in both randomized arms. In the older age group, a better antileukemic effect by allo-SCT may have been counterbalanced by a higher death rate as a result of transplantation complications. The number of transplantations using unrelated donor stem cells was too small to affect the results.

The planned subgroup analysis also showed clinically important superiority of HD cytarabine induction in patients with AML with very-bad-risk cytogenetic abnormalities, with FLT3-ITD mutation, and in patients with secondary AML. This is a particularly important finding since, thus far, only allo-SCT has been proven to favorably affect the dismal prognosis of these patients with bad-risk AML.[20]

In conclusion, HD cytarabine in the induction treatment of patients age 15 to 45 years with AML significantly increased response rate and survival without significant increase in grade 3 to 4 toxicities.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Theo de Witte, Novartis (C) **Stock Ownership:** None **Honoraria:** Theo de Witte, Novartis **Research Funding:** Theo de Witte, Novartis **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

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Acknowledgment

We thank the clinicians, nurses, and data managers of the 64 institutions who entered their patients into the EORTC-GIMEMA AML-12 study and provided the necessary data to make this study possible. In addition we are grateful to those who spent their time to quality control tasks. Finally the study could not have been a success without the continuous efforts of the members of the EORTC and GIMEMA data centers.

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Table A1. Summary of the Four Published Randomized Trials on HD Cytarabine in the Induction Regimen

Reference	Induction Schedule SD Cytarabine *v* HD Cytarabine	CR/Total No. of Patients per Arm and Percentages	Consolidation Schedule	Toxicity of Induction Regimen	OS	*P*
Weick et al[15]	SDAC: SD 200 mg/m^2 per day × 7 days (+ daunorubicin) *v* HDAC: HD 2 or 3 g/m^2 every 12 hours for 12 doses (+ daunorubicin)	After SD 275/493 (55.8%) *v* After HD 120/230 (52.2%)	SD *v* HD cytarabine HD cytarabine	HD cytarabine: more fatal toxicity due to infection or CNS hemorrhage (P = .0033)	At 4 years: SD 22% *v* HD 32% (for patients younger than age 50 years) SD 11% *v* HD 13% (for patients age 50-64 years)	.41
Bishop et al[14]	7-3-7: SD 100 mg/m^2 per day × 7 days (+ daunorubicin + etoposide) *v* HIDAC-3-7: HD 3 g/m^2 every 12 hours on days 1, 3, 5, 7 (8 doses) (+ daunorubicin + etoposide)	After SD 110/149 (74%) *v* After HD 108/152 (71%)	5-2-5: Two courses of SD 100 mg/m^2 per day × 5 days (+ daunorubicin + etoposide)	HD cytarabine: more CNS (P = .04), gastrointestinal, and eye toxicity	At 5 years: SD 25% *v* HD 31%	NSD
Buchner et al[16] (only for patients younger than age 60 years)	TAD: SD 100-200 mg/m^2 per day × 8 days (+ daunorubicin + thioguanine) HAM: TAD followed by HD 3 g/m^2 every 12 hours for 6 doses (+ mitoxantrone) *v* HAM × 2: two courses of HD 3 g/m^2 every 12 hours for 6 doses (+ mitoxantrone)	After SD-HD 305/430 (71%) *v* After HD-HD 279/410 (68%)	TAD 100-200 mg/m^2 per day × 8 days (+ daunorubicin + thioguanine)	Not reported	At 3 years: after SD-HD: 44% *v* after HD-HD: 40%	NSD
Löwenberg et al[17]	Intermediate-dose cytarabine arm: SD 200 mg/m^2 per day × 7 days (+ idarubicin) followed by HD 1 g/m^2 every 12 hours for 12 doses (+ amsacrine) *v* HD cytarabine arm: HD 1 g/m^2 every 12 hours for 10 doses (idarubicin) followed by HD 2 g/m^2 every 12 hours on days 1, 2, 4, and 6 for 8 doses (+ amsacrine)	After SD-HD 343/431 (80%) *v* After HD-HD 351/429 (82%)	Mitoxantrone + etoposide or autologous or allogeneic stem-cell transplantation	More grade 3 to 4 adverse events in HD *v* SD first induction cycle (61% *v* 51%; P = .005)	At 5 years: After SD-HD, 40% *v* After HD-HD, 42%	.27

NOTE. 5-2-5, 7-3-7, HAM, HDAC, HIDAC-3-7,SDAC, and TAD are terms used in the original publications.
Abbreviations: CR, complete remission; HD, high-dose; NSD, nonsignificant difference; OS, overall survival; SD, standard-dose.