ORIGINAL ARTICLE

Cytarabine Dose for Acute Myeloid Leukemia

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ABSTRACT

BACKGROUND

Cytarabine (ara-C) is an important drug in the treatment of acute myeloid leukemia (AML). High-dose cytarabine (2000 to 3000 mg per square meter of body-surface area) is toxic but results in higher rates of relapse-free survival than does the conventional dose of 100 to 400 mg per square meter. Intermediate dose levels have not been thoroughly evaluated.

METHODS

We compared two induction regimens in patients 18 to 60 years of age (median, 49) who had newly diagnosed AML. The intermediate-dose group, totaling 431 patients, received cytarabine at a dose of 200 mg per square meter given by continuous intravenous infusion for 24 hours during cycle 1 of induction therapy and 1000 mg per square meter by infusion for 3 hours twice daily during cycle 2 of induction therapy. The high-dose group, totaling 429 patients, received a dose-escalated regimen of 1000 mg of cytarabine per square meter every 12 hours in cycle 1 and 2000 mg per square meter twice daily in cycle 2. Patients with a complete response did not receive additional cytarabine but received consolidation therapy in a third cycle of chemotherapy (mitoxantrone–etoposide) or underwent autologous or allogeneic stem-cell transplantation. Complete remission rates, survival rates, and toxic effects were assessed for each treatment group.

RESULTS

At a median follow-up of 5 years, no significant differences were noted between the intermediate-dose group and the high-dose group with respect to complete remission rates (80% and 82%, respectively), probability of relapse, event-free survival at 5 years (34% and 35%), or overall survival (40% and 42%). High-dose cytarabine provided no clear advantage in any prognostic subgroup. The high-dose treatment resulted in higher incidences of grade 3 and grade 4 toxic effects (in cycle 1), prolonged hospitalization, and delayed neutrophil recovery (in cycle 2) and platelet recovery (in cycles 2 and 3).

CONCLUSIONS

Induction therapy with cytarabine at the lower dose already produced maximal antileukemic effects for all response end points, suggesting a plateau in the dose–response relationship above this dose level. High-dose cytarabine results in excessive toxic effects without therapeutic benefit. (Netherlands Trial Register number, NTR230.)

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Cytarabine has been one of the cornerstone drugs in the treatment of acute myeloid leukemia (AML) for more than three decades.[1] It was initially used in remission-induction therapy at a dose of 100 to 200 mg per square meter of body-surface area. From about 1975 to 1985, investigators began evaluating the use of high-dose cytarabine therapy, given in a dose of 3000 mg per square meter twice daily for 6 days.[2,3] In single-group studies, high response rates were noted among patients with relapse and promising results were reported for those with a new diagnosis of AML.[2-4] Subsequently, a randomized study showed that four cycles of cytarabine at a dose of 3000 mg per square meter given twice daily on days 1, 3, and 5 and administered after complete remission appeared to be superior to cytarabine at a dose of 100 or 400 mg per square meter with respect to overall survival and relapse-free survival in patients younger than 60 years of age.[5] High-dose cytarabine has become acceptable postremission consolidation therapy in U.S. and European institutions as part of their treatment approach.[6-8] Furthermore, high-dose cytarabine has also been compared with conventional-dose cytarabine as remission-induction treatment in two studies.[9,10] One study[9] evaluated cytarabine at a dose of 3000 mg per square meter twice daily in combination with daunorubicin and etoposide in cycle 1, and the other study[10] evaluated cytarabine at a dose of 2000 mg per square meter (along with daunorubicin) in cycle 1. Both studies showed reductions in the probability of relapse and longer relapse-free survival for the groups treated with high-dose cytarabine. The advantage of fewer relapses was offset by a greater number of deaths during induction therapy (mainly in patients over 50 years of age), and overall survival did not improve.

Although high-dose cytarabine is now being used for induction therapy[11,12] or consolidation therapy,[7,8] it has not been properly compared with intermediate-dose cytarabine, which could result in maximal antitumor effects with less toxicity. Therefore, we compared outcomes for patients given high-dose cytarabine (2000 to 3000 mg per square meter) and for those given an intermediate dose of cytarabine (about one third the total high dose). Here we report the results of a study that compared high-dose cytarabine with intermediate-dose cytarabine as remission-induction therapy in patients with AML and patients with the myelodysplastic syndrome and refractory anemia with excess blasts (RAEB) who were 60 years of age or younger.

METHODS

ELIGIBILITY

Patients with newly diagnosed AML who were 18 to 60 years of age were eligible if they had a pathologically confirmed diagnosis and at least 20% myeloblasts in the bone marrow or RAEB and an international prognostic score[13] of 1.5 or higher (on a scale of 0 to 3.0, with higher scores indicating a poorer prognosis), with a World Health Organization (WHO) performance status score of 2 or lower (on a scale of 0 to 5, with lower numbers indicating better performance status). (Descriptions of the international prognostic score classification and the WHO performance scale, as well as the exclusion criteria for this study, can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

STUDY DESIGN

The study was designed by the Leukemia Working Group of the Dutch–Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK). Patients were randomly assigned to remission-induction regimens with either intermediate-dose cytarabine[14,15] or high-dose cytarabine. The randomization procedure[16] is described in the Supplementary Appendix. Cycle 1 for the intermediate-dose group included idarubicin at a dose of 12 mg per square meter administered as a 3-hour infusion on days 5, 6, and 7 and cytarabine at a dose of 200 mg per square meter administered as a continuous infusion on days 1 through 7.[15] Cycle 1 for the high-dose group was the same regimen except that cytarabine was administered at a dose of 1000 mg per square meter, in a 3-hour infusion, every 12 hours on days 1 through 5. Cycle 2 for the intermediate-dose group consisted of amsacrine at a dose of 120 mg per square meter, in a 1-hour infusion, on days 3, 5, and 7 plus cytarabine at a dose of 1000 mg per square meter given intravenously for 3 hours twice daily on days 1 through 6.[15] Cycle 2 for the high-dose group was the same regimen except that cytarabine was administered intravenously at a dose of 2000 mg per square meter for 6 hours twice daily on days 1, 2, 4, and 6.

During the last part of the study, patients were also randomly assigned to granulocyte colony-stimulating factor (G-CSF) priming or to no priming, in order to confirm the results of a previous HOVON–SAKK study of G-CSF priming in patients with AML (Netherlands Trial Register number, NTR230), in which G-CSF was given on days 0 to 7 during cycles 1 and 2.[15] Patients who had a complete remission after cycle 2 were treated with one consolidation course of additional chemotherapy or autologous or allogeneic stem-cell transplantation according to a risk-adapted strategy (see the Supplementary Appendix).

This investigator-sponsored study did not involve any pharmaceutical companies. It was approved by the ethics committees of the participating institutions and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

The HOVON Data Center was responsible for central data management, and one of the authors performed the analysis. The decision to submit the manuscript for publication was made by the cooperative group. Two of the authors wrote the first draft of the manuscript, which was circulated for comments to the other authors. The study was performed in accordance with the protocol, available at NEJM.org.

CLINICAL CHARACTERISTICS AND RISK CLASSIFICATION

Clinical and hematologic features were registered at diagnosis. On the basis of the karyotype of their leukemic cells, patients were classified into prognostic categories.

RESPONSE CRITERIA AND END POINTS

Complete response rates, relapse rates, and overall survival rates have been defined in detail previously.[17] Event-free survival, the primary end point, was considered to be the interval from randomization to the date of death, relapse, or documentation of failure to induce complete remission within two cycles. Relapse-free survival for patients with a complete remission during the study treatment was measured from the date of the response to relapse or death while the patient was in complete remission. Early death was defined as death within 7 days after the start of cycle 1, and death during induction as death between 8 and 30 days after the start of cycle 1.

STATISTICAL ANALYSIS

The expected complete remission rate in the intermediate-dose group was 80%, with an expected event-free survival rate of 31% at 3 years and 25% at 5 years. The projected enrollment was 800 patients, with an additional follow-up 1 year after entry of the last patient before the final analysis, which would yield 490 events for event-free survival. A two-sided log-rank test at a significance level of 0.05 would give a power of 86% to show an improvement in event-free survival in the high-dose group, with a hazard ratio of 0.76, which corresponds to an increase in the 5-year event-free survival rate from 25% to 35%.

All analyses were performed according to the intention-to-treat principle, irrespective of protocol compliance, but five patients in the intermediate-dose group and four in the high-dose group were excluded as ineligible (see the Supplementary Appendix). Cox regression analysis was used to analyze the effects of treatment group and covariates on event-free survival and overall survival. These analyses were performed with and without adjustment for covariates. The possible heterogeneity of the treatment effects in subgroups was explored post hoc by estimation of the hazard ratios for survival end points for each subgroup, together with 95% confidence intervals and tests for interaction. This analysis was performed for a limited number of subgroups according to age (three groups of similar size), performance status at entry, primary or secondary AML, and cytogenetic risk. The power of the tests of interaction was limited, since the trial was not designed for such tests. Competing risk analysis was used to calculate the cumulative competing risks of treatment failure for patients who had no complete remission on protocol, who had relapse after a complete remission, or who died while in complete remission. All reported P values are two-sided, and they have not been adjusted for multiple testing.

RESULTS

PATIENTS

During the initial phase of the study (January 2001 through September 2001), we randomly assigned 76 patients to one of the two induction regimens, after which the definitive, amended protocol was initiated (see the Supplementary Appendix). Between January 14, 2002, and July 18,

2006, we randomly assigned 860 eligible and evaluable patients who had AML (821) or RAEB (39) to intermediate-dose cytarabine (431) or high-dose cytarabine (429) (Table 1). The median follow-up of patients still living (349) is 66 months.

TREATMENT RESPONSES AND OUTCOMES

A total of 858 patients received cycle 1 induction therapy, 748 (87%) of whom received induction therapy cycle 2, with a similar distribution between the intermediate-dose and high-dose groups (Table 2). During the final part of the study, patients were also randomly assigned to either G-CSF priming (201 [23%]) or to no priming in cycles 1 and 2.[15] Complete remission rates were similar for the intermediate-dose and high-dose treatment groups (80% and 82%, respectively) (Table 2).

Patients with a complete response (694) received a third chemotherapy cycle for consolidation (34%) or underwent autologous stem-cell transplantation (13%) or allogeneic stem-cell transplantation (35%), with no significant difference according to whether they had been assigned to intermediate-dose or high-dose cytarabine (Table 2). The remaining 124 patients (18%) did not receive consolidation therapy after cycle 2.

In the intermediate-dose group, 170 patients had a relapse and 260 died, including 31 while they were in the first complete remission. In the high-dose group, 157 patients had a relapse and 251 died, including 46 during the first complete remission.

At 5 years, there were no significant differences between the intermediate-dose group and the high-dose group in the rate of event-free survival (34% and 35%, respectively) or overall survival (40% and 42%) (Table 2 and Fig. 1). The cumulative 5-year probabilities for the competing risks of failure after complete remission were also similar in these two groups: 39% and 37%, respectively, for relapse and 7% and 11% for death during the first complete remission.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intermediate-Dose Cytarabine Remission-Induction Therapy (N=431)	High-Dose Cytarabine Remission-Induction Therapy (N=429)
Male sex — no. of patients (%)	234 (54)	233 (54)
Age — yr (%)		
≤35	81 (19)	88 (21)
36 to 50	161 (37)	146 (34)
>50	189 (44)	195 (45)
Median age — yr (range)	49 (17–60)	49 (17–60)
WHO performance status score — no. of patients (%)		
0	183 (42)	168 (39)
1	221 (51)	229 (53)
2 to 4	23 (5)	30 (7)
Unknown	4 (1)	2 (0)
Secondary AML — no. of patients (%)		
None	391 (91)	393 (92)
Arising from MDS	19 (4)	15 (3)
Therapy-related	20 (5)	20 (5)
Arising from MDS and therapy-related	1 (0)	1 (0)
RAEB — no. of patients (%)	19 (4)	20 (5)
Extramedullary disease — no. of patients (%)†	62 (14)	65 (15)
White-cell count at diagnosis — no. of patients (%)		
$\leq 20\times10^9$ per liter	240 (56)	254 (59)
$>20\times10^9$ to 100×10^9 per liter	136 (32)	122 (28)
$>100\times10^9$ per liter	55 (13)	53 (12)

Table 1. (Continued.)

Characteristic	Intermediate-Dose Cytarabine Remission-Induction Therapy (N=431)	High-Dose Cytarabine Remission-Induction Therapy (N=429)
Cytogenetic risk — no. of patients (%)‡		
Favorable	43 (10)	45 (10)
t(8;21)	26 (6)	18 (4)
inv(16)	17 (4)	27 (6)
Intermediate	251 (58)	253 (59)
CN –X–Y	197 (46)	203 (47)
CA rest	54 (13)	50 (12)
Adverse	62 (14)	70 (16)
Monosomal karyotype	45 (10)	38 (9)
Not determined	30 (7)	23 (5)

* AML denotes acute myeloid leukemia, MDS myelodysplastic syndrome, RAEB refractory anemia with excess blasts, and WHO World Health Organization.

† Extramedullary disease was usually established clinically, sometimes also pathologically. Hepatomegaly and splenomegaly were assessed on physical examination. Extramedullary sites included hepatomegaly, lymph node enlargement, central nervous system involvement, gingival involvement, skin, and lung.

‡ AML with favorable risk had core-binding factor chromosomal abnormalities: t(8;21)(q22;q22), inv(16)(p13.1;q22), or t(16;16)(p13.1;q22). The "very unfavorable" risk category had a monosomal karyotype, as defined previously.[16,18] The adverse-risk forms of AML were those without a monosomal karyotype or core-binding factor abnormalities but with complex abnormalities[16] — t(6;9), t(6;11), t(11;19), t(9;22), 11q23, abn3q, 5q–, 7q–, –5, or –7.[8] AML without cytogenetic abnormalities or with loss of an X or Y chromosome as the only abnormality was classified as "normal cytogenetics" (CN –X–Y) and AML with any other cytogenetic abnormalities was classified as "CA rest." Patients with CN or CA rest were considered to be at intermediate risk.[16]

PROGNOSTIC FACTORS AND SUBGROUP ANALYSIS

Table 3 shows rates of event-free survival and overall survival at 5 years according to treatment group and prognostic factors. The strongest prognostic factors were cytogenetic features. The 83 patients with a monosomal karyotype had a low complete remission rate (52%) and very poor rates of event-free survival (5%) and overall survival (7%). The 132 patients with adverse cytogenetic abnormalities but without a monosomal karyotype had a higher complete remission rate (77%), with event-free and overall survival rates of 21% and 31%, respectively. Patients with intermediate-risk AML had a higher complete remission rate (85%) and 5-year event-free and overall survival rates of 39% and 44%, respectively. More favorable results were apparent in the 88 patients with abnormalities of core-binding factor, with a complete remission rate of 91% and 5-year event-free and overall survival rates of 52% and 65%, respectively. Outcomes at 5 years were inferior among patients who were older than 50 years of age (event-free survival, 27%, vs. 40% for those 50 years of age or younger, and overall survival, 33% vs. 46%; P<0.001) and those who had secondary AML (event-free survival, 24%, vs. 36% for those without secondary AML [P<0.005], and overall survival, 28% vs. 42% [P<0.004]). Adjustment for these factors in Cox multivariate regression analysis did not change the fact that the two treatment groups had similar outcomes.

In order to explore a possible differential effect of high-dose cytarabine treatment in any of the subgroups, the effect of treatment was estimated separately by hazard ratios for event-free survival and overall survival, with associated 95% confidence intervals combined with tests for interactions. In none of these cases were the tests for interactions significant (all P values for interactions >0.01). The data do not indicate a benefit of high-dose cytarabine treatment in patients with core-binding factor AML. Only in the subgroup with a monosomal karyotype were 5-year event-free survival rates (13% vs. 0%) and overall survival rates (16% vs. 0%) better in the high-dose group (with five long-term survivors and data censored after 50 to 64 months).

Given the similar distribution of the different types of consolidation therapy in both treatment groups, it is unlikely that different postremission

treatments mask an effect of induction treatment. A landmark analysis with end points of overall survival and relapse-free survival from the start of consolidation therapy did not reveal an interaction between type of consolidation therapy and type of induction therapy (Table 1 in the Supplementary Appendix).

TOXIC EFFECTS

More patients in the high-dose cytarabine group had grade 3 to 4 adverse effects after cycle 1 (61%, vs. 51% in the intermediate-dose group; P=0.005). Specifically, skin reactions and gastrointestinal and ocular toxic effects were noted after cycles 1 and 2 in the high-dose group (Table 5 in the Supplementary Appendix).

No significant differences were noted between the high-dose and intermediate-dose groups in 30-day mortality (10% for both) (Table 2). However, the number of deaths in the first 3 months was greater in the high-dose group (72, vs. 52 in the intermediate-dose group; hazard ratio, 1.41; P=0.057).

Time to neutrophil or platelet recovery between the two groups did not differ after cycle 1, but after cycle 2 recovery for both neutrophils and platelets was delayed in the high-dose cytarabine group (Table 3 in the Supplementary Appendix). Patients in the high-dose group spent more nights in the hospital after cycle 2 and received significantly more platelet transfusions after cycles 1 and 2 (Table 4 in the Supplementary Appendix); they also had a considerably prolonged interval of thrombocytopenia after cycle 3 consolidation therapy.

DISCUSSION

Although high-dose cytarabine has been shown to be more effective than the low conventional dose in AML, a more detailed dose–response relationship has never been defined. It is possible

Table 2. Phases of Cytarabine Treatment for AML, and Outcomes.*

Treatments and Outcomes	Intermediate-Dose Cytarabine Remission-Induction Therapy (N=431)	High-Dose Cytarabine Remission-Induction Therapy (N=429)	Odds Ratio or Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Treatment phase				
Remission induction				
Cycle 1	429 (100)	429 (100)		
Cycle 2†	383 (89)	366 (85)		
With G-CSF priming	96 (22)	105 (24)		
No consolidation after complete remission‡				
After cycle 1	40 (9)	70 (16)		
After cycle 2	8 (2)	6 (1)		
Consolidation				
Cycle 3	116 (27)	110 (26)		
Other chemotherapy	5 (1)	5 (1)		
Autologous SCT	48 (11)	43 (10)		
Allogeneic SCT	126 (29)	117 (27)		
Outcome				
Complete remission§	343 (80)	351 (82)	1.14 (0.81–1.60)	0.45
Early	259 (60)	284 (66)		
Late	84 (19)	67 (16)		
Induction failure¶				
Early death	2 (0)	4 (1)		
Induction death	19 (4)	17 (4)		
On-treatment death	52 (12)	72 (17)	1.41 (0.99–2.01)	0.06

Table 2. (Continued.)

Treatments and Outcomes	Intermediate-Dose Cytarabine Remission-Induction Therapy (N=431)	High-Dose Cytarabine Remission-Induction Therapy (N=429)	Odds Ratio or Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Event-free survival‖**	144 (34)	148 (35)	0.98 (0.83–1.15)	0.79
No complete remission	87 (20)	78 (18)		
Relapse	170 (39)	157 (37)		
Death during first complete remission	31 (7)	46 (11)		
Overall survival**				
Living	171 (40)	178 (42)	0.99 (0.83–1.17)	0.87
Dead	260 (60)	251 (58)		

* CI denotes confidence interval, G-CSF granulocyte colony-stimulating factor, and SCT hematopoietic stem-cell transplantation.
† Over half the patients (247 [57%] in the intermediate-dose group and 260 [61%] in the high-dose group) were already in complete remission when they received cycle 2.
‡ Of the patients in complete remission, 11% of the intermediate-dose group and 16% of the high-dose group did not receive consolidation therapy; among these patients, consolidation therapy was not given in 14% of the intermediate-dose group and 22% of the high-dose group (P=0.01) mainly because of more toxic effects, persistent marrow hypoplasia, or early death during the first complete remission (48 patients in the high-dose group and 22 in the intermediate-dose group), early relapse (12 and 10 patients, respectively), or other reasons (16 and 17 patients).
§ Complete remission occurred while the patient was on protocol; one patient moved away, was lost to follow-up 1 month after cycle 1, could not be evaluated for remission, and was censored for event-free and overall survival at 1 month. Early refers to complete remission attained after cycle 1; late refers to complete remission attained after cycle 2.
¶ Death was considered early if it occurred within 7 days after the start of cycle 1 or before the start of treatment. Induction death occurred between 8 and 30 days after the start of cycle 1. On-treatment death occurred during the first 3 months.
‖ Seven cases of therapy-related leukemias or myelodysplastic syndrome that occurred during follow-up were also considered events and were classified as relapse.
** Percentages reported for event-free and overall survival are actuarial 5-year probabilities.

that the current high-dose cytarabine is far above the maximally effective dose, possibly enhancing toxicity without conferring increased antileukemic effects. An initial randomized study had shown a reduced relapse rate after high-dose cytarabine was given after remission (3000 mg per square meter vs. 100 mg and 400 mg per square meter), more frequent toxic effects, and an overall survival benefit, although only in a subgroup younger than 60 years of age.[5] However, it was possible that the antileukemic benefit could be maximized at some dose between 3000 mg and 100 mg per square meter. Two studies of remission-induction therapy with high-dose cytarabine reported reduced relapse probabilities, but they also reported higher rates of fatal toxicity[9] and no overall survival advantage.[9,10] Both studies included relatively small numbers of patients (high-dose cytarabine in 149 patients[9] and in 172 patients[10]). Moreover, one of these studies reported an exceptionally low complete remission rate of 54%, which is not representative of current standards.[10] Another problem is that high-dose cytarabine was also used during consolidation therapy, thus complicating the analysis.[10] A more recent study of AML treatment provided preliminary data about a comparison between high-dose cytarabine and conventional-dose cytarabine as consolidation therapy in the patients with a complete response.[19] No differences were seen in relapse-free survival or overall survival, thus raising further doubts about the therapeutic necessity of high-dose cytarabine in patients with previously untreated AML.

The phase 3 multicenter study presented here compared intermediate-dose cytarabine with high-dose cytarabine during remission-induction therapy. The results suggest that the antileukemic effects of cytarabine may reach a maximum at doses well below the maximum tolerated dose. Patients assigned to the high-dose cytarabine regimen received doses about nine times higher than the intermediate doses in cycle 1. In cycle 2, dose levels were doubled. The results are not con-

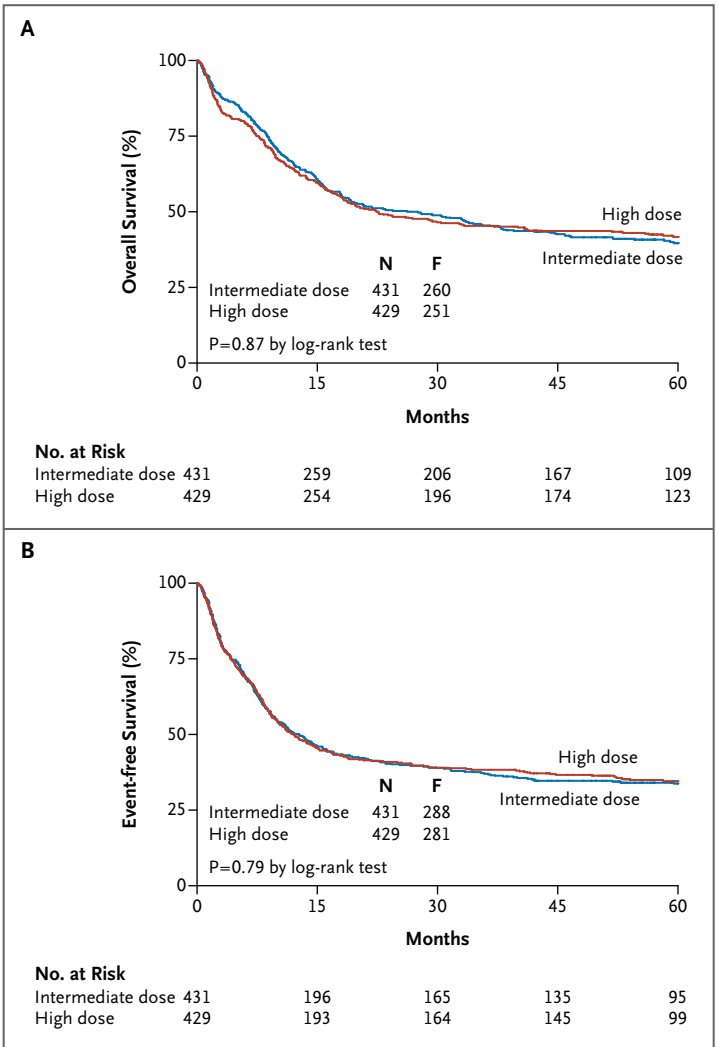

Figure 1. Overall and Event-free Survival Rates among Patients with Acute Myeloid Leukemia, According to Remission-Induction Chemotherapy at Intermediate-Dose versus High-Dose Levels of Cytarabine.

During the first and second induction cycles of combination chemotherapy, patients were randomly assigned to intermediate-dose cytarabine (200 mg per square meter of body-surface area for cycle 1 and 1000 mg per square meter for cycle 2) or to high-dose cytarabine (1000 mg per square meter for cycle 1 and 2000 mg per square meter for cycle 2). F denotes number of failures (i.e., death in the case of overall survival, and death during the first complete remission, relapse, or no complete remission in the case of event-free survival), and N number of patients.

founded by the subsequent use of cytarabine after remission. This study was large, and compliance to assigned treatments was high. Nearly all the patients received the planned cycle 1 regimens according to randomization. At least 85% received their assigned cycle 2, of whom about 60% had already shown a complete remission (Table 2). After a median follow-up period of 66 months in 860 patients, the results indicate that increasing the dose of cytarabine to more than 1000 mg per square meter provides no greater antileukemic activity than does the intermediate dose. In fact, without exception, the remission, relapse, and survival end points in the two groups were equivalent. Hence, the dose–response relationship for cytarabine appears to plateau above a dose level of 1000 mg per square meter.

Although multiple cycles of high-dose cytarabine have commonly been applied, accumulated evidence is consistent with the notion that administering a single cycle of high-dose cytarabine for induction or consolidation therapy is sufficient and produces maximal antileukemic effects.[10-12,20] For several years the HOVON–SAKK cooperative groups have employed a condensed treatment program in adults with AML that involves a backbone of two induction cycles with a first cycle of standard-dose cytarabine and a second cycle of intermediate-dose cytarabine and a third and final consolidation cycle without cytarabine.[15] The HOVON–SAKK treatment approach served as control treatment in the current phase 3 study and generated 5-year survival estimates (event-free survival, 34%; overall survival, 39%; and relapse-free survival, 54%) that are equivalent to results reported previously for high-dose cytarabine therapy in phase 3 studies,[5,9,10] even though our patient population had a comparatively high median age (49 years) and included both therapy-related and secondary AML and RAEB.

Pharmacokinetic studies of cytarabine concentrations in the plasma and the accumulation of its active 5-triphosphate metabolite (Ara-C triphosphate) in the leukemic cells have suggested that dose levels of cytarabine at 3000 mg per square meter are far above saturating concentrations (i.e., there is no additional progressive increase in generation of the active mebatolite).[21] The dose-level issue is clinically relevant because high-dose cytarabine is associated with life-threatening toxic effects.[5,9,10] Therefore, the use of high-dose cytarabine is generally avoided in patients 60 years of age or older. In the study presented here, the high-dose cytarabine regimen resulted in considerable toxic effects, was significantly more myelosuppressive, and required more platelet transfusions and prolonged hospitalization. Myelosuppression of high-dose cytarabine appears cumulative and is carried over to postremission chemotherapy. Patients in complete remission

Table 3. Effects of Intermediate-Dose and High-Dose Cytarabine Treatment on Survival, According to Patient Age, WHO Performance Status, Secondary AML, Cytogenetic Findings, and Tests of Interaction.*

Variable	No. of Patients	Overall 5-Year Survival					Event-Free Survival at 5 Years				
		No. of Patients Who Died	Intermediate-Dose Group (%)	High-Dose Group (%)	Hazard Ratio (95% CI)†	P Value‡	No. of Patients with Events§	Intermediate-Dose Group (%)	High-Dose Group (%)	Hazard Ratio (95% CI)†	P Value‡
Total	860	511	40	42			569	34	35		
Age — yr						0.27 (for interaction)					0.76 (for interaction)
≤35	169	89	42	52	0.73 (0.48–1.11)	0.14	105	35	41	0.80 (0.61–1.31)	0.56
36 to 50	307	166	46	47	1.08 (0.80–1.47)	0.61	185	40	41	1.05 (0.79–1.40)	0.75
>50	384	256	34	33	1.02 (0.80–1.30)	0.89	279	27	27	0.94 (0.74–1.19)	0.61
WHO performance status¶						0.03 (for interaction)					0.12 (for interaction)
0	351	207	43	38	1.24 (0.95–1.63)	0.12	232	36	33	1.14 (0.88–1.48)	0.31
>0	509	304	37	44	0.84 (0.67–1.05)	0.12	337	32	36	0.88 (0.72–1.08)	0.22
Secondary AML						0.41 (for interaction)					0.31 (for interaction)
No	784	456	41	42	1.01 (0.84–1.21)	0.93	512	35	35	1.00 (0.84–1.19)	0.96
Yes	76	55	23	33	0.79 (0.47–1.35)	0.39	57	21	27	0.74 (0.44–1.24)	0.25
Cytogenetic risk‖						0.045 (for interaction)					0.12 (for interaction)
Favorable	88	30	64	67	1.03 (0.50–2.10)	0.94	42	58	47	1.51 (0.82–2.78)	0.19
Intermediate	504	279	45	44	1.05 (0.83–1.33)	0.70	313	37	40	0.97 (0.78–1.21)	0.80
Adverse	132	92	31	30	1.09 (0.72–1.64)	0.69	103	24	18	1.11 (0.75–1.63)	0.61
Monosomal karyotype	83	78	0	16	0.58 (0.37–0.91)	0.02	78	0	13	0.58 (0.37–0.91)	0.02

* The results of a similar analysis for white-cell count at the time of diagnosis in acute myeloid leukemia (AML) versus refractory anemia with excess blasts are given in Table 2 in the Supplementary Appendix. CI denotes confidence interval, and WHO World Health Organization.
† The hazard ratio is for high-dose as compared with intermediate-dose cytarabine treatment.
‡ P values are for the difference between the two treatment groups within subgroups. P values designated "for interaction" are for the test of interaction between the specific factor and the treatment group.
§ The number of patients with events are patients who had a relapse, who did not have a complete remission, or who died during the first complete remission. Seven cases of therapy-related leukemias or myelodysplastic syndromes during follow-up were also considered events and were classified as relapse.
¶ The WHO performance status is scored on a scale of 0 to 5, with lower numbers indicating better performance status.
‖ See Table 1 for a complete description of the cytogenetic findings and risk.

who received consolidation therapy with mitoxantrone–etoposide in cycle 3 had prolonged thrombocytopenia when they had been induced with high-dose cytarabine. There were also more deaths during the first 3 months in patients who were on treatment and did not relapse.

Exploratory studies had suggested that AML with core-binding factor cytogenetic abnormalities (CBFAML) in particular might benefit from high-dose cytarabine.[22-24] However, because of the retrospective analysis of previous studies and the contradictory results in one subsequent study,[20] the preferential sensitivity of CBFAML to high-dose cytarabine has not been conclusively settled. In our study, we do not find evidence that CBFAML is selectively responsive to high-dose cytarabine. In fact, we did not see a therapeutic benefit of cytarabine escalation above 1000 mg per square meter in any particular subgroup of patients with AML, although the relapse rate after high-dose cytarabine therapy was reduced in those with the adverse monosomal karyotype. Since in our study the number of patients in this latter subgroup was small, and the results were derived from a post hoc exploratory analysis, these data should be interpreted with caution.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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