

# Possible benefit of consolidation therapy with high-dose cytarabine on overall survival of adults with non-promyelocytic acute myeloid leukemia

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## Abstract

In adults with non-promyelocytic acute myeloid leukemia (AML), high-dose cytarabine consolidation therapy has been shown to influence survival in selected patients, although the appropriate doses and schemes have not been defined. We evaluated survival after calculating the actual dose of cytarabine that patients received for consolidation therapy and divided them into 3 groups according to dose. We conducted a single-center, retrospective study involving 311 non-promyelocytic AML patients with a median age of 36 years (16-79 years) who received curative treatment between 1978 and 2007. The 131 patients who received cytarabine consolidation were assigned to study groups by their cytarabine dose protocol. Group 1 (n = 69) received  $<1.5 \text{ g/m}^2$  every 12 h on 3 alternate days for up to 4 cycles. The remaining patients received high-dose cytarabine ( $\geq 1.5 \text{ g/m}^2$  every 12 h on 3 alternate days for up to 4 cycles). The actual dose received during the entire consolidation period in these patients was calculated, allowing us to divide these patients into 2 additional groups. Group 2 (n = 27) received an intermediate-high-dose ( $<27 \text{ g/m}^2$ ), and group 3 (n = 35) received a very-high-dose ( $\geq 27 \text{ g/m}^2$ ). Among the 311 patients receiving curative treatment, the 5-year survival rate was 20.2% (63 patients). The cytarabine consolidation dose was an independent determinant of survival in multivariate analysis; age, karyotype, induction protocol, French-American-British classification, and *de novo* leukemia were not. Comparisons showed that the risk of death was higher in the intermediate-high-dose group 2 (hazard ratio [HR] = 4.51; 95% confidence interval [CI]: 1.81-11.21) and the low-dose group 1 (HR = 4.43; 95% CI: 1.97-9.96) than in the very-high-dose group 3, with no significant difference between those two groups. Our findings indicated that very-high-dose cytarabine during consolidation in adults with non-promyelocytic AML may improve survival.

Key words: Acute myeloid leukemia; Chemotherapy; Consolidation therapy; High-dose cytarabine; Prognosis

## Introduction

Treatment outcomes for acute myeloid leukemia (AML) have been less favorable than expected despite recent advances in understanding underlying disease biology. Except for those with acute promyelocytic leukemia (APL), a disease that had its natural history rewritten after the advent of all-trans-retinoic acid (1,2), the survival rates of patients with AML are still low (3,4).

Currently, the effects of various factors on AML prognosis, such as age, karyotype, primary (*de novo*) or secondary AML, molecular rearrangements, achievement of complete remission (CR), and the use of high-dose cytarabine consolidation therapy, are well known (5-8).

Initially described as a successful treatment for AML with a favorable karyotype (9,10), the high-dose cytarabine consolidation regime has proven to be a key influence on

overall survival, disease-free survival, and event-free survival rates (11,12). However, it is still not clear which patients truly benefit from intensive cytarabine consolidation and what is the best dose and regimen (13-15). We retrospectively evaluated a cohort of adults with non-promyelocytic leukemia who were treated in a single center to identify variables that could have affected the outcomes, including the role of three distinct doses of cytarabine administered in the consolidation phase.

## Patients and Methods

### Patients

This study initially included all 499 patients diagnosed with AML of any kind who were treated at Hospital das

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Clínicas, Faculdade de Medicina, Universidade de São Paulo, Brazil between 1978 and 2007. We evaluated patients with either primary (*de novo*) or secondary AML associated with drugs (e.g., alkylating agents and topoisomerase II inhibitors) or diseases (e.g., myelodysplastic syndromes and myeloproliferative syndromes).

The diagnosis of AML was based on the morphological and cytochemical analysis of bone marrow aspirates, in accordance with the criteria proposed by the French-American-British (FAB) cooperative group (16,17). Immunophenotype tests were incorporated in the early 1990s when they became available, and karyotype analysis was included in the routine practice at this institution in 1997. Bone marrow sampling was performed for the corresponding investigation. Cytogenetic markers were used to classify patient prognosis as follows. Patients with t(8;21), inversion of chromosome 16, t(16;16) or deletion (16q) were included in a favorable risk group. Those with alterations at 3q, 5, 7, and 11q, t(6;9) and t(9;22) or complex karyotypes comprised a group with unfavorable risk, and patients with normal karyotypes or other types of chromosomal alterations were assigned to an intermediate risk group.

Of the 499 patients initially diagnosed with AML, 115 were excluded because they had received palliative treatment, were eligible for curative treatment but died before treatment initiation, or treated elsewhere. An additional 73 patients diagnosed with APL and t(15;17) were excluded as they had received a specific treatment schedule.

The remaining 311 patients diagnosed with AML who received full treatment were considered for analysis. Of these, 155 reached CR after induction treatment, but only 149 completed the consolidation phase, as 6 died in CR before the consolidation phase could be started. Among these 149 patients, 131 had known doses of cytarabine done during consolidation and were considered for outcome comparison between different doses. To facilitate data analysis, patients were divided into 3 consolidation groups, as described below.

Patients who received  $<1.5$  g/m<sup>2</sup> intravenous cytarabine every 12 h on 3 alternate days for up to 4 cycles were included in a low-dose cytarabine consolidation group. High-dose cytarabine consolidation was defined as an intravenous dose  $\geq 1.5$  g/m<sup>2</sup> every 12 h on 3 alternate days for up to 4 cycles. Subsequently, the median actual total dose of cytarabine during consolidation in the high-dose group was calculated by adding up all the doses of the drug actually received. The median total dose received was 27 g/m<sup>2</sup>, which motivated us to divide those patients into 2 subgroups, an intermediate-high-dose cohort receiving a total dose  $<27$  g/m<sup>2</sup> and a very-high-dose cohort receiving a total dose  $\geq 27$  g/m<sup>2</sup>.

The low-dose group (group 1) was assigned to protocols that did not contemplate the use of high-dose cytarabine consolidation therapy ( $<1.5$  g/m<sup>2</sup>) comprised 69 individuals. The group that received high-dose cytarabine consolidation included 27 patients with a total

dose  $<27$  g/m<sup>2</sup> (intermediate-high-dose, group 2) and 35 patients with a total dose  $\geq 27$  g/m<sup>2</sup> (very-high-dose, group 3).

### Study design

This was a retrospective study conducted at a single center. We evaluated the hospital records of the patients without interfering with the treatment. The Research Ethics Committee of the hospital approved the study in 2005.

### Treatment

In this historical series, the protocols R1A5T5 (18), D2A5T5 (19), DAT (20), M3A7 (21), common D3A7, and intensified D3A7 were used (22,23). R1A5T5 was the protocol of choice for all patients in 1978 and was subsequently replaced by D2A5T5 and then DAT, which was used until 1989. Common D3A7 and intensified D3A7 were used for most of the patients. Common D3A7 was used from 1990 to 2000, and intensified D3A7 has been used since 2000. Common D3A7 comprised induction with daunorubicin (50 mg·(m<sup>2</sup>)<sup>-1</sup>·day<sup>-1</sup>) on the first 3 days, combined with cytarabine (100 mg·(m<sup>2</sup>)<sup>-1</sup>·day<sup>-1</sup>) on the first 7 days for 1 or 2 cycles depending on the response. Bone marrow was evaluated 14 days after therapy initiation. In cases achieving CR, consolidation therapy was initiated with 6 doses of cytarabine (1.5 g/m<sup>2</sup>) on 3 alternate days, for up to 4 four cycles, as tolerated. Intensified D3A7 comprises induction with daunorubicin (60 mg·(m<sup>2</sup>)<sup>-1</sup>·day<sup>-1</sup>) on the first 3 days and cytarabine (200 mg·(m<sup>2</sup>)<sup>-1</sup>·day<sup>-1</sup>) on the first 7 days for 1 or 2 cycles. Consolidation, in cases achieving CR, comprised 6 doses of cytarabine (2.5 g/m<sup>2</sup>) on 3 alternate days for up to 4 cycles. Patients who did not achieve CR after 2 cycles of induction with any of the protocols were excluded from consolidation analysis.

Individuals older than 60 years of age or with severe comorbidities and poor performance status were generally treated with less aggressive regimens such as M3A7 and consolidated with lower cytarabine doses.

### Statistical analysis

The response variables that were analyzed included CR, death within the first 30 days after induction chemotherapy, overall survival, disease-free survival, and event-free survival. Patients were stratified by age, karyotype, FAB classification, treatment protocol, cytarabine dose during consolidation, and AML etiology.

The level of statistical significance was set at  $P < 0.05$ , and Pearson's chi-square tests were used for comparisons. The survival curves were calculated using the Kaplan-Meier method and compared statistically using log-rank tests. Multivariate analysis was based on the Cox regression model and performed for all variables with  $P < 0.20$  in the univariate analysis. The statistical tests were performed using the Stata software program, version 11.0 (StataCorp LP, USA).

**Table 1.** Clinical and demographic characteristics of the patients.

Variable	n (%)
Age (n = 311)	
<60 years	242 (77.8%)
≥60 years	69 (22.2%)
Median (years)	36
Interval (years)	16-79
Gender (n = 311)	
Male	164 (52.7%)
Female	147 (47.3%)
Karyotype (n = 110)	
Favorable	8 (7.3%)
Intermediate	80 (72.7%)
Unfavorable	22 (20.0%)
Etiology of AML (n = 311)	
Primary	253 (81.4%)
Secondary	58 (18.6%)
Induction protocol (n = 311)	
R1A5T5	15 (4.8%)
D2A5T5	42 (13.5%)
DAT	36 (11.6%)
Common D3A7	80 (25.7%)
Intensive D3A7	113 (36.3%)
M3A7	25 (8.0%)
FAB classification (n = 311)	
M0	9 (2.9%)
M1	44 (14.1%)
M2	83 (26.7%)
M4	86 (27.7%)
M5	35 (11.3%)
M6	15 (4.8%)
M7	9 (2.9%)
Not classified	30 (9.6%)
Cytarabine dose during consolidation (n = 131)	
Low dose	69 (52.7%)
Total dose <27.0 g/m <sup>2</sup>	27 (20.6%)
Total dose ≥27.0 g/m <sup>2</sup>	35 (26.7%)

AML: acute myeloid leukemia; FAB: French-American-British (cooperative group).

## Results

Between 1978 and 2007, 311 patients met the analysis criteria. Most (77.8%) were younger than 60 years of age and had primary (*de novo*) AML (81.4%). The median age was 36 years (range 16-79 years); 52.7% were male. There were 131 patients with known doses of cytarabine during consolidation: 82 (62.7%) with either common or intensified D3A7, 21 (16%) with D2A5T5, 14 (10.7%) with DAT, 7 (5.3%) with R1A5T5, and 7 (5.3%) with M3A7. Of the 110 patients with known karyotypes, 8 (7.3%), 80 (72.7%), and 22 (20.0%) had favorable, intermediate, and unfavorable prognoses, respectively. The principal demographic and

clinical characteristics of the patients are shown in Table 1.

### Complete remission

Of the 311 patients who received curative treatment, 155 (49.8%; 95% confidence interval [CI]: 44.3-55.%) achieved CR. CR correlated with age ( $P=0.012$ ), favorable karyotype ( $P=0.010$ ), and AML etiology ( $P=0.022$ ) but was not correlated with the induction protocol ( $P=0.888$ ) or the FAB classification ( $P=0.128$ ). These data are summarized in Table 2.

### Death within the first 30 days after induction chemotherapy

There were 75 deaths within the first 30 days after induction therapy, including 6 of the 155 patients who achieved CR, an early mortality rate of 24.1% (95% CI: 19.3-28.9). Age was correlated with early mortality ( $P=0.037$ ), with 33.3% of those ≥60 years dying at this time compared with 21.5% of younger patients. Karyotype ( $P=0.290$ ), induction protocol ( $P=0.433$ ), FAB classification ( $P=0.133$ ), and AML etiology ( $P=0.295$ ) did not significantly affect the number of deaths within the first 30 days after induction chemotherapy.

### Mortality and causes of death

Among the 311 patients who received curative therapy, there were 120 deaths at anytime after the induction date, a mortality rate of 38.5% (95% CI: 34.1-42.8). Infection was by far the leading cause of death (94 patients, 78.3%), followed by bleeding (17 patients, 14.2%), and minor causes including acute myocardial infarction, hepatic failure, and pulmonary embolism (9 patients, 7.5%).

### Overall survival

Among the 311 AML patients who received curative treatment, the 5-year overall survival rate was 20.2% (63 patients). Overall survival was higher among patients younger than 60 years of age ( $P=0.019$ ) and those who had an FAB classification of M2 or M4 ( $P=0.003$ ), as shown in Figures 1 and 2, respectively. There was a trend towards better overall survival among patients presenting a favorable cytogenetic prognosis, but it did not reach statistical significance ( $P=0.066$ ). *De novo* or secondary AML ( $P=0.092$ ) and induction protocol ( $P=0.731$ ) were not significantly associated with overall survival.

Among the 131 patients who reached CR after induction therapy and received consolidation with known doses of cytarabine, the very-high-dose group had better overall survival ( $P<0.001$ ) than either the low-dose and intermediate-high-dose groups, which showed similar results (Figure 3).

Multivariate analysis of the outcomes in patients who achieved CR and the results of the Cox regression model revealed that, unlike consolidation with high-dose cytarabine ( $P<0.001$ ), age ( $P=0.595$ ), FAB classification

**Table 2.** Distribution of age, cytogenetic prognosis, treatment protocol, FAB classification, and etiology of AML regarding complete remission.

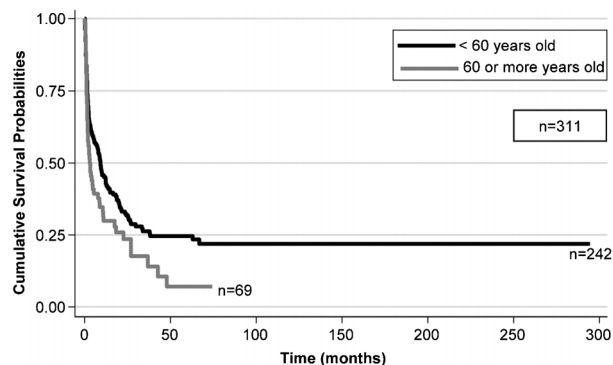
Variable/Category	Complete remission	
Age (years)*	Yes (n = 155)	No (n = 156)
<60 years	131 (54.1%)	111 (45.9%)
≥60 years	24 (34.8%)	45 (65.2%)
Cytogenetic prognosis*	Yes (n = 62)	No (n = 48)
Favorable	7 (87.5%)	1 (12.5%)
Intermediate	45 (56.3%)	35 (43.7%)
Unfavorable	10 (45.5%)	12 (54.5%)
Treatment protocol	Yes (n = 155)	No (n = 156)
D2A5T5	22 (52.4%)	20 (47.6%)
Intensified D3A7	59 (52.2%)	54 (47.8%)
Common D3A7	41 (51.3%)	39 (48.7%)
DAT	17 (47.2%)	19 (52.8%)
M3A7	9 (36.0%)	16 (64.0%)
R1A5T5	7 (46.7%)	8 (53.3%)
FAB classification	Yes (n = 155)	No (n = 156)
M0	4 (44.4%)	5 (55.6%)
M1	19 (43.2%)	25 (56.8%)
M2	51 (61.5%)	32 (38.5%)
Not classified	10 (33.3%)	20 (66.7%)
M4	44 (51.2%)	42 (48.8%)
M5	17 (48.5%)	18 (51.5%)
M6	7 (46.6%)	8 (53.4%)
M7	3 (33.3%)	6 (66.7%)
Etiology of AML*	Yes (n = 155)	No (n = 156)
Primary	135 (53.4%)	118 (46.6%)
Secondary	20 (34.5%)	38 (65.5%)

AML: acute myeloid leukemia; FAB: French-American-British cooperative group.

\*  $P < 0.05$ , statistically significant (Pearson's chi-square test).

( $P = 0.092$ ), karyotype ( $P = 0.116$ ), induction protocol ( $P = 0.607$ ), and *de novo* or secondary AML ( $P = 0.920$ ) were not significantly related to risk of death.

The administration of very-high-dose cytarabine during

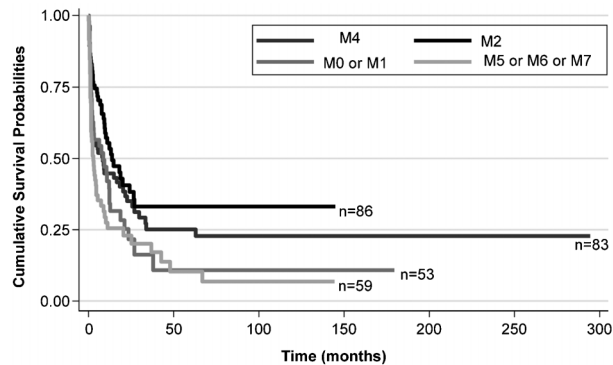


**Figure 1.** Overall survival, by age ( $P = 0.019$ , log-rank test).

consolidation seemed to have an impact on the overall survival rate. When age, karyotype, FAB classification, induction protocol, and *de novo* or secondary of AML were constant, the risk of death, was similar in the low-dose and intermediate-high-dose groups compared to the very-high-dose group. The risk of death was 4.51 times (95% CI: 1.81-11.21) higher in the intermediate-high-dose and 4.43 times (95% CI: 1.97-9.96 times) higher in the low-dose group. We did not find an increase in death rate within the first 180 days after consolidation with very-high-dose cytarabine; no deaths occurred in that group during that time. However, 5 of 27 patients (18.5%) in the intermediate-high-dose and 27 of 69 (39.1%) in the low-dose group died.

#### Disease-free survival

Among those who reached CR, a statistical difference in disease-free survival was observed when the total dose of cytarabine given in the consolidation phase was analyzed ( $P < 0.001$ , Figure 4). Karyotype ( $P = 0.683$ ),



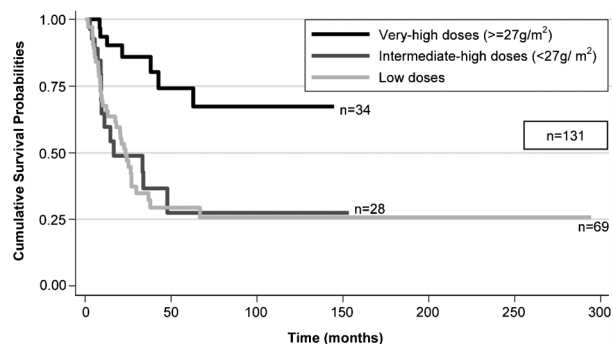
**Figure 2.** Overall survival, by French-American-British (FAB) classification ( $P=0.003$ , log-rank test).

age ( $P=0.525$ ), FAB classification ( $P=0.413$ ), induction protocol ( $P=0.232$ ), and *de novo* or secondary AML ( $P=0.758$ ) were not associated with disease-free survival.

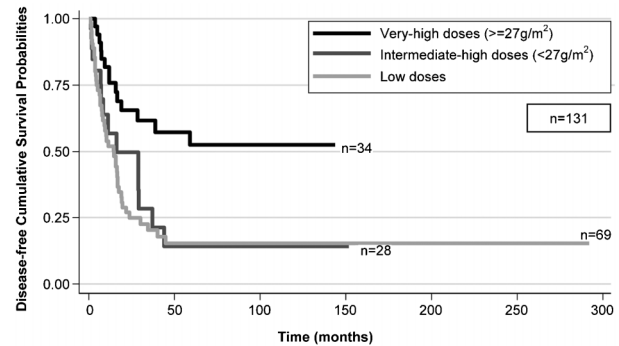
We found that at 60 months after achieving CR, disease-free survival was 52.5% for those patients who received very-high-dose cytarabine compared with 14.2% for the intermediate-high-dose and 15.3% for the low-dose group. Also, the risk of recurrence was higher in these latter two groups when compared with very-high-dose patients; it was 2.60 times higher in the intermediate-high-dose (95% CI: 1.25-5.41) and 3.01 times higher in low-dose patients (95% CI: 1.64-5.51).

### Event-free survival

Among those who reached CR, when considering any event related to AML, such as recurrence, bone marrow transplantation, or death, patients who received very-high-dose cytarabine in consolidation had higher event-free survival than those in the intermediate-high and low-dose groups ( $P<0.001$ , Figure 5). A statistical difference regarding karyotype was also observed ( $P=0.009$ ), but age ( $P=0.852$ ), FAB classification (0.083), induction



**Figure 3.** Overall survival of patients consolidated with cytarabine, by total dose administered.  $P<0.001$ , comparing different doses (log-rank test).



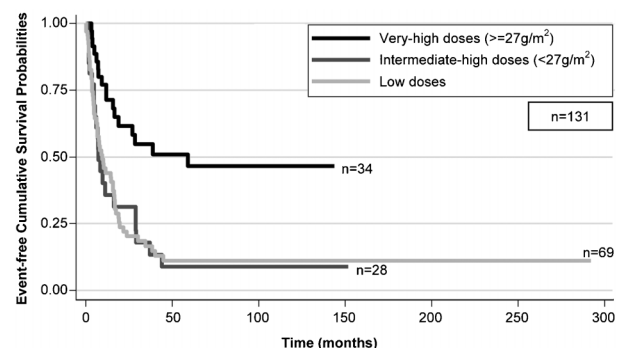
**Figure 4.** Disease-free survival of patients consolidated with cytarabine, by total dose administered.  $P<0.001$ , comparing different doses (log-rank test).

protocol (0.660), and AML etiology ( $P=0.397$ ) were not associated with event-free survival.

After 60 months of CR, event-free survival was 46.7% in those patients who received very-high-dose cytarabine, 8.9% for the intermediate-high-dose group, and 10.7% for the low-dose group. As expected, the risk of events was higher in the latter groups compared with very-high-dose patients. It was 3.01 times higher in intermediate-high-dose (95% CI: 1.59-5.68) and 2.94 times higher in low-dose (95% CI: 1.70-5.09) patients. Higher event-free survival was also documented in patients who had better cytogenetic prognosis (Figure 6).

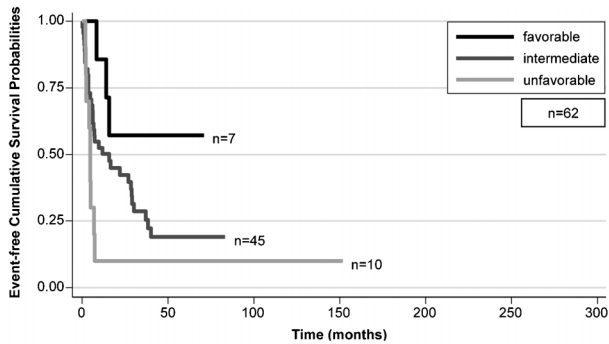
### Discussion

In younger patients without limiting comorbidities, it is common practice to use higher doses of anthracyclines during the induction regimen. It has recently been suggested that the induction doses should be increased, even in older patients, in order to promote CR and overall survival (24). A recent study reported higher CR rates and overall survival in patients given higher doses of



**Figure 5.** Event-free survival of patients consolidated with cytarabine, by total dose administered.  $P<0.001$ , comparing different doses (log-rank test).





**Figure 6.** Event-free survival of patients who reached CR, by karyotype.  $P=0.009$ , comparing cytogenetic prognosis (log-rank test).

daunorubicin, with no significant increase in toxicity (25). On the other hand, the use of high-dose cytarabine during induction is controversial. One study found that 1 to 2 g/m<sup>2</sup> cytarabine in induction therapy had greater toxicity and no better therapeutic effect than 200 mg/m<sup>2</sup> (26), but another study reported higher remission and survival rates with 3 g/m<sup>2</sup> cytarabine, especially in patients younger than 46 years of age (27).

As would be expected, CR is associated with an age less than 60 years, favorable cytogenetic alterations, and *de novo* AML. In this study, approximately 50% of the patients achieved CR. As our sample included patients with secondary AML, this might have been responsible for the fact that the rate of CR was lower than that routinely reported.

Furthermore, there were no differences in CR, death within the first 30 days (or anytime) after induction chemotherapy, or survival rates between patients given the standard dose or the intensified dose of the D3A7 induction protocol. Even considering that changes have taken place in supportive care over the years (transfusions, growth factors, better antibiotic and anti-fungal therapy), we did not find a direct influence pointing to improved survival. Infection due to neutropenia and immunologic impairment was still the leading cause of death. The overall survival rate was better in younger patients and FAB subgroups M2 and M4.

Those who had karyotypes indicative of favorable risk would most likely have shown better overall survival if more cytogenetic analyses had been performed. Of the 110 known karyotypes, only 8 patients had a favorable prognosis compared with a larger heterogeneous group of karyotypes with an intermediate prognosis, which included a significant number of patients with normal karyotypes and some with other alterations of unknown significance.

We know that this group would be better stratified with the aid of molecular biology and the characterization of

mutations such as FLT3, NPM-1 and CEBPA (28-30), but those resources were not available or had not yet been incorporated into routine practice. It is likely not a coincidence that FAB subgroups M2 and M4 are generally associated with favorable karyotypes, such as t(8;21) and inv(16), respectively.

The use of high-dose cytarabine consolidation could also be responsible for the positive impact on overall survival for those who reached CR and had received a total dose of cytarabine  $\geq 27$  g/m<sup>2</sup> (the median total dose) during consolidation. We found that at 60 months after achieving CR, overall survival was 75.3% in patients who received very-high-dose cytarabine versus 22.0% for the intermediate-high-dose group and 29.4% for the low-dose group.

In the multivariate analysis, we observed that the difference in the total doses of cytarabine during consolidation was the only independent variable that could have influenced overall survival in the studied patients. Therefore, total doses of cytarabine equal to or greater than the median dose (27 g/m<sup>2</sup>) after 4 cycles could have been correlated with a significant increase in overall survival at 5 years. This obviously would apply to patients who can tolerate this intensified cytarabine regimen. Significant toxicity, including myelotoxicity, is expected to occur more frequently in this subset of patients, but we did not observe any impact on overall survival or death within the first 180 days. No deaths occurred in that interval in the very-high-dose group, but 39.1% and 18.5% of patients in the low-dose and intermediate-high-dose groups, respectively, died during the first 180 days. Toxicity requires dose reduction or even the suspension of subsequent cycles.

We observed that individuals consolidated with doses of cytarabine  $< 1.5$  g/m<sup>2</sup> (considered a low dose in the present study) or with intermediate-high-dose (total  $< 27$  g/m<sup>2</sup> at the end of consolidation) had similar risks of death more than 4 times higher than those given a total dose of cytarabine  $\geq 27$  g/m<sup>2</sup>. Also, there were no differences in disease-free or event-free survival between patients who were given low or intermediate-high doses of cytarabine due to toxicity or clinical indication. Very-high doses of cytarabine could have been associated with significantly better outcomes when disease-free survival and event-free survival were compared.

Even considering the limitations of a retrospective study in a single center using different treatment protocols over decades and evaluating only a small proportion of patient karyotypes, our results suggest that consolidation therapy with very-high-doses of cytarabine may have a role in better overall, disease-free, and event-free survival in adults with non-promyelocytic AML. Specifically designed prospective studies are needed to confirm this hypothesis and determine the optimal total cytarabine dose for the consolidation phase.

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