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Induction chemotherapy with standard-dose cytarabine, daunorubicin and etoposide (7+3+7) *versus* high-dose cytarabine and daunorubicin in young patients with newly diagnosed acute myeloid leukemia.

Quimioterapia de inducción con dosis estándar de citarabina, daunorrubicina y etopósido (7+3+7) *vs* dosis alta de citarabina y daunorrubicina en pacientes jóvenes con leucemia mieloide aguda recién diagnosticada.

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Abstract

OBJECTIVE: To compared two more intensive induction regimens than 7+3: 7+3+ etoposide (7+3+7) *versus* high-dose cytarabine and daunorubicine (HiDAC-D) in patients with acute myeloid leukemia.

MATERIAL AND METHOD: A comparative study of 18-55 years old patients treated at National Institute of Medical Sciences and Nutrition Salvador Zubiran, Mexico City, from November 2010 to November 2016. Induction regimens used in this study included 7+3+7 (cytarabine 100 mg/m^2/day on days 1-7, daunorubicin 45 mg/m^2/day on days 1-3 and etoposide 75 mg/m^2/day on days 1-7), and HiDAC-D (cytarabine 3000 mg/m^2/day on days 1-3 and daunorubicin 45 mg/m /day on days 1-2).

RESULTS: There were included 40 patients. In the 7+3+7 group, CR (complete remission) was achieved in 76.2% of patients, while in the HiDAC-D treatment group it was 89.4% (17/19; p = 0.44). The group of patients who received the 7+3+7 regimen had a median overall survival (OS) of 17.2 months, while the group that received HiDAC-D had a median OS of 18.9 months (p = 0.620). Unfavorable risk patients treated with the 7+3+7 presented a median OS of 8.8 months *versus* 5 months for the HiDAC-D treatment group (p = 0.037).

CONCLUSION: Both induction regimens increased CR rates with one or two cycles without increasing mortality in patients with AML less than 55 years of age in comparison with our historical cohort with 7+3.

KEYWORDS: Acute myeloid leukemia; Etoposide; Cytarabine; Daunorubicine.

Resumen

OBJETIVO: Comparar dos esquemas de inducción mas intensivos que 7+3: 7+3+etopósido (7+3+7) *vs* dosis altas de citarabina y daunorrubicina (HiDAC-D) en pacientes con leucemia mieloide aguda.

MATERIAL Y MÉTODO: Estudio comparativo de pacientes de 18 a 55 años de edad tratados en el Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, de noviembre de 2010 a noviembre de 2016. Se incluyeron adultos jóvenes. Los esquemas de inducción incluyeron: 7+3+7 (citarabina 100 mg/m^2/día) los días 1-7, daunorubicina 45 mg/m^2/día los días 1-3 y etopósido 75 mg/m^2/día los días 1-7), y HiDAC-D (citarabina 3000 mg/m^2/día los días 1-3 y daunorubicina 45 mg/m^2/día los días 1-2).

RESULTADOS: Se incluyeron 40 pacientes. En el grupo 7+3+7, la CR (remisión completa) se alcanzó en 76.2% (16/21) de los pacientes, mientras en el grupo HiDAC-D

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fue de 89.4% (17/19; p = 0.44). El grupo que recibió el esquema 7+3+7 tuvo mediana de supervivencia global de 17.2 meses, mientras que el grupo que recibió HiDAC-D tuvo mediana de supervivencia global de 18.9 meses (p = 0.620). Los pacientes con riesgo desfavorable tratados con 7+3+7 tuvieron supervivencia global de 8.8 meses contra 5 meses en el grupo de tratamiento HiDAC-D (p = 0.037).

CONCLUSIÓN: Ambos esquemas de inducción incrementaron la tasa de remisión completa con uno o dos ciclos sin incremento de la mortalidad en pacientes con leucemia mieloide aguda menores de 55 años de edad en comparación con cohorte histórica tratada con 7+3.

PALABRAS CLAVE: Leucemia mieloide aguda; etopósido; citarabina; daunorrubicina.

BACKGROUND

Acute myeloid leukemia (AML) represents a heterogeneous group of conditions, characterized by an uncontrolled proliferation of neoplastic hematopoietic precursors, with a concomitant decrease in normal hematopoietic elements.[1,2]

AML is a curable condition in approximately 35-45% of patients under the age of 60, and in roughly 5-15% of patients older than 60.[3,4]

Forty years after its introduction, the combination of an anthracycline (daunorubicin or idarubicin) administered over the course of three days, plus the continuous infusion of cytarabine (100-200 mg/m^2/daily) during 7 days (known as a 7+3) continues to be the standard induction treatment.[4,5]

Complete remission (CR) rates in patients who undergo the 7+3 regimen are approximately 70% in patients under 60 years of age.[2]

In one study in patients under the age of 55, adding etoposide to the 7+3 significantly improved remission duration by 14 months (p = 0.01) and the global survival for 8 months (p = 0.03).[6]

Another study by Willemze et al. compared standard dose (SD) cytarabine (100 mg/m^2/every 24 hours for 10 days) *versus* high dose (HD) cytarabine (3000 mg/m^2/every 12 hours on days 1, 3, 5 and 7), plus daunorubicin and etoposide. Results from this trial showed that patients receiving the HD cytarabine achieve a higher CR rate (75.6% SD *vs* 82.4% HD, *p* = 0.01), 6 year overall survival (OS) (43.6% SD *vs* 51.9% HD p = 0.09) and 6 year event-free survival (EFS) (35.1% SD *vs* 43.6% HD p = 0.003). All outcomes favored the HD regimen in patients under 46 years of age.[7]

In our center, we previously report CR rates of 39.5% when using the 7+3 regimen in a single cycle, and 62.6% with 2 cycles in patients with a median age of 44 years (15-79).[8]

Based on the previous results, we performed the present study with the objective to compare two more intensive induction regimens: 7+3 + etoposide (7+3+7) *versus* high-dose cytarabine and daunorubicine (HiDAC-D).

MATERIAL AND METHOD

A retrospective, comparative study of patients treated at National Institute of Medical Sciences and Nutrition Salvador Zubiran, Mexico City, from November 2010 to November 2016. AML diagnosis and classification was performed according to the WHO 2008 classification.[9]

We included young adults: 18-55 years. We excluded patients with acute promyelocytic leukemia (APL), those who received previous chemotherapy regimens or with incomplete clinical files. Leukemia lineage was established through flow cytometry using the following panel of monoclonal antibodies: CD45, CD34, CD10, CD19, CD20, CD22, CD79a, CD2, CD3, CD5, CD13, CD33, CD15, CD14, CD64, CD117 and MPO. A conventional karyotype was performed with G bands and FISH (fluorescence *in situ* hybridization) to some patients to identify *PLM/RAR alfa* translocation, and thus exclude cases of APL. Patients with an unknown karyotype (either for lack of study or lack of metaphases in study) were considered as non-available karyotype. Cytogenetic risk was established as recommended by the NCCN guidelines.[10] We didn't analyze recurrent genetic mutations in all the patients.

Treatment

The patients were randomized to receive induction regimens used in this study: 7+3+7 (cytarabine 100 mg/m^2/day on days 1-7, daunorubicin 45 mg/m^2/day on days 1-3 and etoposide 75 mg/m^2/day on days 1-7),[6] and HiDAC-D (cytarabine 3000 mg/m^2/day on days 1-3 and daunorubicin 45 mg/m^2/day on days 1-2). All patients were planned to receive 3 consolidations with HD cytarabine (3000 mg/m^2/12 hours on days 1-3 and daunorubicin 45 mg/m^2 on days 1 and 2). Patients were individually considered for allogeneic hematopoietic stem-cell transplantation (Allo-HSCT) based on cytogenetic risk.

Response criteria

CR was defined as less than 5% blasts in bone marrow (BM) by light microscopy examination, absence of blast cells in peripheral blood (PB), absence of Auer bodies, and absence of extra medullar leukemia, aside from a restoration of normal hematopoiesis defined as total neutrophils of 1 x 10^9/L and platelets of 100 x 10^9/L.[11] In case of disease persistence, all the patients received re-induction chemotherapy with cytarabine 3000 mg/m^2/12 hours on days 1-3 and daunorubicin 45 mg/m^2 on days 1 and 2. Relapse was defined as appearance of ≥ 5% blasts in PB or BM in patients who had previously achieved a CR, also the presence of extramedullary disease. Severe neutropenia was defined as less than < 500 neutrophils/μL. Disease free survival (DFS) was measured from CR up until relapse or last follow-up. OS was measured from time of diagnosis of AML up until death by any cause or last follow-up.

Statistical analysis

Categorical variables were reported as proportions and frequencies, while continuous variables are summarized as arithmetic means, medians. Comparisons between categorical variables were assessed through a χ^2 test and Fisher's exact test. Median comparisons were assessed through a Mann-Whitney U test. The time-to-event variables (OS, DFS) were obtained through the Kaplan-Meier method and differences determined by log-rank tests. Cox regression analyses were performed on factors related to survival. A p value of ≤ 0.05 was considered statistically significant. The statistical analyses were performed using SPSS version 21.0 (SSPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 40 patients were included. Of these, 17 were male patients (42.5%) and 23 were women (57.5%). Median age was 40.5 years (18-55 years): 39 years in the 7+3+7 group and 41 years in the HiDAC-D group (p = 0.287). Median follow up was 16 months. **Table 1** summarizes the general characteristics of the study population, which do not show differences among treatment groups. A normal karyotype was reported in 34% of the patients, a complex karyo-

Table 1. General characteristics

Total n = 40 (100%)	HiDAC-D n= 19 (47.5%)	7+3+7 n = 21 (52.5%)	p
Gender			
Male 17 (42.5)	9 (47.4)	8 (38.1)	0.554
Female 23 (57.5)	10 (52.6)	13 (61.9)	
Complete remission			
CR with 1 cycle 27 (67.5)	13 (68.4)	14 (66.7)	0.72
CR with reinduction 6 (15)	4 (21)	2 (9.5)	1
CR total 33 (82.5)	17 (89.4)	16 (76.2)	0.44
ECOG			
0-1 35 (87.5)	18 (94.7)	17 (80.9)	0.414
2-4 5 (12.5)	1 (5.2)	4 (19.0)	
Comorbidities			
DM2 5 (12.5)	1 (5.2)	4 (19)	0.212
Hypertension 1 (2.5)	1 (5.2)	0	
Cancer 3 (7.5)	2 (10.5)	1 (4.7)	
Other 10 (25)	7 (36.8)	3 (14.2)	
None 21 (52.5)	8 (42.1)	13 (61.9)	
Cytogenetic			
Normal 13 (34)	8 (42)	5 (23.8)	0.290
t (8;21) 3 (7.8)	2 (10.5)	1 (4.7)	
Alt. 16 1 (2.6)	1 (5.2)	0	
Complex 10 (26)	4 (21)	6 (28.5)	
Other 6 (15.7)	2 (10.5)	4 (18.8)	
NA 7 (17.5)	2 (10.5)	5 (23.8)	
Extramedullary 4 (10)	3 (15.7)	1 (4.7)	0.431
Cytogenetic risk (n = 38)			0.242
Favorable 4 (10.5)	3 (15.7)	1 (4.7)	
Intermediate 17 (44.7)	10 (52.6)	7 (33)	
Unfavorable 12 (31.5)	4 (21.0)	8 (38)	
AML Classification			0.709
With recurrent genetic abnormalities 5 (12.5)	3 (15.7)	2 (9.5)	
With myelodysplasia-related changes 1 (2.5)	0	1 (4.8)	
Treatment-associated 3 (7.5)	1 (5.2)	2 (9.5)	
Other 31* (77.5)	15 (78)	16 (76.1)	

HiDAC: high-dose cytarabine and daunorubicine; CR: complete remission; DM2: type 2 diabetes mellitus; ECOG: Eastern Cooperative Oncology Group performance status; NA: not available.
* Do not meet criteria to be included in any other category according to the WHO classification.

type in 26%, t(8;21) in 7.8%, inv(16) in 2.6% and 13% of samples did not have analyzable metaphases. Regarding cytogenetic risk, 44.7% of the patients had intermediate risk, 31.5% unfavorable risk and 10.5% had a favorable risk.

Treatment response

From the 40 patients included in the study, 21 patients received the 7+3+7, while 19 received HiDAC-D.

In the 7+3+7 group, 66% of the patients (14/21) achieved a CR with only one induction cycle, while the HiDAC-D group achieved a CR in 68% of the patients (13/19; p = 0.721). Two patients from the 7+3+7 group died before we could evaluate treatment response. In this same group, 3 patients received re-induction with HD cytarabine and CR was achieved in 2 out of the 3 patients. In the HiDAC-D group 6 patients received re-induction with HD cytarabine achieving a CR in 4 out of the 6 patients (p = 1). In the 7+3+7 treatment group 2 patients did not receive a second induction cycle, since they chose to receive palliative care instead.

The CR in the entire cohort was of 67% with one induction cycle (27/40) and 82% with the re-induction (33/40). In the 7+3+7 group, CR with the re-induction was achieved in 76.2% of patients, while in the HiDAC-D treatment group it was 89.4% (17/19; p = 0.44).

The relapse rate in the entire cohort was 45% (18/33), by treatment arm the results yield that 42% (9/16) of the patients in the 7+3+7 group relapsed, while in the HiDAC-D treatment group it was 47% (9/17) of patients (p = 0.84). **Table 2**.

Allogeneic Hematopoietic Stem Cell Transplant (Allo-HSCT) was performed in 12.5% (5/40) of the patients, 19% (4/21) in the 7+3+7 treatment group and 5% (1/19) in the HiDAC-D treatment group (p = 0.188). HCT indications were a second CR in 4 patients, and a high cytogenetic risk profile at diagnosis for 1 patient. In the unfavorable risk group allogeneic Hematopoietic Stem Cell Transplant was not performed for lack of complete remission in 5 patients, lack of donor in 1 patient, death due to infectious complications prior to Allo-HSCT in 2 patients and relapse in 1 patient.

Table 2. Treatment response with one and two cycles of induction to remission

Total CR/total (%)	HiDAC-D CR/total (%)	7+3+7 CR/total (%)	p
CR with one cycle 27/40 (67.5)	13/19 (68.4)	14/21 (66.7)	0.72
CR with reinduction 6/40 (15)	4/19 (21)	2/21 (9.5)	1
CR total 33/40 (82.5)	17/19 (89.4)	16/21 (76.2)	0.44
Relapse 18/33 (45)	9/17 (47)	9/16 (42)	0.84

CR: complete remission; HiDAC: high-dose cytarabine and daunorubicine.

Toxicity

From the 40 patients included in the analysis, 2 patients died after receiving the first induction cycle and previous to treatment-response evaluation. Both patients died with bone marrow aplasia and pneumonia.

Median neutrophil-recovery time was 18 days (9-27) in the 7+3+7 group and 21 days (3-30) in the HiDAC-D group (p = 0.307). Frequency of severe neutropenia and fever for the 7+3+7 group was 100% while it was 94% for the HiDAC-D group (p = 0.47). In 50% of cases the infectious agent was identified through cultures, with Gram-negative bacilli being the most commonly isolated without statistical difference between treatment arms (p = 0.19). The most frequent infection in both groups was pneumonia without statistical difference (p = 0.22). 15% of patients experienced septic shock during induction, without

any difference between treatment arms (p = 1.0). 15% of patients required invasive mechanical ventilation during induction, without significant differences between treatment groups (p = 0.84).

Survival outcomes

Median OS for this cohort was 18.9 months (95%CI 11.5-26.3 months). Of those patients who achieved CR, DFS was 22 months (95%CI 10.3-33.8 months).

We did not find any differences in OS according to treatment arm: the group of patients who received the 7+3+7 regimen had a median OS of 17.2 months (95%CI 7.4-27 months), while the group that received HiDAC-D had a median OS of 18.9 months (95%CI 0.1-37.8 months) (p = 0.620). Median DFS in the 7+3+7 group was 21.2 months (95%CI 0-61 months), while median DFS in the HiDAC-D group was 22 months (95%CI 3.8-40 months), without any differences between treatment arms (p = 0.83). **Figures 1-2**

Regarding cytogenetic risk, patients who had a favorable risk profile had a non-reached (NR) median OS, those with an intermediate risk profile had a median OS of 25 months (95%CI 15.7-34.2) and those with an unfavorable risk profile presented a median OS of 7.8 months (95%CI 6.3-9.2 months; p = 0.0002). **Figure 3**

The cytogenetic risk was further analyzed in relation to the treatment regimen received. A favorable significant difference was observed between unfavorable risk patients treated with the 7+3+7 regimen compared to those treated with HiDAC-D, the first presented a median OS of 8.8 (95%CI 2.5-15) months *versus* 5 months (95%CI 2.1-7.9) for the latter (p = 0.037). **Figure 4**

There was no difference in patients with intermediate risk (p = 0.219) in relation to the treatment received (**Figure 5**).

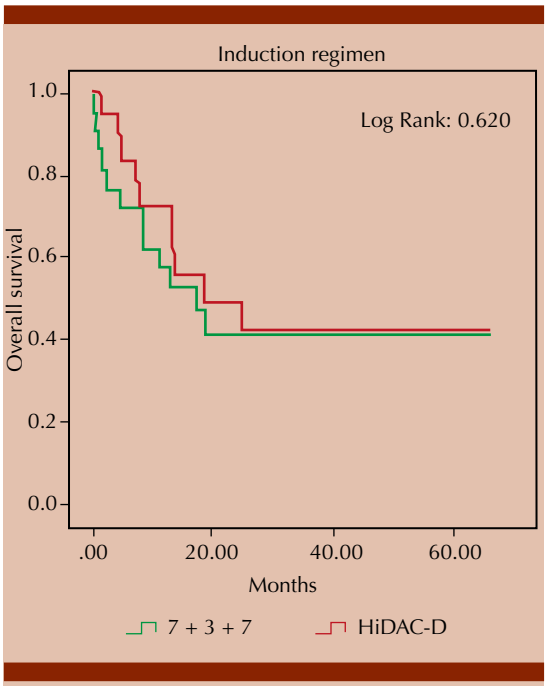

Figure 1. Overall survival according to treatment scheme (7+3+7 *vs* HiDAC-D). Kaplan-Meier method (n = 40).

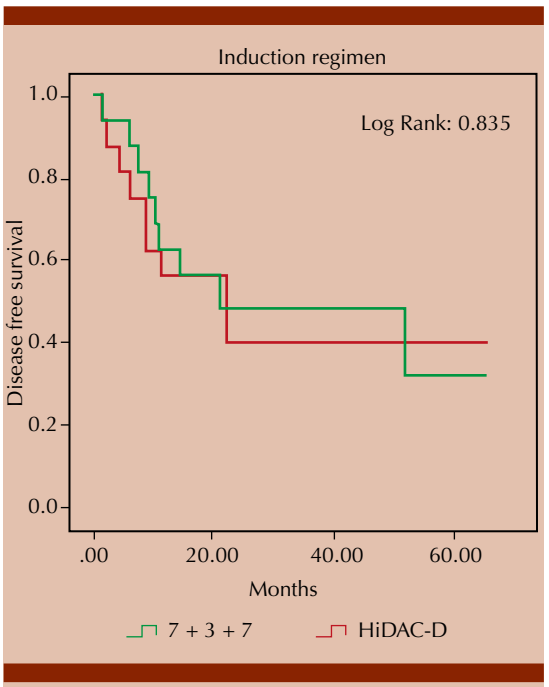

Figure 2. DFS according to treatment scheme (7+3+7 *vs* HiDAC-D). Kaplan-Meier method (n = 40).

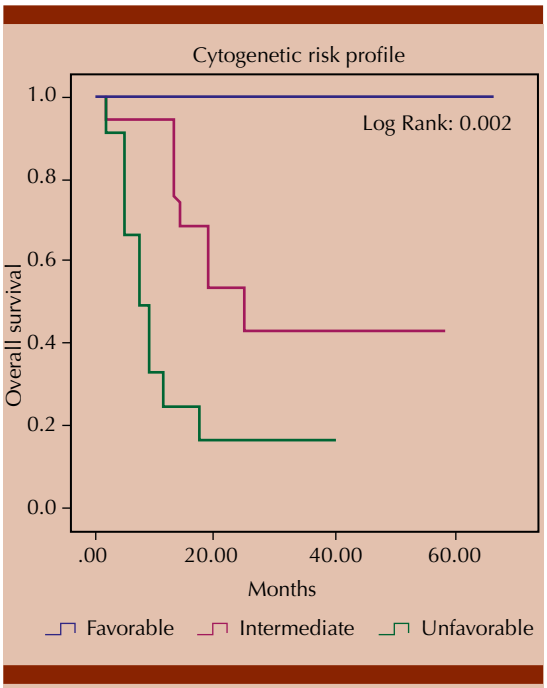

Figure 3. Overall survival according to cytogenetic risk profile. Kaplan-Meier method (n = 33).

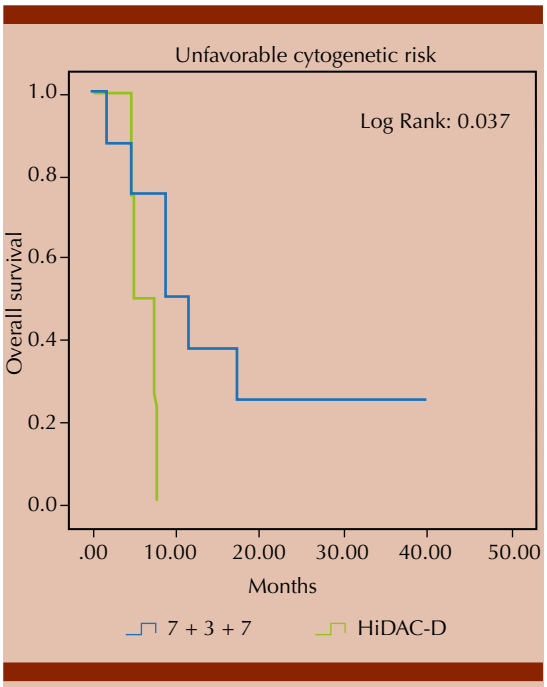

Figure 4. Overall survival in patients with unfavorable risk profile according to treatment scheme. Kaplan-Meier method (n = 12).

We performed univariate and multivariate analyses for OS. Several factors were associated with a poor OS outcome: having a poor functional status (p = 0.001; HR 1.9; 95%CI 1.2-2.8), higher cytogenetic risk profile (p = 0.001; HR 4.0; 95%CI 1.7-9.5), and septic shock at the time of induction (p = 0.03; HR 3.3; 95%CI 1.0-10). Age younger than 40 years was a protective factor (p = 0.02; HR 0.33; 95%CI 0.13-0.85). At multivariate analysis the factors that remained significant were: age < 40 (p = 0.01; HR 0.18; 95%CI: 0.04-0.7), cytogenetic risk (p = 0.002; HR 6.7; 95%CI 1.9-22) and septic shock (p = 0.03; HR 14.6; 95%CI 1.1-17). **Table 3**

DISCUSSION

Similar to what has been previously reported in other studies (52-80%), cytogenetic abnormalities were observed in 50% of our study population.[12]

Regarding cytogenetic risk distribution, 10% of our studied patients presented with a favorable profile, 42.5% had an intermediate risk profile, 30% had an unfavorable profile and 17.5% had an unknown profile, the latter which is in agreement with data reported by international study groups, such as ECOG and SWOG[13] and with a lower amount of intermediate risk patients compared with reports from the CALGB (71%).[14] Nonetheless, lack of molecular analysis in this study is an important limitation for risk classification.

The present study compared two intensive chemotherapy regimens in young patients with AML. Our data shows that one cycle of any of these two treatment regimens produced a higher CR rate when compared with the conventional 7+3 used in our historic cohort: 68% CR with HiDAC-D, 66% CR with 7+3+7 (p = 0.72), which compare favorably to the 39% seen in

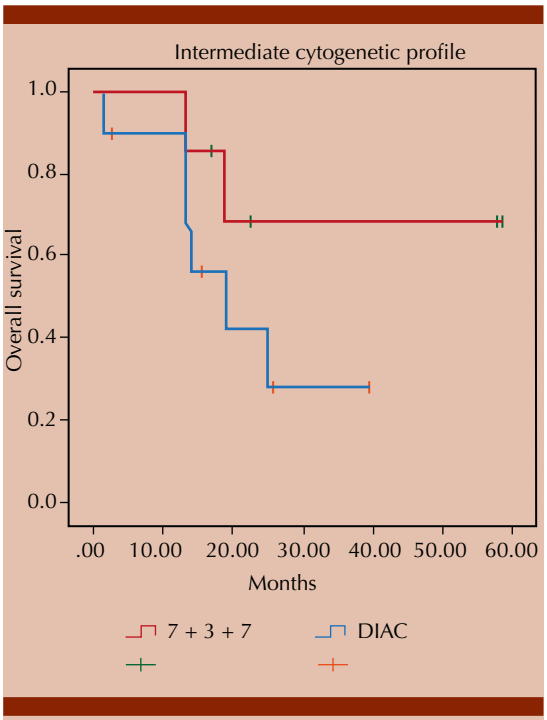

Figure 5. Overall survival in patients with intermediate risk profile according to treatment scheme. Kaplan-Meier method (n = 12).

our retrospective cohort. With HD cytarabine re-induction, the CR achieved rises to 89% in the group receiving HiDAC-D and 76% in the 7+3+7 group (p = 0.44), compared to a 62% with 2 induction cycles seen in the historic cohort. In our historic cohort median OS with 7+3 was 17.5 months, with a DFS of 16.1 months, meanwhile patients who undergo either of the more intensive regimens we tested have a median OS of 18.9 months and a median DFS of 22 months.

A study by Bishop et al. AML patients < 55 years shows no advantage in CR when adding etoposide to the 7+3 regimens (7+3+7), although this addition did in fact improve the median of remission duration as well as OS compared to 7+3.[15,16]

Bishop et al.[17] compared the use of HD cytarabine plus etoposide and daunorubicin against 7+3+7, and observed an increase in the median response duration and a longer DFS in favor of the group receiving HD cytarabine.

In our data, the outcomes were similar between both treatment arms, although the cytarabine dose used in the present study was lower to the one used in the previously cited clinical trials. However, there is evidence that HD cytarabine has no advantage over the standard treatment dose (200 mg/m^2), and studies suggest that increasing the dose over 1000 mg/m^2 has no improved antileukemic activity, but does importantly increase the toxicity profile. In this case, the dose-response relation for cytarabine appears to level and plateau at doses higher than 1000 mg/m^2. Additionally, pharmacokinetic studies regarding cytarabine plasma concentrations and the accumulation of the 5-triphosphate metabolite in leukemic cells suggest that doses of 3000 mg/m^2 achieve levels high above saturating concentrations.[18]

Table 3. Risk factors associated to overall survival. Cox regression analysis (n = 40)

Characteristic	Univariate analysis			Multivariate analysis		
	p	HR	IC95%	p	HR	IC95%
Age<40 years	0.022	0.334	0.13-0.85	0.01	0.18	0.04-0.70
ECOG	0.001	1.931	1.2-2.8	0.80	1.08	0.59-1.9
Cytogenetic risk	0.001	4.075	1.7-9.5	0.002	6.7	1.9-22
Septic shock	0.034	3.32	1.09-10	0.03	14.6	1.2-175

ECOG: Eastern Cooperative Oncology Group performance status.

When survival was analyzed in regard to the cytogenetic risk profile, we observed a benefit in OS for those patients who had an unfavorable risk profile and received 7+3+7 (median OS 8.8 *vs*. 5 months, respectively, (p =0.03). Our results suggest that adding etoposide to this group of patients provides a survival benefit.

It is important to consider that the daunorubicin dose used in the present work were of 45 mg/m^2 since there is evidence supporting that higher induction doses of this agent (60 to 90 mg/m^2) increase the CR rate as well as OS in young patients (< 60 years) without increasing toxicity,[19,20] particularly in patients with intermediate and favorable cytogenetic risk,[18] though other studies observe this benefit only in patients with intermediate risk profiles.[20,21]

This invariably leads to the question of whether the use of a 7+3+7 or HiDAC-D with 60mg/m^2 of daunorubicin instead of 45 mg/m^2 may increase OS without additional treatment-associated toxicity or mortality in our study population.

There is a clear benefit of Allo-HSCT on intermediate and high-risk patients with AML in first CR.[22] In our study Allo-HSCT was performed only in 5 patients and only in 1 case in first CR.

The data we present shows a significant OS benefit in patients who undergo Allo-HSCT in spite of the small number of studied patients.

In the present study only 5 patients were submitted to Allo-HSCT and only one of them in first complete remission. Considering that the benefit of Allo-HSCT has been demonstrated in patients with intermediate or high cytogenetic risk, 90% of our patients were candidates for transplantation. However, the lack of a donor and the lack of economic resources have been the most important limiting factors in our country. At present there are social programs that facilitate the realization of Allo-TCH from the economic point of view and on the other hand the haploidentic transplants have allowed to attenuate the lack of donor in our institution. Therefore, our objective is to increase the number of patients who are transplanted in first complete remission.

Our study is limited by several factors, namely its retrospective design, the small number of patients as well as a lack of mutational profile, which would allow for a better risk stratification of these patients.

CONCLUSION

The present work compared two intensive induction regimens, both increased CR rates without increasing mortality in patients with AML less than 55 years of age in comparison with our historical cohort with 7+3. These 2 intensive induction regimens are effective and tolerated in young adult patients with AML.

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