Journal Pre-proof

Acute myeloid leukemia in Mexico: the specific challenges of a developing country. Results from a multicenter national registry

Roberta Demichelis-Gómez, Nidia Zapata-Canto, Faustino Leyto-Cruz, Eduardo Terreros-Muñoz, Angel Carrillo, Efreen Montaño-Figueroa, Juan Carlos Solís-Poblano, Perla Colunga-Pedraza, Guillermo Díaz-Vargas, Lauro Fabían Amador-Medina, Ramón Martínez-Hernández, Francisco Turrubiates, Alvaro Cabrera-García, Alva Zaragoza, Ramiro Espinoza, Ruth Gutiérrez-Serdán, Elia Apodaca, Carolina Moreira, Carolina García-Castillo, Lilia García-Stivalet, Alejandro Limón, David Gómez-Almaguer, Etta Rozen-Fuller, Karla Adriana Espinosa-Bautista, Erick Crespo-Solís, Luis Meillón

PII: S2152-2650(19)32237-2

DOI: https://doi.org/10.1016/j.clml.2019.12.015

Reference: CLML 1498

To appear in: *Clinical Lymphoma, Myeloma and Leukemia*

Received Date: 9 October 2019

Accepted Date: 13 December 2019

Please cite this article as: Demichelis-Gómez R, Zapata-Canto N, Leyto-Cruz F, Terreros-Muñoz E, Carrillo A, Montaño-Figueroa E, Solís-Poblano JC, Colunga-Pedraza P, Díaz-Vargas G, Amador-Medina LF, Martínez-Hernández R, Turrubiates F, Cabrera-García A, Zaragoza A, Espinoza R, Gutiérrez-Serdán R, Apodaca E, Moreira C, García-Castillo C, García-Stivalet L, Limón A, Gómez-Almaguer D, Rozen-Fuller E, Espinosa-Bautista KA, Crespo-Solís E, Meillón L, Acute myeloid leukemia in Mexico: the specific challenges of a developing country. Results from a multicenter national registry, *Clinical Lymphoma, Myeloma and Leukemia* (2020), doi: https://doi.org/10.1016/j.clml.2019.12.015.

Title: Acute myeloid leukemia in Mexico: the specific challenges of a developing country. Results from a multicenter national registry.

Short title: Survival analysis of adult AML in Mexico

Authors: Roberta Demichelis-Gómez[1*], Nidia Zapata-Canto[2], Faustino Leyto-Cruz[3], Eduardo Terreros-Muñoz[4], Angel Carrillo[5], Efreen Montaño-Figueroa[6], Juan Carlos Solís-Poblano[7], Perla Colunga-Pedraza[8], Guillermo Díaz-Vargas[9], Lauro Fabían Amador-Medina[10], Ramón Martínez-Hernández[11], Francisco Turrubiates[11], Alvaro Cabrera-García[12], Alva Zaragoza[13], Ramiro Espinoza[2], Ruth Gutiérrez-Serdán[9], Elia Apodaca[1], Carolina Moreira[3], Carolina García-Castillo[5], Lilia García-Stivalet[7], Alejandro Limón[7], David Gómez-Almaguer[8], Etta Rozen-Fuller[6], Karla Adriana Espinosa-Bautista[2], Erick Crespo-Solís[11], Luis Meillón[14]

Affiliations: [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [2]Instituto Nacional de Cancerología, Mexico City, Mexico; [3]Hospital Juárez de México, Mexico City, Mexico; [4]Centro Médico Nacional siglo XXI, IMSS, Mexico City, Mexico; [5]Hospital Central Militar, SEDENA, Mexico City, Mexico; [6]Hospital General de México, Mexico City, Mexico; [7]Hospital de Especialidades CMN "Manuel Ávila Camacho", IMSS, Puebla, Mexico; [8]Hospital Universitario "Dr. José Eleuterio González", Monterrey, Mexico; [9]Centro Oncológico Estatal, ISSEMyM, Estado de México, Mexico; [10]Hospital Regional de Alta Especialidad del Bajío, León, Mexico; [11]Hospital Regional de Alta Especialidad de Ciudad Victoria, Ciudad Victoria, Mexico; [12]Hospital Regional de Alta Especialidad de Ixtapaluca, Estado de México, Mexico;

[13]Hospital General Regional n°1, IMSS, Chihuahua, Mexico; [14]Centro Médico ABC, Mexico City, Mexico

Please address correspondence to:

Roberta Demichelis-Gómez

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Vasco de Quiroga 15, Belisario Domínguez, Tlalpan, 14080

Mexico City, Mexico

+52154870900 ext 2700

robertademichelis@gmail.com

Microabstract (58/60):

This large retrospective multicenter report of AML in Mexico including 525 patients shows the principal survival-related factors in a developing country. The majority (80.2%) was treated with intensive chemotherapy. In this group, a high-rate of induction related-mortality (17.8%), the lack of complete genetic and molecular assessment and the low rate of Allo-HSCT (8.2%) are our main medium-term challenges.

Abstract (242/250)

Background: In the last decades, long-term survival outcomes for younger patients with acute myeloid leukemia (AML) have improved. Nonetheless, developing nations might be lagging behind, highlighting the need to assess real-world outcomes in such regions.

Methods: We performed a multicenter retrospective study, which included patients with AML diagnosed between January 2013 and December 2017 from 13 centers in Mexico.

Results: A total of 525 patients with AML met the inclusion criteria and were included in the study. Median age for the entire cohort was 47 years. The patients were classified according to cytogenetic risk: favorable 16.0%, intermediate 55.6% and unfavorable 28.4%. Most patients received intensive chemotherapy (80.2%), and among these 74.1% underwent a 7+3 induction regimen. A complete remission was achieved in 71.3% of patients. Induction related mortality occurred in 17.8% and we identify as independent risk factors: >60 years (OR=2.09 (1.09-4.02)), ECOG>2 (OR=4.82 (2.46-9.43)), prior solid tumor (OR=3.8 (1.24-11.59)) and active infection (OR=1.82 (1.06-3.12)). Further, AlloHSCT was performed in 8.2% in CR1. The 3-year overall survival (OS) was 34.8%. In a multivariate analysis several factors were independently associated with a worse OS, including secondary AML (HR=2.14 (1.15-4.01)) and unfavorable cytogenetic risk (HR=1.81 (1.16-2.82)), whereas maintenance therapy (HR=0.53 (0.32-0.86)) and allogeneic HSCT (HR=0.40 (0.17-0.94)) were associated with better OS.

Conclusions: This is the first multicenter report analyzing AML-survival in Mexico. Challenges in this setting include a high induction-related mortality and low AlloHSCT rate, which should be addressed in order to improve outcomes.

Keywords: acute myeloid leukemia, developing nations, survival, Mexico

Introduction

Acute Myeloid Leukemia (AML) references a heterogeneous group of hematopoietic neoplasms, characterized by the clonal proliferation of myeloid progenitors with a decreased capacity for differentiating into mature blood elements[1]. Approximately 80% of acute leukemias in adults are classified as AML, with a median age at diagnosis of 67 years[2]. Prognosis is highly variable, and depends partly on patient characteristics (age, comorbidities, functional status), though it is mostly influenced by the genetic and molecular features of the disease[3-6]. The European Leukemia Net, endorsed in the NCCN, recommends a risk stratification score based on the analysis of cytogenetic alterations, along with a comprehensive search for mutations in *FLT3* (*ITD* and *TKD*), *NPM1*, *CEBPA*, *ASXL1*, *RUNX1* and *TP53*[6,7]. As a result of novel approaches, the prognosis for patients with AML treated with intensive chemotherapy has considerably improved, reaching long-term survival rates of 40%[8]. Nonetheless, these improvements do not generally fully translate into the outcomes of patients from developing nations, where patient characteristics and challenges differ from those identified in developed countries. Studies performed in the US, for instance, suggest that Hispanic AML patients present with a younger age at diagnosis (median age of 59 years *vs*. 71 years in Non-Hispanic whites), but have a worse prognosis in terms of survival (HR: 1.79 [95%CI: 1.1-2.9]; p=0.02)[9]. Despite these important differences, data from within many Latin American countries is mostly limited to small retrospective single-center series. In Mexico, such studies have reported a

median age at diagnosis ranging from 32 and 43 years of age; similar to reports from other developing countries, including Brazil, India and Malaysia (median age at diagnosis 33-44 years)[10-13].

Another important challenge in developing nations includes the limited access to adequate cytogenetic classification and increased mortality. For example, in Mexico only 46-60.8% of patients have an evaluable karyotype[12,13], while the induction mortality rate remains high (13.9-18.9%)[12-15].

There are currently no multicenter studies in Mexico which consistently evaluate the characteristics associated with overall survival (OS) in adult patients with AML treated with intensive chemotherapy. In this study, we present the largest compilation of AML patients from Mexico through a collaborative effort from 13 different reference centers. We sought to describe the characteristics pertaining to this population, as well as survival outcomes and features associated with prognosis.

Methods

We performed an observational analysis of patients diagnosed with AML, between January 2013 and December 2017. Baseline characteristics, as well as genetic and molecular features, therapeutic regimens and clinical outcomes were recorded.

Patient selection:

We include patients with AML, according to the WHO criteria[16]. Patients were diagnosed with AML if they had at least 20% blasts in blood or bone marrow or with the demonstration of t(8;21) or inv(16)/t(16;16). The myeloid cell origin was confirmed in all cases by immunophenotyping with flow cytometry. All the patients were treated in an adult hemato-oncology service and were older than 14 years. We exclude patients with acute promyelocytic leukemia, mixed phenotype acute myeloid leukemia and isolated extramedulary disease. Patients were identified and data was retrospectively collected from local databases in 13 centers across the country. Survival analysis was made only in patients receiving frontline intensive chemotherapy.

Definitions:

Induction regimens in patients who underwent intensive chemotherapy were classified as follows: 7+3 (7-day continuous infusion (24 hours) of cytarabine [dose: 100-200 mg/m^2] on days 1 to 7 and an anthracycline on days 1 to 3), 5-+2 (5-day continuous infusion (24

hours) of cytarabine [dose:100-200 mg/m^2] on days 1 to 5 and an anthracycline on days 1 and 2), and 7+3+? (7+3 scheme associated to a third cytotoxic chemotherapy drug). For post-remission therapeutic strategies, we considered high-dose cytarabine as doses exceeding 1gr/m^2 for 6 doses. As to rescue regimens, these included FLAG(Ida) (fludarabine, cytarabine, granulocyte colony-stimulating factor +/- idarubicin) or MEC (mitoxantrone, etoposide and cytarabine).

Complete remission (CR) was defined according to the Cheson criteria (<5% blasts in bone marrow with trilineage hematopoiesis, hematopoietic recovery with absolute neutrophil counts >1000/µL and platelet counts >100,000/µL; absence of blasts in peripheral blood and/or extramedullary disease)[17].

Induction related mortality was defined as death by any cause, which occurred during the first month post-diagnosis in patients who received induction chemotherapy. Overall survival was defined as the date from diagnosis until death or last follow-up.

Cytogenetic risk was classified by the Medical Research Council cytogenetic classification system. *FLT3* or *NPM1* mutations were not used for the risk stratification since they were not assessed in the majority of the patients.[18]

Statistical considerations:

Continuous variables were described as medians and interquartile ranges and categorical variables were summarized as proportions. Medians were compared using the Mann Whitney U test, and percentages using the χ^2 test and Fisher´s exact test. In order to identify risk factors associated with induction-related mortality, we calculated the odds ratio (OR) and performed a logistic regression in order to perform a multivariate analysis. Survival

outcomes were analyzed using the Kaplan-Meier method and comparisons were made using the log-Rank test. We performed a landmark analysis at 3 months after induction for patients undergoing allogeneic hematopoietic stem cell transplantation (Allo-HSCT) or maintenance. Prognostic factors associated with OS were analyzed using a Cox regression model. A multivariate regression model was performed including the variables that were significant ($p<0.05$) in the univariate analysis. All analyses were performed using the SPSS software (version 22). The study was approved by the ethics and research committee of each independent participating center.

Results

A total of 525 patients diagnosed with AML between January 2013 and December 2017 were included in the analysis. Median age was 47 years (range: 14-95 years). An evaluable karyotype was available in 69.1% of cases. Specific genetic features were sought in a small proportion of patients, and the most frequently evaluated included mutations in FLT3 (performed in 12.2% of cases; positive result in 22% of cases) and NPM1 (performed in 8.2% of cases; positive result in 12% of cases).

Among the studied population, 80.2% (n=421) received intensive chemotherapy. Population characteristics as per therapeutic strategy are detailed in Table 1. Patients who underwent intensive chemotherapy were younger, had less comorbidities and had a lower frequency of secondary leukemias. The most frequently used induction regimen in patients who received intensive chemotherapy was 7+3 (74.1% of patients) followed by 5+2 (10.5% of patients), 7+3+? (9% of patients) and other (6% of patients). The type and dose of anthracycline used varied among the population, however the most frequently used drug was daunorubicin in 66% of patients at varying doses (60mg/m^2 in 43.7%; 45mg/m^2 in 23.4% and 90mg/m^2 in 0.2%). Idarubicin was used in 20.7% of patients, also at varying doses (12mg/m^2 in 18.8% and 10mg/m^2 in 2.2%). Last, 11.7% of patients received mitoxantrone. A complete remission (CR) was achieved with one or two induction cycles in 71.3% of patients. When only considering the first induction cycle, the CR rate was 53.9%,

and according to the type of anthracycline used in the scheme the CR rate decreased in the following order: idarubicin 12mg/m^2 67.5%; daunorubicin 60mg/m^2 53.6%; mitoxantrone 52.1%; idarubicin 10mg/m^2 50%, daunorubicin 45mg/m^2 46.9%; and daunorubicin 90mg/m^2 0% (of note, only 1 patient received this dosage).

Induction related mortality occurred in 17.8% of cases. Table 2 summarizes a univariate and multivariate analysis of risk factors. Age (>60 years), ECOG >2, prior solid tumor and active infection at diagnosis are independent risk factors related to induction related mortality. Hyperleukocytosis was not associated with a higher rate of induction related mortality.

A total of 68.6% of patients received postremission consolidation therapy in the form of high-dose cytarabine, 23.6% received high-dose cytarabine associated with a second drug, and 7.9% received a different consolidation regimen. The dose of cytarabine varied among patients, 42% received 3gr/m^2 for a total of 6 doses, while 56.2% received 1-2.9gr/m^2 for a total of 6 doses. Median number of consolidation cycles was 3 (range: 1-9). Thereafter, 28.2% of patients in remission following consolidation therapy received maintenance therapy. The most frequently used treatment in these cases was 6-mercaptopurine and methotrexate in 66.3% of cases, followed by cytarabine-based maintenance in 27.7% of cases and last, a low proportion of patients received maintenance with hypomethylating agents (8%).

Only 8.2% of patients underwent consolidation with Allo-HSCT following the first CR. Among patients who achieved a CR, 47.7% relapsed. A total of 60.2% of relapsed patients underwent rescue chemotherapy: 33.3% received FLAG(ida), 27.8% received MEC and

38.9% received a different regimen. Following rescue therapy, 49.1% of patients achieved a second CR.

Among the entire study population, 3-year OS was 34.8%. Median OS was 14.0 months (95%CI: 10.9-17.1) for the entire cohort, however patients with a favorable cytogenetic risk had a statistically significant longer median OS compared with those with an intermediate and unfavorable risk stratification (45.3 months [95%CI: 26.0-64.7] **vs.** 20.5 months [95%CI: 8.5-32.5] *vs.* 12 months [95%CI: 9.3-14.7], respectively; p=0.001) (**Figure 1**).

A clear survival benefit was also identified as per the type and dose of anthracyclene used during induction therapy (**Figure 2**). Patients who received high dose idarubicin (12mg/m^2) or daunorubicin (60-90 mg/m^2) had a median OS of 23.1 months (95%CI: 13.4-32.9), compared with patients who received mitoxantrone, whose median OS was 15.3 months (95%CI: 9.7-20.9) and patients who received low dose idarubicin (10mg/m^2) or daunorubicin (45mg/m^2), who had a median OS of 9.0 months (95%CI: 6.8-11.2)(p< 0.001). No differences in terms of OS were identified when comparing the dose of cytarabine during consolidation (3gr/m^2 for 6 doses *vs.* 1- 2.9gr/m^2 for 6 doses).

In a 3-month landmark analysis, patients who received maintenance therapy had a longer OS compared with patients who did not receive any type of maintenance (median OS: Non-reached [NR] vs. 24.1 months; p=0.017) (**Figure 3**). We performed a subgroup analysis for patients who received maintenance according to the type of treatment, and identified that OS benefit was only significant in patients who received cytarabine-based maintenance therapy compared with no maintenance (median OS NR vs. 24.1 (12.3-25.8) months; p=0.032). This difference was not significant for patients who received maintenance with

6-mercaptopurine and methotrexate (49.3 (17.1-81-6) vs. 25.9 (13.8-38.1) months; p=0.115). Also, this survival benefit of maintenance was only significant for patients with intermediate cytogenetic risk (median OS NR vs. 30.9 (13.7-48.0) months; p= 0.021) in contrast with patients with favorable or unfavorable cytogenetic risk.

In a 3-month landmark analysis, patients who received consolidation therapy with AlloHSCT during the first CR had a significantly improved OS compared with patients not consolidated with AlloHSCT (median OS NR vs. 25.7 months; p=0.003) (**Figure 4**).

We identified several factors as independently associated with a worse OS during the multivariate analysis, including patients with secondary AML and unfavorable cytogenetic risk. Meanwhile, maintenance treatment and AlloHSCT were identified as independently associated to a prolonged OS (**Table 3**).

Discussion

Similar to previous single-center studies performed in Mexico, in this larger, multicenter study we identify that our patient population presents at a younger age compared with developed countries, with a median age of 47 years in patients included in this study. This data however is challenging to interpret, owing to the fact that this study is based on the retrospective collection of information from hospital records, rather than a population-based registry. In this regard, it is important to note that the population pyramid structure in Mexico differs from other developed countries, with a median age in 2015 of 27 years of age, compared with the US population, which has a median age of 37.8 years. Nonetheless, there is also the possibility that AML in older adults in Mexico is under-diagnosed, and therefore under-registered in our country[19,20].

In this study we report a shorter median OS compared with data from developed countries. Two main factors could be associated with this poorer prognosis. Foremost, we report a high rate of induction-related mortality. A large study performed at the MD Anderson center reported toxicity outcomes during induction in 1,543 patients treated with different regimens within this institution[21]. Overall, mortality during the first 6 weeks of treatment was reported to be 10% in patients younger than 60 years of age and 24% in patients older than 60 years. Among our population, 86.4% of the patients who underwent intensive chemotherapy were aged <60 years and therefore, considering this data, the overall

induction-related mortality which we observe in our population (17.8%) is considerably high. Supportive care, including antifungal prophylaxis has proven fundamental in order to decrease mortality in developing countries. The experience derived from the SWOG and the MD Anderson center has demonstrated that providing patients with best supportive care can significantly decrease treatment-related mortality, from 1991-1995 mortality reported by these groups ranged from 16% (MD Anderson) to 18% (SWOG). However, these have further decreased in more recent series, ranging from 3% (SWOG) to 4% (MD Anderson) in the period comprised from 2006-2009[22]. As previously demonstrated in other series, our data shows that age, ECOG functional status, and secondary leukemias were associated with higher odds of death during induction[5,21,23,24]. Further, our data shows that the presence of an active infection at diagnosis and treatment start is associated with higher induction-related mortality. This information is highly relevant, due to the fact that over one third of our study population presented with an active infection at the time of diagnosis. This might be related with delays in the health system for reference to centers capable of offering diagnostic and treatment.

Another important finding in this study is the low proportion of patients who undergo AlloHSCT. Despite the fact that 82% of the patients presented with an intermediate or unfavorable cytogenetic risk, only 8.2% received a transplant. A previous meta-analysis sought to identify the benefit of first-line AlloHSCT in AML, considering studies which evaluated AlloHSCT strategies compared with other therapeutic schemes. In this study, 37% of the included patients received consolidation with AlloHSCT, and this strategy proved beneficial in terms of OS and relapse-free survival (RFS) in patients with intermediate or unfavorable cytogenetic risk[25]. This study included trials published between

1991 and 2007, a time period when the lack of a compatible donor was one of the most frequent reasons to forego AlloHSCT consolidation. Currently, through improvements in the transplant techniques for alternative donors, this previously mentioned reason is becoming obsolete. In Mexico, although the population is large, there are very few highly specialized centers for transplants, and therefore the rate of any-indication transplants in the country ranges from 5-6 transplants/million inhabitants. This figure is alarming, especially when considering other countries, such as Spain, perform 10 times more transplants[26].

Interestingly, our study also shows that despite the limited evidence pertaining to its efficacy, administering maintenance treatment is a common practice within our setting. We identified that maintenance therapy was independently associated with prolonged OS, particularly in patients treated with cytarabine, and in patients with an intermediate cytogenetic risk. Other studies have shown similar findings, in a previously reported Italian trial a consistent benefit was observed for non-transplanted patients with myelodysplastic syndrome or high-risk AML who received maintenance with low-dose chemotherapy, including cytarabine and 6-mercaptopurine. Maintenance treatment decreased the incidence of relapse and improved OS[27]. Similarly, as far back as 1998 the EORTC and HOVON groups had already reported a benefit with maintenance therapy, though this was only the case for disease-free survival (DFS) and not for OS, in patients older than 60 years who received low-dose subcutaneous cytarabine[28]. The benefit in terms of OS of maintenance therapy has therefore remained controversial, due to conflicting data in diverse studies. Our results show that when using intermittent high-dose intravenous cytarabine pulses an independent improvement in OS is observed. It is possible that the impact of this strategy could be overestimated in our population, owing to the fact that most patients did not

receive a transplant, therefore further studies are necessary to reach robust conclusions. A large phase 3 study recently demonstrated a beneficial role in terms of DFS for hypomethylating agents when used in maintenace schemes. In this study, the authors compare the effect of azacitidine vs. observation in adults older than 60 years after receiving at least 2 cycles of intensive chemotherapy[29]. Conclusions regarding the role of hypomethylating agents within our population cannot be drawn due to the low number of patients who received this maintenance scheme.

Regarding the molecular and genotypic characteristics of our population, it is important to highlight that in 30% of the cases the karyotype was unavailable or non-evaluable, due to insufficient evaluable metaphases or due to lack of access. Specific mutations were sought in the minority of patients. In the population subgroup with available information, most patients (55%) were classified as intermediate risk. This is a result of the high proportion of patients with a normal karyotype, which reached 44.9% in our study, which is comparable to data from large American and British series, which ranges from 38-48%[18,30-31]. Concrete evidence supports the current recommendation to actively search for specific mutations in order to perform adequate risk stratification, particularly in patients with normal karyotypes; there are 6 specific mutations which are part of the current risk classification by the ELN. Among patients with a normal karyotype, approximately 20-28% can be re-classified in a different risk strata due to the presence of specific mutations[32,33]. Additionally, several mutations are actionable by targeted therapies (*FLT3, KIT, IDH1* and *IDH2*), while others can serve as biomarkers for minimally residual disease[34,35]. Altogether, this information should be considered in order to reassess the challenge of molecular typing of AML in patients in Mexico.

Based on the information generated in this multicenter study, we can establish the following mid-term challenges to address:

1. Decrease induction-related mortality through the implementation of an early-referral system in patients with clinical suspicion of leukemia, and a standardized supportive care program.

2. Improve risk stratification through wide implementation of cytogenetic and molecular analyses. A prospective study will be initiated in order to implement standardized testing in local laboratories.

3. Improve access to AlloHSCT programs. This will be aided by a sub-analysis from the data acquired in this study which will seek to identify factors associated with the lack of transplants in patients with an indication for the procedure.

The main strenght of this study is the large number of patients from a multicenter experience. The main limitation is the retrospective nature.

Conclusions

This is the first multicenter study of AML in Mexico, taking into consideration factors associated with OS in patients who were candidates for intensive chemotherapy. Our data reproduces well-studied prognostic factors in a multivariate model, including a shorter OS in patients with secondary leukemias and unfavorable cytogenetic risk; likewise, we show that patients who were consolidated with AlloHSCT have better OS. We identified that our population is characterized by a high induction-related mortality, and that only a very low proportion of patients receive a transplant. This retrospective study warrants the design and

implementation of further strategies and prospective trials with the objective of improving clinical outcomes of AML patients in Mexico.

Figure legends

Figure 1. Overall Survival according to cytogenetic risk

Figure 2. Overall survival according to anthracycline dose during induction-chemotherapy

Figure 3. Overall survival according to maintenance therapy, a 3-month landmark analysis.

Figure 4. Overall survival according to AlloHSCT following first complete remission, a 3-month landmark analysis.

Acknowledgements

To Novartis and the Mexican Society of Hematology for supporting this project.

References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127: 2391-2405.

2. SEER.https://seer.cancer.gov/csr/1975_2014/browse_csr.php?sectionSEL=13&pageSEL=se ct_13_table.13.html (Accessed on June 07, 2017)

3. Shah A, Andersson TM, Rachet B, Bjokholm M, Lambert PC. Survival and cure of acute myeloid leukaemia in England, 1971-2006: a population-based study. Br J Haematol. 2013; 162(4):509-16.

4. Applebaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood. 2006; 107(9):3481-85.

5. Estey EH. Therapeutic options for acute myelogenous leukemia. Cancer. 2001; 92(5):1059-73.

6. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017; 129(4):424-47.

7. Tallman MS, Wang ES, Altman JK, et al. Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019; 17(6):721-49.

8. Kantarjian H. Acute myeloid leukemia--major progress over four decades and glimpses into the future. Am J Hematol. 2016; 91:131-45.

9. Darbinyan K, Shastri A, Budhathoki A, et al. Hispanic ethnicity is associated with younger age at presentation but worse survival in acute myeloid leukemia. Blood Advances. 2017; 1(24): 2120-23.

10. Gómez-Almaguer, Marcos-Ramírez ER, Montaño-Figueroa E, et al. Acute Leukemia Characteristics are Different Around the World: the Mexican Perspective. Clin Lymphoma Myeloma Leuk. 2017; 17(1):46-51.

11. Colunga-Pedraza PR, Gomez-Cruz GB, Colunga-Pedraza JE, Ruiz-Argüelles GJ. Geographic Hematology: Some Observations in Mexico. Acta Haematologica. 2018; 140:114-20.

12. Buitrón-Santiago N, Arteaga-Ortiz L, Rosas-López A, Aguayo A, López-Karpovitch X, Crespo-Solís E. Acute myeloid leukemia in adults: experience at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán from 2003 to 2008. Rev Invest Clin 2010; 62(2):100-8.

13. Alvarado-Ibarra M, Guerra-Alarcón VM, Mena-Zepeda V, et al. Frontline Treatment of Acute Myeloid Leukemia in Adults Long-Term Results in a Mexican Medical Center. Canc Therapy & Oncol Int J. 2018; 10(5): 555800

14. Jaime-Pérez JC, Brito-Ramirez AS, Pinzon-Uresti MA, et al. Characteristics and clinical evolution of patients with acute myeloblastic leukemia in northeast Mexico: an eight-year experience at a university hospital. Acta Haematol 2014; 132(2):144-51.

15. Jaime-Pérez JC, Padilla-Medina JR, Fernández LT, et al. Outcomes of Adolescents and Young Adults With Acute Myeloid Leukemia Treated in a Single Latin American Center. Clin Lymphoma Myeloma Leuk. 2018; 18(4):286-92.

16. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, Swerdlow SH, Campo E, Harris NL, et al. (Eds), IARC Press, Lyon 2016.

17. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003; 21(24):4642-9.

18. Grimwade D, Hills RK, Moorman AV. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010;116(3):354-65

19. INEGI. https://www.inegi.org.mx/temas/estructura/. (Accessed on July 01, 2017)

20. https://www.statista.com/statistics/241494/median-age-of-the-us-population/. (Accessed on July 01, 2017)

21. Atallah E, Cortes J, O´Brien et al. Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia. Blood. 2007;110:3547-3551

22. Othus M, Kantarjian H, Petersdorf S, et al. Declining rates of treatment-related mortality in patients with newly diagnosed AML given 'intense' induction regimens: a report from SWOG and MD Anderson. Leukemia. 2014;28(2):289-292.

23. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol. 2011; 29(33):4417-23.

24. Krug U, Röllig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet 2010; 376(9757):2000-8.

25. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission Systematic Review and Meta-analysis of Prospective Clinical Trials. JAMA. 2009; 301(22):2349-61.

26. Limón JA. El trasplante de células hematopoyéticas en México. Una perspectiva desde la III Jornada Académica de Trasplante Hematopoyético en el IMSS de Puebla Rev Hematol Mex. 2018; 19(2):101-4.

27. Ferrero D, Crisà E, Marmont F, et al. Survival improvement of poor-prognosis AML/MDS patients by maintenance treatment with low-dose chemotherapy and differentiating agents. Ann Hematol. 2014; 93(8):1391-400.

28. Lowemberg B, Suciu S, Archimbaud E. Mitoxantrone versus daunorubicin in induction-consolidation chemotherapy- the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report of the Leukemia Cooperative Group of the European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group Randomized Phase III Study AML-9. J Clin Oncol. 1998; 16(3):872-81.

29. Huls G, Chitu DA, Havelange V, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. Blood. 2019; 133(13):1457-64.

30. Byrd J, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002; 100(13):4325-36.

31. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group study. Blood. 2000; 96(13):4075-83.

32. Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012; 366(12):1079-89.

33. Boddu PC, Kadia TM, García-Manero G, et al. Validation of the 2017 European LeukemiaNet classification for acute myeloid leukemia with NPM1 and FLT3-internal tandem duplication genotypes. Cancer. 2019; 125(7):1091-100.

34. Estey EH. Acute myeloid leukemia: 2019 update on risk-stratification and management. Am J Hematol. 2018; 93:1267–91.

35. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018; 131(12):1275-91.

Tables

Characteristic	Total (N=525)	Intensive chemotherapy (N=421)	Non-intensive treatment (N=104)	p
Age, years (range)	47 (14-95)	43 (14-95)	70 (23-87)	<0.001
Gender (% male)	51.2%	51.8%	49.0%	0.662
Comorbidity				
- Diabetes	15.2%	12.1%	27.9%	<0.001
- Obesity	12.4%	13.0%	9.6%	0.407
- Infection at diagnosis	36.6%	34.4%	45.2%	0.053
- HCT-CI≥3	16.2%	11.2%	32.7%	<0.001
Bone marrow blasts	60 (2-100)	60 (2-100)	60(16-100)	0.966
White blood cells (x10^9/L)	14.6 (0.1-612)	14.2 (0.1-612)	20.2 (0.3-314)	0.404
Hemoglobin (g/dL)	8 (2.19-18.8)	7.9 (2.19-18.8)	8.1 (3.2-15.5)	0.658
Platelets (x10^9/L)	36 (1-1286)	36 (1-1286)	33 (3-450)	0.569
WHO classification				
- Recurrent genetic abnormalidies	7.4%	8.8%	2.0%	<0.001
- MDS-related	11.6%	9.3%	21.2%	
- Treatment related	2.3%	1.4%	5.8%	
- NOS	78.7%	87.6%	71.2%	
Secondary AML	13.8%	10.5%	26.9%	<0.001
Cytogenetic risk				
- Favorable	16.0%	16.9%	10.0%	
- Intermediate	55.6%	56.2%	52.0%	0.207
- Unfavorable	28.4%	25.8%	38.0%	

HCT-CI: hematopoietic stem-cell transplant comorbidity index

Table 1. Baseline characteristics according to treatment

Factor	Univariate analysis, OR (95 % CI), p	Multivariate analysis, OR (95% CI), p
Age > 60 years	2.39 (1.29-4.40), p=0.007	2.09 (1.09-4.02), p=0.027
Female	1.72 (1.03-2.87), p=0.042	
ECOG>2	5.61 (2.93-10.72), p<0.001	4.82 (2.46-9.43), p<0.001
Prior solid tumor	4.35 (1.53-12.40), p=0.008	3.80 (1.24-11.59), p=0.019
Active infection	2.01 (1.21-3.33), p=0.007	1.82 (1.06-3.12), p=0.003
HCT-CI ≥3	2.76 (1.49-5.36), p=0.004	

ECOG: Eastern Cooperative Oncology Group, HCT-CI: hematopoietic stem-cell transplant comorbidity index

Table 2. Risk factors for induction-related mortality

Factor	Univariate analysis, HR (95 % CI), p	Multivariate analysis, HR (95% CI), p
Age >60 años	2.06 (1.50-2.82) *p*<0.001	
Secondary AML	1.86 (1.31-2.64), p=0.001	2.14 (1.15-4.01) p=0.017
ECOG >2	2.14 (1.49-3.08), p<0.001	
Unfavorable cytogenetic risk	1.71 (1.25-2.33), p=0.001	1.81 (1.16-2.82) p=0.009
HCT-CI ≥3	1.76 (1.23-2.50), p=0.004	
Maintenance	0.56 (0.37-0.86), p=0.007	0.53 (0.32-0.86) p=0.011
AlloHSCT in CR1	0.25 (0.12-0.54), p<0.001.	0.40 (0.17-0.94) p=0.035

ECOG: Eastern Cooperative Oncology Group, HCT-CI: hematopoietic stem-cell transplant comorbidity index, AlloHSCT: allogeneic hematopoietic stem-cell transplant, CR1: first complete remission.

Table 3. Prognostic factors for OS (univariate and mutlivariate analysis)

OS

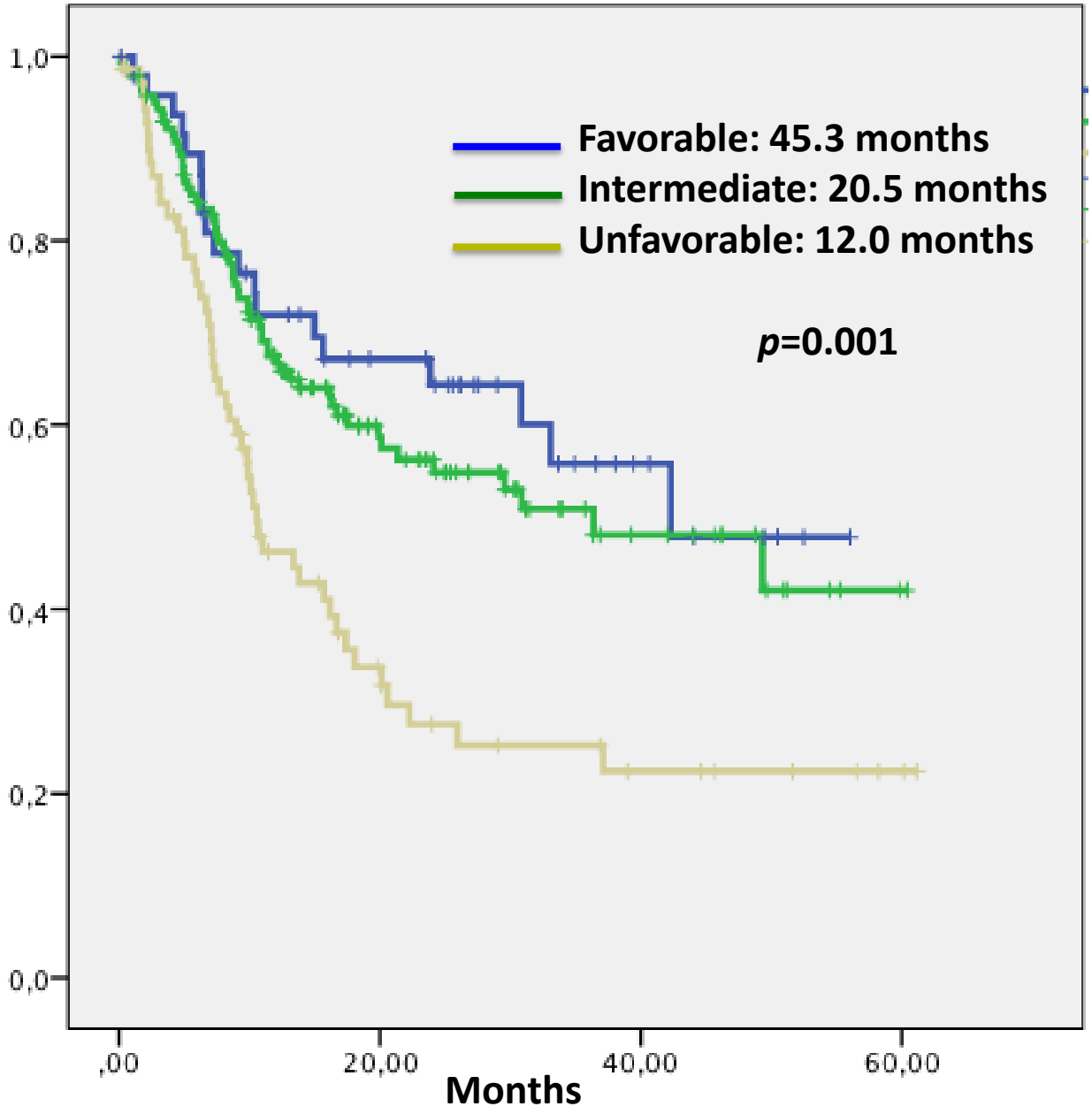
1,0
0,8
0,6
0,4
0,2
0,0
,00
20,00
40,00
60,00
Months
Favorable: 45.3 months
Intermediate: 20.5 months
Unfavorable: 12.0 months
p=0.001

Figure 1.

OS

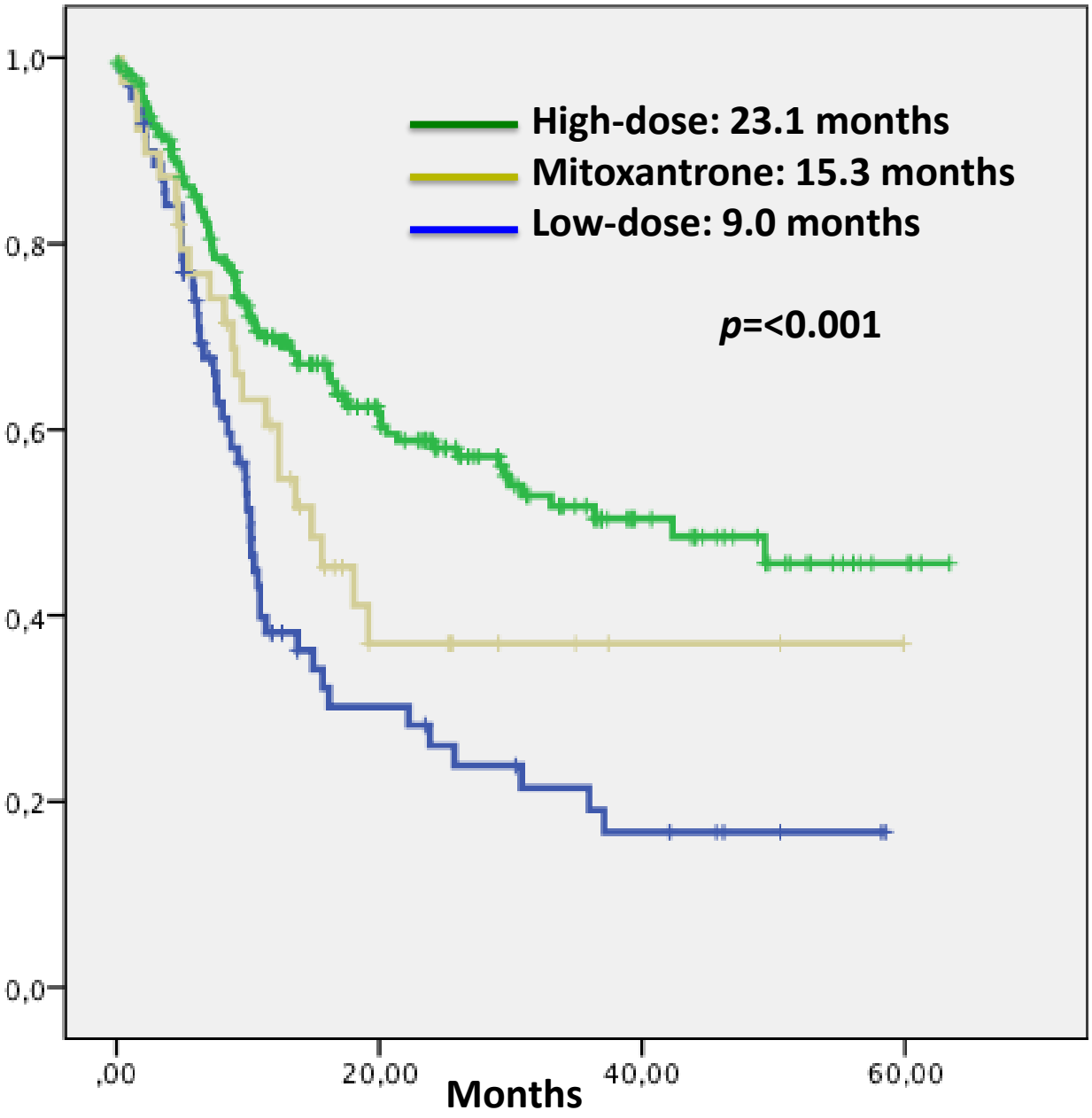
1,0
0,8
0,6
0,4
0,2
0,0
,00
20,00
40,00
60,00
Months
High-dose: 23.1 months
Mitoxantrone: 15.3 months
Low-dose: 9.0 months
p=<0.001

Figure 2.

OS

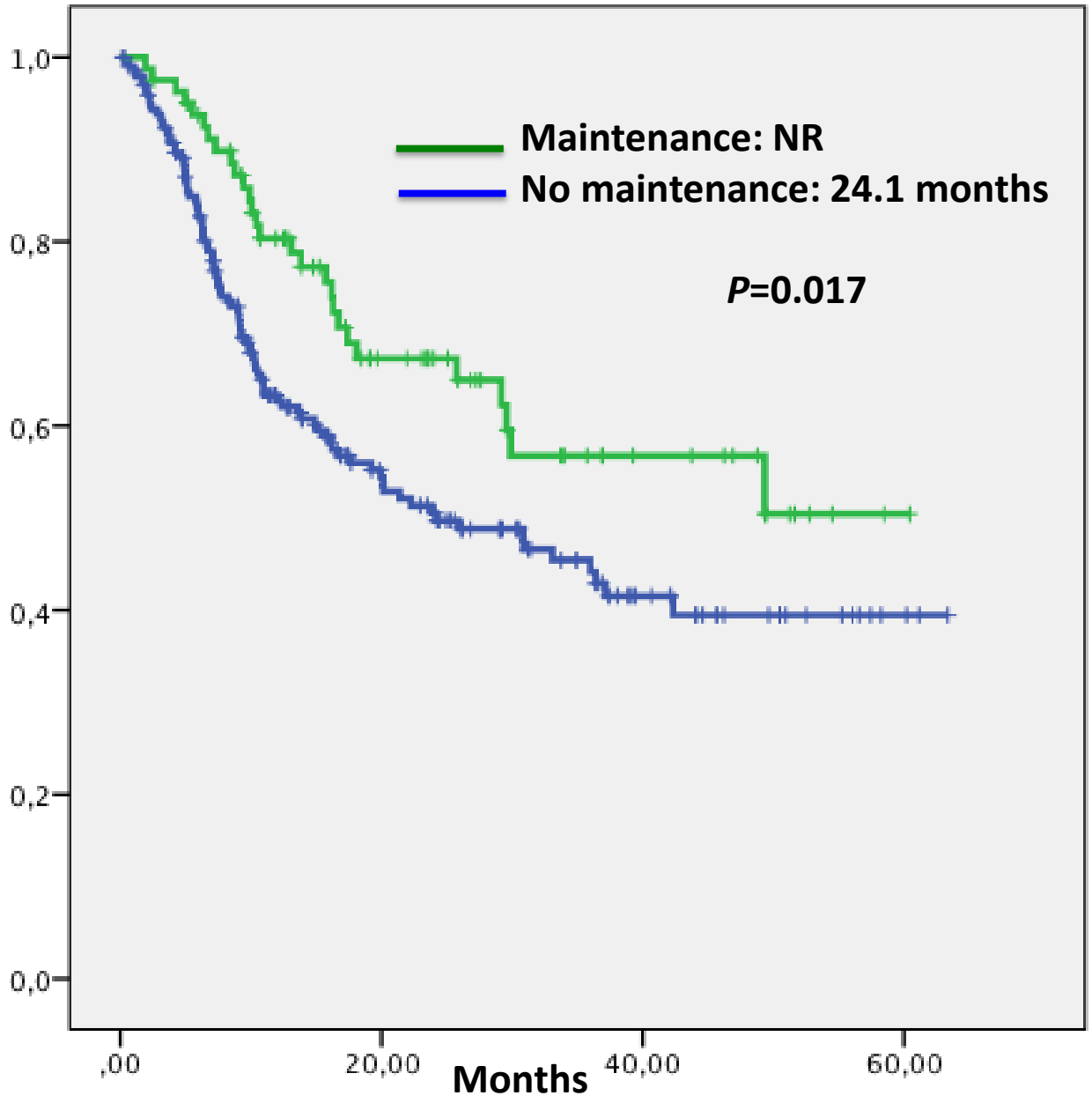
1,0
0,8
0,6
0,4
0,2
0,0
Maintenance: NR
No maintenance: 24.1 months
P=0.017
,00
20,00
40,00
60,00
Months

Figure 3.

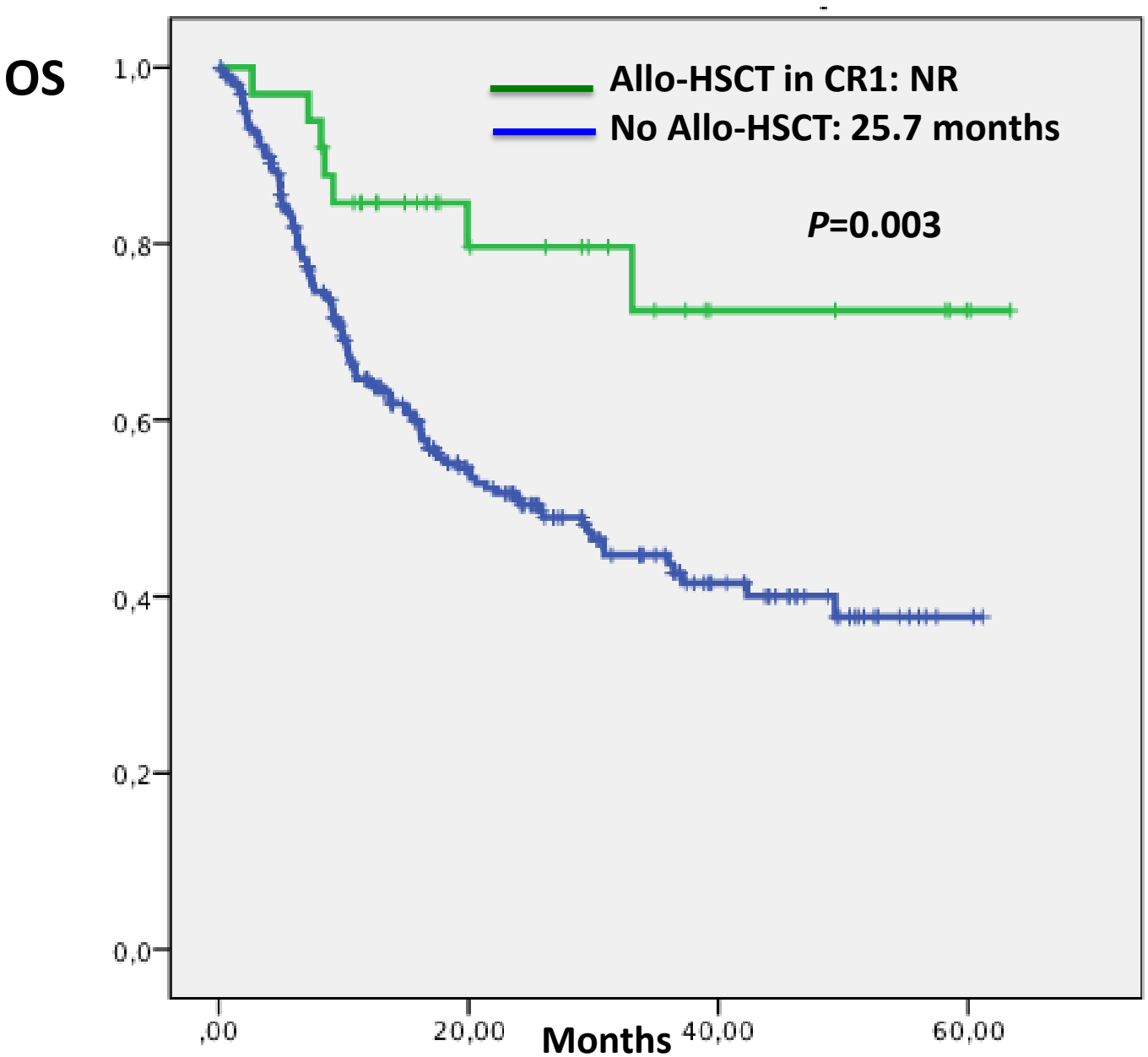
OS
1,0
0,8
0,6
0,4
0,2
0,0
Allo-HSCT in CR1: NR
No Allo-HSCT: 25.7 months
P=0.003
,00
20,00
40,00
60,00
Months

Figure 4.