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Survival of patients with acute leukemia after hematopoietic cell transplantation: A 8-years single-center study in Mexico

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Abstract

Introduction: Hematopoietic stem cell transplantation (HSCT) is the treatment for acute leukemia in children and is the most common type of cancer in children. The objective of the present study was to determine the overall and disease-free survival in a group of patients undergoing HSCT and to explore the risk factors for pediatric patients with acute leukemia.

Methodology: This observational study included all pediatric patients diagnosed with acute myeloid leukemia (AML) or lymphoid leukemia (ALL) undergoing HSCT from March 2011 to March 2018 at the Federico Gómez Children's Hospital. Kaplan–Meier curves were constructed for overall survival by subgroups according to the type of leukemia and disease-free status, as well as a multivariable study to measure risk factors.

Results: Fifty-three patients were included in the analysis. Five patients (11%) had primary graft failure. Overall survival was 28% at 24 months. Thirty patients (67%) died. The median overall survival was 11 months. For AML, it was 8.9 months, and for ALL, it was 12.4 months. One of the risk factors was age >10 years at the time of transplant (OR 5.2 (1.07-25.12), P=0.04) and the number of relapses prior to transplant (OR 4.3 (1.2-15.07), *P* =0.025).

Conclusion: Patients who survived one year free of the disease had a better prognosis. In studies related to HSCT, it has not been reported that there is an age range of transplant recipients related to higher mortality, which is why it is a significant and independent risk factor.

Keywords:

MESH: Bone Marrow Transplantation; Bone Marrow, Child; Leukemia, Myeloid, Acute; Precursor Cell Lymphoblastic Leukemia-Lymphoma; Survival

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Introduction

Hematopoietic stem cell transplantation (HSCT) is the treatment for acute leukemia in children, the most common type of cancer. In an international study [1], the 12-month survival of patients with allogeneic bone marrow transplants performed between 1987 and 2012 was analyzed; a survival of more than 80% was reported; however, the first cause of death was relapse of 43% and infections in 18% [2]. Associated complications, such as cataracts, growth hormone alterations, and gonadal dysfunction, were also reported as the most important. The study concludes that very few studies analyze survival in the first years after transplantation. In a study in Stockholm [3], two protocols performed for allogeneic hematopoietic cell transplantation in patients <18 years old were compared; two periods, P1 (1992-2002) and P2 (2003-2013), were compared; at P2, a mortality rate of 12% VS was observed. 18% at P1 (P=0.03). At five years posttransplant, a mortality rate of 21% was observed for P1 and 14% for P2 (P = 0.03); it is concluded that in the last ten years, some changes have been achieved in better prevention of the disease graft-versus-host disease (GVHD) as well as less aggressive conditioning prior to transplantation.

In 2010, the European group of blood and bone marrow transplantation (EBMT) published a study about the experience of haploidentical hematopoietic cell transplantation in pediatric patients with high-risk acute lymphoblastic leukemia (ALL) in the years 1995-2004. In total, there were 127 patients whose leukemia remission status changed among them prior to transplantation. They reported that all patients with active disease at the time of transplantation died in the post-transplantation period, the incidence of relapse at five years was 36%, the 5-year disease-free survival rate was 27%, and the 5-year overall survival rate was 29%. It was shown that patients with >80% mortality were those who had not achieved complete leukemia remission, so it was established that the recommendation not to subject patients to transplantation until complete remission had been achieved; additionally, it was recommended to make a distinction in the number of remissions, since if the patient had a second or third remission before HSCT, survival was reduced by >10%.

Allogeneic HSCT offers the possibility of improving survival in patients with acute leukemia with high-risk factors or relapse since, in these cases, the survival expectancy is less than 20% [4]. Survival of HSCT also depends on timing, remission number, type of HSCT (matched related donor, matched unrelated donor, haploidentical), and hematopoietic cell source (umbilical cord blood, peripheral blood, or bone marrow). Survival varies from 35% to 65%. In Latin America, there are limited data due to the few pediatric transplant centers, so this study aimed to describe the survival of patients with acute leukemia undergoing HSCT in a reference center for bone marrow transplantation in children.

Population and methods

Design of the investigation

This trial is a retrospective, longitudinal observational study.

Scenery

The study was carried out in the onco-hematology service of the Federico Gómez Children's Hospital of Mexico of the National Institute of Health (Mexican Ministry of Health). The study period was from January 1, 2011, to December 31, 2018 (8 years).

Inclusion criteria

Hospitalized pediatric patients with an established diagnosis of AML, ALL who underwent HSCT, entered the study. Incomplete records were excluded from the analysis.

Studio size

The universe was patients admitted to the institution. The sampling was nonprobabilistic for convenience, and all possible cases were included in the study period.

Variables

The variables were diagnosis, age, sex, leukemia type classification, leukemia risk classification, number of relapses, site of relapse, number of remissions, type of HSCT, source of hematopoietic cells, presence of graft-versus-host disease acute, the requirement for admission to intensive care or emergency room, events of sepsis or septic shock, survival at 12 months,

survival at 24 months, follow-up time, absence of disease at 12 and 24 months, relapse, and time of HSCT relapse.

Data sources/measurement

The data were collected in a specific electronic form for this purpose. The hospital's electronic system of clinical records was used to investigate cases.

Bias avoidance

Every effort was made to avoid the following possible biases in the study. Selection bias in which extensive research was conducted considering related diagnoses and possibly misinterpreted diagnoses after hospital admission, thus avoiding bias in the selection procedure. Loss-to-follow-up bias was avoided with direct referrals to patient guardians. Measurement bias was avoided with a protocol-approved questionnaire.

Statistical method

The data analysis is univariate and descriptive with frequencies and percentages. Kaplan–Meier curves were used for survival analysis. The odds ratio was used to measure the association with predisposing factors, comparing the group of deceased patients vs. the group of living patients. The 95% confidence intervals and P values are presented. The STATA statistical package (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Results

Forty-five cases were analyzed.

General characteristics of the study group

They were 24/45 men (53%). A total of 10 patients (22%) were in failure at their first induction, and 35 patients (78%) had one or more relapses prior to transplantation; 29 patients (64%) presented isolated relapses to the bone marrow (BM) (Table 1).

Transplant Characteristics

In total, 53 transplants were performed in patients with acute leukemia. Each transplant event was counted as a single event, even from the same patient. The time elapsed between the primary diagnosis and the performance of the transplant was 21.5 months (interquartile range 12.2-39.3 months).

Table 1. Main characteristics of the study group.

Variable	Frequency (n=45)	Percentage
Sex		
Men	24	53%
Woman	T21	46%
Age at transplant		
0-24 months	4	8%
2 to 5 years	8	18%
5.1 to 12 years	14	31
>12 years	19	42%
Diagnosis		
Acute lymphoid leukemia	31	69%
AML	14	31%
Leukemia risk		
Usual	5	11%
High risk**	35	78%
Very high risk	5	11%
Status prior to HSCT		
First induction failure	10	22%
1st relapse	25	56%
>1 relapse	10	22%

** All patients with diagnoses of AML are considered high risk.

Five patients (11%) had primary graft failure or relapse, so more than one transplant was performed in the years studied: one patient underwent four transplants (3 haploidentical transplants from a maternal donor and one allogeneic transplant from an unrelated donor).), one patient underwent three transplants (1 haploidentical patient from a maternal donor and two allogeneic transplants from a nontwin brother), two patients underwent two transplants (2 haploidentical transplants from a maternal donor), and one patient underwent two transplants (1 allogeneic umbilical cord transplant from an unrelated donor and a haploidentical transplant from a maternal donor). The average number of days of hospitalization after transplantation was 44 days, with a median of 31 days (18 days-141 days). During the years studied, it was considered if these patients required admission to the Pediatric Intensive Care Unit (PICU) on any occasion after receiving the transplant. Sixteen patients (35%) had a single admission to the PICU. Two patients (4%) who had two admissions to the PICU were reported, of which the two patients had more than one transplant. A patient received two transplants and had 6 PICU admissions during the study years (Table 2).

Table 2. Characteristics of HSCT

Variable	Frequency n=53	Percentage
BMT type		
Haploidentical	25	47%
Allogeneic	27	51%
Syngeneic	1	two%
donor		
Mother father	26	49%
Not twin brother	20	38%
Not related	6	11%
Monozygotic twin	1	2%
Graft versus host disease		
No	20	38%
Yes	33	62%

BMT: bone marrow transplant.

Survival and relapse

Of the 45 patients studied, 30 (67%) died (Table 3). Four of the five patients who required more than one transplant died (80%). Nine patients with posttransplant relapse were documented, of whom 100% died.

Table 3. Survival of HSCT

Survival	6 months	12 months	24 months
OS	31 (68%)	18 (40%)	13 (28%)
DFS	26 (62%)	18 (40%)	13 (28%)

OS: overall survival. DFS: disease-free survival.

The time elapsed between the performance of the transplant and the documentation of the relapse of the disease had a mean of 6.6 months, a median of 3.17 interquartile range (4.5- no data for 75%), with 60% relapsed before six months. .

The overall survival to the first transplant, considering the end of survival, death, or primary transplant failure, had a median of 11 months (Figure 1).

Patients with AML had a median survival of 8.9 months vs. 12.4 months for patients with ALL; on average, patients with ALL survived 3.5 months longer. (Figure 2). According to the type of transplant in the present study, only one patient had a syngeneic transplant; better survival was observed with the type of independent allogeneic transplant if the donor was related (Figure 3).

Association analysis

The multivariate analysis reported two risk factors for death or posttransplant relapse: age at the time of transplant greater than ten years and the number of relapses before the transplant. The median age of the patients at the time of the transplant was 9.8 years, so ten years was taken as a study cutoff point, finding that they are 5.2 times more likely to die or present a relapse compared to those under ten years of age. Patients with AML tended to have a higher risk, but the difference was not significant (Table 4).

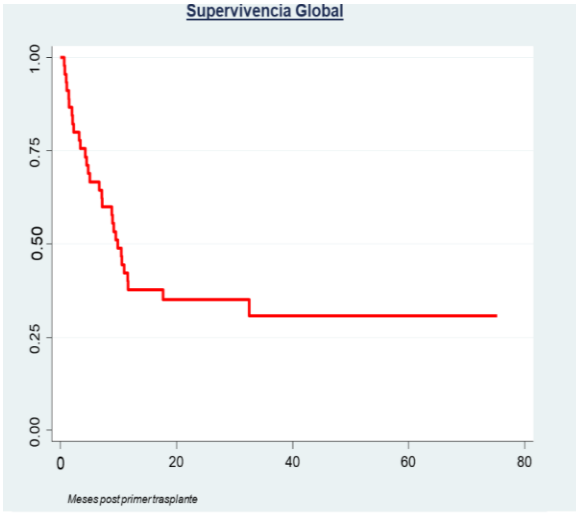

Figure 1. Overall survival of pediatric patients with AML and ALL with bone marrow transplant

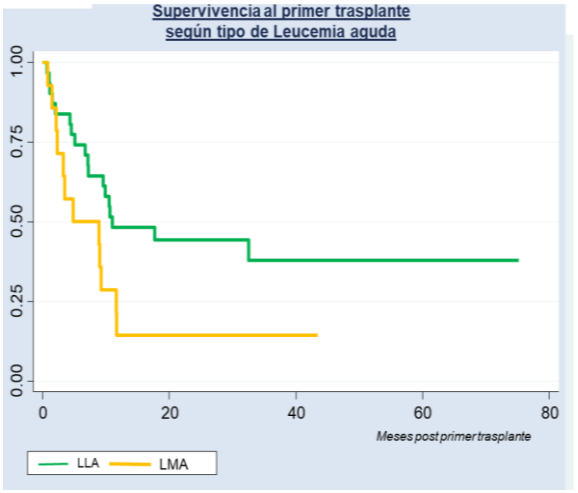

Figure 2. Attributable survival to the type of leukemia (AML VS ALL) with bone marrow transplant.

Table 4. Multivariate analysis

Logistic regression for death or relapse n=45			
	OR	CI95%	*P*
Age at transplant ≥10 years	5.2	1.07-25.12	0.04
Myeloid VS Lymphoid Leukemia	3.95	0.67-23.2	0.128
previous relapses	4.3	1.2-15.07	0.025
Cox regression for death or relapse n=45			
	HR	CI95%	*P*
Number of previous relapses	1.92	1.07-3.42	0.028
Type LMA VS. ALL	1.70	0.76-3.78	0.19
Age at transplant ≥10 years	2.26	1.12-6.07	0.026
Sex	0.76	0.34-1.66	0.48
Cox regression for death n=45			
Number of previous relapses	1.96	1.14-3.38	0.015
Type LMA VS. ALL	2.01	0.95-4.3	0.07
Age at transplant ≥10 years	1.93	0.90-4.18	0.09
Sex	0.63	0.30-1.33	0.23

OR: odds ratio, CI: confidence interval, HR: Hazard ratio, AML: acute myeloid leukemia, ALL: acute lymphocytic leukemia.

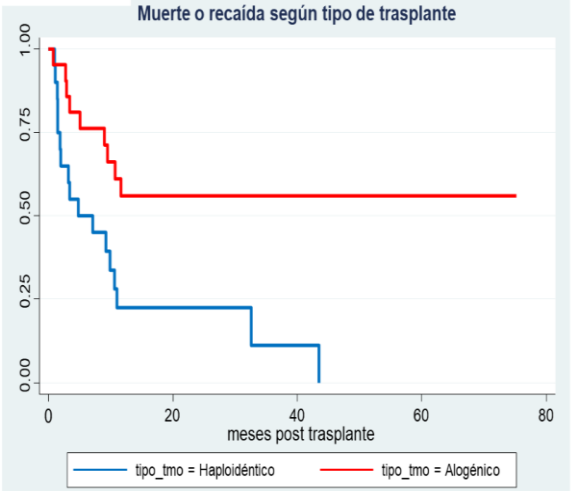

Figure 3. Attributable survival to the type of donor with a bone marrow transplant.

Discussion

Hematopoietic stem cell transplantation is a procedure that uses allogeneic or autologous cells to reconstitute the hematopoietic system [6-9]. In the case of leukemia, this restitution leads to a new effect called graft-versus-leukemia activity, which is biologically eliminated through the activity of the donor's T and NK lymphocytes and the recipient's residual leukemia blasts. Since intense myeloablative therapy with chemotherapy and radiotherapy has to be used prior to transplantation, the susceptibility to developing infectious and immunological complications is high, so this procedure is recommended for cancer conditions that do not have the possibility of being cured with standard chemotherapy therapy. According to the literature [10-13], patients with acute lymphoblastic leukemia presented a relapse event or leukemias with criteria of high risk of relapse in the first remission within the indications for HSCT included. According to various studies, the benefit of performing a transplant in patients with bone marrow relapse and second complete remission is superior to patients who only receive chemotherapy. Seventy-eight percent of the patients in the study were on their first relapse. It has been shown that relapses isolated to the bone marrow have a worse prognosis than relapses combined with extramedullary sites. The best explanation for this is that extramedullary relapse can originate from cells that survived the first line of therapy that were less exposed or that it is another cell line; on the other hand, when it is isolated to MO, it means that the cancer cells are coming from the site origin of the disease and are probably chemoresistant. Sixty-four percent of the patients studied presented one or more isolated relapses to BM, equivalent to a worse prognosis.

The risk of posttransplant relapse is 20-60% for patients with ALL [13]. In the present study, it was 26%. In several previous protocols [1, 14], it has been mentioned that posttransplant relapse is one of the leading causes of death. Graft-versus-host disease (GVHD) is a complication that can be divided according to the time of evolution (acute, chronic) and in degrees of severity in its acute phase (I-IV and in the chronic phase (extensive and limited), depending In this study, only the presence of graft-versus-host disease was qualitatively taken into account since due to lack of information in the records, it was not possible to make the specific classification by affected organ or by the severity of all cases, which was only taken as a qualitative variable. More than half of the patients presented some degree of GVHD. It is known that the degree of GVHD is proportionally related to an increase in morbidity/mortality, so it is essential to classify and analyze new studies on our patients to determine what type of

prognosis they may have. Likewise, it would be convenient to assess whether, as in the international literature, a risk factor for developing GVHD is the donor's age. The multicenter study by Klingebiel, Thomas, et al. [4] reported a study with 45 patients with a survival rate of 5 of 18%. Watkins et al. [15] reported that age >12 years is at significant risk for developing chronic GVHD. The literature has mainly reported comparing the donor's age vs. the recipient's age and the consequences of having an elderly donor, in most cases, recommending a young donor. In the present study, the age of the transplant recipient greater than ten years of age was associated with higher patient mortality. According to the literature for acute lymphoblastic leukemia, age >10 years is a criterion for classifying leukemia as high risk; however, no studies related to HSCT have been reported indicating that there is an age range of recipients related to higher mortality, which is why it is necessary to obtain data in the present study [16]. This study has the limitations of losing follow-up in some patients, and some patients have not completed the 12 or 24 months posttransplant; new studies should include prospective and multicenter cuts.

Conclusions

Patients who survived one year without disease had a better prognosis overall. In studies related to HSCT, it has not been reported that there is an age range of transplant recipients related to higher mortality, which is why it is essential data as an independent risk factor.

Abbreviations

OS: overall survival.
DFS: disease-free survival.
ALL: acute lymphocytic leukemia.
AML: acute myeloid leukemia.
GVHD: graft versus host disease.
BM: bone marrow
HSCT: hematopoietic progenitor cell transplant

Supplementary information

None declared by the authors.

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Author contributions

Andrea Michelle Ordoñez Cuetto: Research, Data Curation, Research, Fundraising, Software, Statistical Analysis. Writing – original draft.
Ivan Castorena Villa: Conceptualization, Writing - original draft, Supervision.
Felix Gaytan Morales1: Conceptualization, Writing - Edition.
María Fernanda Castilla Peón: Methodology, Research.
All authors read and approved the final version of the manuscript.

Financing

The authors financed the expenses incurred in the production of this research. The costs incurred for bone marrow transplants are part of the regular hospital cost and do not represent an additional expense to the parents or guardians of the patients.

Availability of data and materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available through the corresponding author upon reasonable academic request.

Statements

Ethics committee approval and consent to participate

The Ethics Committee approved the research protocol of the Teaching Committee of the Hospital Infantil de México Federico Gómez.

Publication consent

It is not required in articles in which physical examination images, radiographs, tomography, or magnetic resonance studies are not published.

Conflicts of interest

The authors declare no conflicts of interest.

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