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LETTER TO THE EDITOR

Safety and feasibility of outpatient hematopoietic cell transplantation in pediatric patients during the COVID-19 pandemic: A single-center experience

To the Editor:

Hematopoietic cell transplantation (HCT) represents a potentially curative treatment for children with high-risk hematological malignancies, and pediatric patients typically require hospitalization to undergo HCT.[1] The recent COVID-19 pandemic has raised concerns regarding HCT in an inpatient setting, considering that nosocomial outbreaks of COVID-19 have been reported in hematological wards,[2,3] and HCT recipients are admitted to a general hospital ward in centers without a conventional HCT unit, where the limited trained nurse personnel are shared within patients. Thus, ambulatory HCT rises as a possible approach in this situation.[4,5] Our hematology unit has more than 20 years of experience conducting HCTs in an outpatient setting in adults.[6,7]

We report the pediatric outpatient HCT-related outcomes during the COVID-19 pandemic (March–December 2020) at a referral center providing care for the general, open-population in Northeast Mexico. The study protocol was approved by the ethics and research committees. All legal guardians signed informed consent before any procedure.

The standard pediatric HCT protocol remained unaffected, except for the implementation of an outpatient approach. HCTs were categorized as inpatient if the stem cell infusion occurred while admitted to the hospital and outpatient if both the conditioning regimen and stem cell infusion were administered in the outpatient clinic. Eligibility for outpatient HCT included children with a Lansky score ≥70%, an adequate venous access and normal cardiac and renal function, temporary residence near the hospital (≤1 hour of travel distance), and an adequate caregiver.

The conditioning regimen for allogeneic-HCT consisted of 3 days of fludarabine 25 mg/m^2/day and cyclophosphamide 350 mg/m^2/day, and melphalan 70–100 mg/m^2 for 2 days with or without 2 Gy of total body irradiation and antithymocyte globulin in aplastic anemia. Graft-versus-host disease (GVHD) prophylaxis included cyclophosphamide 50 mg/kg/day for 2 days (+3 and +4), mycophenolic acid 2 g/day from day +5 to day +35, and oral cyclosporine 6 m/kg/day from day +5, adjusted to 150–300 ng/ml and tapered between day +100 and day +180. For autologous transplants, the regimen varied according to diagnosis. Pediatric disease-risk index (DRI) was calculated for malignant diseases.[8] After infusion, patients remained under observation and were then sent home under the care of their guardians. These were previously instructed on hygienic preventive measures and the need of strict isolation procedures. For those receiving an inpatient HCT, patients and a single caregiver were requested to remain in their rooms and keep external contact to a minimum.

Quantitative variables were analyzed with descriptive statistics; the Mann–Whitney *U* test was used for comparisons. Overall survival (OS) was assessed using the Kaplan–Meier method.

Nineteen children were analyzed. Fifteen (79%) were considered for an ambulatory intent, and four (21%) were admitted for conditioning and stem cell infusion. Six (32%) patients were female and 13 (68%) male, with a median age of 9 (1–18) years. Median time from diagnosis to HCT was 12 (2–90) months and most frequent diagnoses included acute lymphoblastic leukemia (ALL) (n = 7, 37%), acute myeloblastic leukemia (n = 3, 18%), and Hodgkin disease (n = 3, 18%). Four (21%) HCTs were autologous and 15 (79%) allogeneic, all from haploidentical donors. Most frequent complications included non-COVID-19 infections (n = 8, 42%) and acute GVHD (n = 8/15, 53%). Median follow-up was 163 (4–313) days. Relevant features are displayed in Table 1.

Four (21%) patients developed COVID-19 after HCT; all received an allogeneic-HCT and were hospitalized to treat the infection. Two belonged to the inpatient HCT group and required ventilatory support; one was an 8-month-old female with hemophagocytic lymphohistiocytosis (HLH) who acquired COVID-19 during her HCT hospitalization and died from respiratory failure on day +4. The other was a 9-year-old male with high-risk ALL and posttransplant relapse in palliative care who contracted the infection in the community on day +97 and died after 2 days of hospitalization due to multiple system organ failure. The other two, who belonged to the outpatient HCT group, none required ventilatory support nor died from the disease. Both were males of 1 and 15 years, developed the infection on day +4 and +12, and were hospitalized for 8 and 10 days, respectively. Additional characteristics and outcomes are presented in Table S1.

For the entire cohort, the 100-day OS after HCT was 88.0% (95% CI, 86.3–89.4), whereas inpatient HCT recipients had a 100-day OS of 50.0% (95% CI, 45.0–54.7). At 100-day post-HCT none of the children of the outpatient group had died.

This report demonstrates the feasibility of an outpatient HCT setting for pediatric hemato-oncology patients. Evidence of an outpatient approach in hematological pediatric population is scarce. A recent study conducted in the United States evaluated the safety of autologous-HCT in an outpatient basis in children with primary central nervous system tumors, with a +100 transplant-related mortality of 0%,[9] same as the 100-day OS for our outpatient HCT

TABLE 1 Clinical features and transplant-related outcomes of outpatient and inpatient HCT pediatric recipients at a hematology referral academic center in Northeast México

	Outpatient HCT ($n = 15$)	Inpatient HCT ($n = 4$)	p-Value
Age at HCT, years, median (range)	13 (1–18)	5 (1–9)	.080
Gender, *n* (%)			
Male	10 (67)	3 (75)	
Female	5 (33)	1 (25)	
Diagnosis, *n* (%)			.277
ALL	6 (40)	1 (25)	
AML	2 (13)	1 (25)	
HD	3 (20)	0 (0)	
Others	4 (27)	2 (50)	
Time from diagnosis to HCT in months, median (range)	12 (2–90)	16 (5–86)	.961
HCT type, *n* (%)			.245
Autologous	4 (27)	0 (0)	
Allogeneic	11 (74)	4 (100)	
Pediatric DRI, *n* (%)[a] Low/intermediateHigh/very high	9 (90) 1 (10)	2 (50) 1 (25)	.423
Median CD34+ cells × 10^6/kg (range)	10 (2–21)	7 (4–11)	.185
Engraftment days, median (range)			
Myeloid	14 (12–18)	14 (13–20)	.768
Platelets	17 (12–25)	19 (13–21)	.676
Hospitalizations after HCT, *n* (%)	11 (73)	1 (25)[b]	.313
Fever and neutropenia	5 (33)	0 (0)	
Post-HCT cyclophosphamide administration COVID-19	3 (20)2 (13)	0 (0)1 (100)	
Grade 3 mucositis	1 (7)	0 (0)	
Days HCT-hospitalization, median (range)	7 (3–140)	NA[c]	
Days hospitalized, median (range)	9 (2–21)	NA[c]	
Complications, *n* (%)			
Fever and neutropenia	4 (27)	1 (25)	.888
Infection (any type)	5 (33)	3 (75)	.163
COVID-19	2 (13)	2 (50)	.110
Mucositis (I–IV)	2 (13)	1 (25)	.612
aGVHD	6 (40)	2 (50)	.719
Mortality, *n* (%)	2 (13)	2 (50)	.110
Secondary to COVID-19	0 (0)	2 (100)	
Time from HCT to the last visit in days, median (range)	163 (10–250)	150 (4–313)	.810

Abbreviations: aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; COVID-19, coronavirus disease 2019; DRI, disease risk index; HCT, hematopoietic cell transplantation; HD, Hodgkin disease.

[a]Only for allogeneic transplantation in malignant diseases.

[b]One additional patient, an 8-month female contracted COVID-19 during her HCT hospitalization before grafting, thus is not included in this post-HCT hospitalization table.

[c]One inpatient HCT recipient had a 2-day hospitalization on day +97 due to COVID-19.

recipients, while for the inpatient group it was 50%. The higher mortality rate in the latter might be attributed to their poor clinical status that favored the decision for an inpatient HCT. Nonetheless, the results of the outpatient approach are important as centers worldwide have decreased their HCT activity in pediatric population, attributed to the risk of nosocomial SARS-CoV-2 infection as well as reduced resources of health care systems for inpatient care.[4,5,10]

Studies have shown a mild course of COVID-19 in the general pediatric population.[11] In our cohort, four patients developed COVID-19 after HCT; the two patients that belonged to the inpatient group had a severe course requiring advanced care and subsequently died of the disease. These outcomes could be attributed to their high-risk baseline characteristics. In contrast, the two patients from the outpatient group presented a mild course, consequence of a better clinical status, compatible to previous reports.[12,13]

There are several practical considerations when performing HCT in an outpatient pediatric setting, including ensuring adequate isolation measures of patients and their caregivers, achieving an appropriate hydration when using post-HCT cyclophosphamide, or during mucositis due to alkylator agents, and difficulty in assessing proper central line care at home.

In conclusion, our results demonstrate the importance of continuing to perform HCTs in pediatric patients despite the outbreak, because an outpatient approach can help reduce exposure to SARS-CoV-2 and avoid irreversible disease progression.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

José Carlos Jaime-Pérez
Mariana González-Treviño
Jesús D. Meléndez-Flores
Eugenia M. Ramos-Dávila
Julia E. Colunga-Pedraza
Perla R. Colunga-Pedraza
Valentine Jiménez-Antolinez
David Gómez-Almaguer

Hematology Service, Internal Medicine Division, "Dr. José Eleuterio González" University Hospital and School of Medicine, Universidad Autónoma de Nuevo León, Monterrey, México

Correspondence
José Carlos Jaime-Pérez, Hematology Service, Internal Medicine Division, "Dr. José Eleuterio González" University Hospital and School of Medicine, Universidad Autónoma de Nuevo León, Monterrey, México.
Email: carjaime@hotmail.com

ORCID

José Carlos Jaime-Pérez https://orcid.org/0000-0001-6804-9095
Mariana González-Treviño https://orcid.org/0000-0002-2957-9760
Jesús D. Meléndez-Flores https://orcid.org/0000-0001-5252-3637
Eugenia M. Ramos-Dávila https://orcid.org/0000-0002-1105-2848
Julia E. Colunga-Pedraza https://orcid.org/0000-0001-7933-094X
Perla R. Colunga-Pedraza https://orcid.org/0000-0002-9937-439X
Valentine Jiménez-Antolinez https://orcid.org/0000-0002-7988-8094
David Gómez-Almaguer https://orcid.org/0000-0002-0460-6427

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