**Cancer does not wait: safeguarding care for pediatric acute lymphoblastic leukemia patients during the COVID-19 pandemic in a Mexican hospital.**

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Abstract: 250 words

Main Text: 1915 words

Brief running title: Leukemia treatment during COVID-19 era.

Tables: 3

Figures: 0

Supporting Information files: 0

**Keywords:** Leukemia, COVID-19 pandemic, chemotherapy

**Abbreviations:**

**ALL:** Acute Lymphoblastic Leukemia

**LA:** Latino America

**COVID-19:** Coronavirus disease 2019

**HSCT:** Hematopoietic Stem Cell Transplantation

**MAS Collaborative:** Mexico in Alliance with St. Jude Quality Improvement Collaborative

**Abstract**

**Introduction:** Safeguarding care of acute lymphoblastic leukemia (ALL) patients during the COVID-19 pandemic has posed a significant challenge to health systems. We documented continuity (timeliness and compliance) of curative treatment in pediatric ALL patients, and the incidence and outcomes of patients infected with SARS-Cov2 in our institution.

**Materials and methods:** We included all ALL patients aged <16 years who received treatment in "Hospital Universitario Dr. José Eleuterio Gonzalez" from March 2020 to June 2021. The causes of non-compliance and the outcomes of patients with COVID-19 were reported.

**Results:** We analyzed 553 visits from 89 patients with ALL. Chemotherapy administration was timely and compliant with our treatment protocol in 83% (n=459) of the records reviewed. Treatment continuity goals of ≥80% were achieved for all treatment phases, except for the consolidation (66%) and intermediate maintenance phases (60%). The main causes of treatment delays or treatment modifications included lack of financial resources (2.5%), lack of inpatient beds (1.8%) and chemotherapy stock-outs (1.3%), and the treatment abandonment rate was 3.3%. Twenty-two patients (24.7%) were diagnosed with COVID-19. Of these, seven (32%) developed pneumonia, five (22.7%) required oxygen, and two (9%) developed multisystem inflammatory syndrome. For patients with COVID-19, the median length of stay was 9.5 days, and the 30-day mortality rate was 4.5%.

**Discussion:** The continuity of curative treatment for ALL in the context of COVID-19 was >80% in our hospital. Adapting diagnosis and treatment protocols and implementing strategies to minimize the risk of infection were fundamental to safeguarding continuity care for cancer patients.

**Introduction**

The rapid onset of Coronavirus Disease 2019 (COVID-19) pandemic represents a major challenge to global public health [1]. Latin America (LA) has registered some of the highest COVID-19 death rates globally [2], and the pandemic has negatively impacted the continuity of care for many diseases, including Acute Lymphoblastic Leukemia (ALL) [3].

In Mexico, access to quality care for children with leukemia before the COVID-19 pandemic was already poor, with 5-year survival rates of 40-60% compared to 90-95% in developed countries [4,5]. The impact of the pandemic was compounded by pre-existing challenges and weaknesses in the local health care system, including the dismantlement, in late 2019, of ¨Seguro Popular¨, the government's financial program that covered catastrophic health expenditures ("Gastos Catastróficos") for patients. Furthermore, before the COVID-19 pandemic, Mexican health institutions had already been experiencing chemotherapy stock-outs (including Vincristine, Cyclophosphamide, Cytarabine, and Methotrexate), affecting patients’ continuity of care [6].

Several external factors affecting treatment adherence and continuity of care for children with ALL during this pandemic have been identified in other settings, and recommendations have been made to guarantee access to high-quality health care services [7-9].

Ours is a tertiary university hospital that offers services to the uninsured population in northeast Mexico. From the beginning of the COVID-19 pandemic, we adapted patient care protocols for pediatric hematology. The aim of this study was to evaluate the continuity (timeliness and compliance) of care for all patients with ALL diagnosis from our center as part of the Mexico in Alliance with St. Jude Quality Improvement Collaborative (MAS Collaborative).

**Materials and methods**

***Study design***

This was an observational, descriptive, and prospective study conducted by reviewing all cases with ALL from the Hospital Universitario “Dr. José E González”, in Monterrey, Mexico between March 2020 and June 2021.

Patients with ALL diagnosis who were 16 years old or younger and were on active treatment as of March 2020 were eligible. Demographic characteristics, clinical data, and outcomes were obtained from clinical records.

***Procedures***

We reviewed the schedule of patients who visited the outpatient clinic and the hospitalization area to receive chemotherapy twice a week. We assessed the variables associated with continuity of care.

To document compliance, we examined the time of administration, dose, and change or omission of the chemotherapy indicated in our protocol. For cases identified as non-compliant, we documented the duration of the treatment interruption, the reason, and whether the reason for non-compliance was associated with changes related to the pandemic. Table 1 shows the operational changes we implemented during the COVID-19 pandemic in our center.

***Criteria and data collection***

We defined adequate continuity of care for ALL patients as timely administration of chemotherapy (infusion on the scheduled day +/- 3 days) and compliance with the chemotherapy treatment plan (components, dosage, sequence, and time). Modifications to treatment were classified as intrinsic or extrinsic. Intrinsic modifications were those related to infection or toxicity, while extrinsic modifications were defined as all external factors not related to the treatment itself or toxicity (i.e., chemotherapy stock-outs, viral exposure, and infection).

A confirmed COVID-19 diagnosis was established by polymerase chain reaction (PCR) or antigen test. Cases were classified as mild, moderate, severe, and critical according to the COVID-19 treatment guidelines from the National Institutes of Health [10,11].

**Results**

At the onset of the pandemic, 47 pediatric patients with ALL were receiving chemotherapy in our service, and 42 new cases were added since the Covid-19 pandemic started. The median age of the patients was 6 years (10 months-16 years).

We analyzed 553 visits. Chemotherapy was administered in compliance with institutional treatment guidelines in 83% (n= 459) of the patients. Intrinsic modifications were documented in 12.8% (n=71) and extrinsic modifications were documented in 5.8% (n=32) of the patients. The causes of delays or treatment modifications included: hematological toxicity in 43 patients (7.7%); infection in 21 patients (3.8%); lack of financial resources in 13 patients (2.4%); lack of inpatient beds in ten patients (1.8%); chemotherapy stock-outs in seven patients (1.3%); and lack of venous access in four patients (0.7%). The treatment abandonment rate was 3.3% (3/89). An induction mortality rate of 14.3% (6/42) was observed. The causes of death documented in these patients were septic shock (5 patients), and intracranial bleeding (1 patient).

Continuity was achieved in more than 80% of all ALL patients, with 100% compliance for newly diagnosed patients, 90% for patients in induction therapy treatment phase, 83% for patients in intensification phase, and 91% for patients in maintenance phase. However, the compliance goal was not reached for the consolidation and intermediate maintenance phases (60.9% and 64%, respectively). Patients visits characteristics are summarized in Table 2.

Social work support was provided for 87% of the appointments (n=481), psychological support for 44% (n=243), and telemedicine orientation for 32% (n=117).

Eligibility criteria for conditioning regimen and stem cell infusion were administered in the outpatient clinic 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. 12 patients received an haploidentical HSCT ; Eight of them were performed in outpatient settings, 4 of them in hospital due to lack of compliance with the criteria, 2 of the patients had a delay 100 days and 3 patients could not be transplanted due to financial troubles.

During this time, 22 patients (24.7%) had a positive PCR test for SARS-CoV2 (Table 2). In this group, the median age was five years (range, 0.9-15). Two patients (9%) were diagnosed with COVID-19 and ALL simultaneously; eight patients (36%) were diagnosed with COVID-19 in the intensive phase of treatment; nine (40%) with extended maintenance, and one patient in palliative care. Two patients were diagnosed after haploidentical HSCT (Day +1 and day +6). Disease severity was mild in 15 patients (68%), moderate in three (13.6%), severe in one (4.5%), and critical in three (13.6%). Of these cases, twelve (54%) were managed at home, all of whom had mild disease and >500 neutrophil counts. Seven patients (32%) developed pneumonia, and two patients (9%) developed multisystem inflammatory syndrome. Five patients (22.7%) required oxygen support, and two (9%) required mechanical ventilation. The median hospital length of stay was 9.5 days (range, 3-29 days), with a 30-day mortality rate of 4.5%. Three patients (13.6%) currently have late sequelae, two with hypertension and one with secondary diabetes.

A recently diagnosed patient with severe disease received treatment with Capizzi achieving complete remission on day 36. Two patients (14%) in HSCT protocol continued the treatment without modifications; 17 patients (77%) had treatment postponed for at least 14 days (according to institutional protocol), one patient was in palliative care without receiving chemotherapy. The characteristics of the patients are summarized in Table 3.

**Discussion**

The impact of ALL treatment modifications associated to the COVID-19 pandemic on patient outcomes has not been clearly established. In our center, the treatment modifications we made to safeguard continuity of care included strengthening the area of ​​outpatient chemotherapy administration and having specialized staff available in this area; offering telemedicine follow-up 24/7; providing social support through our social work team; and partnering with non-governmental organizations to assist families in paying for chemotherapy when needed; and continuing with the transplant program with outpatient intent.

The main challenges to continuity of cancer care associated to COVID-19 reported by oncology centers in low and middle-income countries include missed or delayed diagnosis, chemotherapy shortages, deferral in chemotherapy, shortfall of blood products [10], and closure of HSCT programs (73% of centers) [5]. Gratz et al. assessed the global impact of the COVID-19 pandemic on pediatric oncology in 213 institutions worldwide. About a third of those institutions (n=68) reported decreased financial support from public or governmental institutions, 141 (66%) reported a reduction in clinical staff, and 41 (19%) experienced a decrease in available pediatric oncology beds [12]. Another fundamental challenge was to continue with the hematopoietic transplant programs during the COVID-19 pandemic.

Other multicenter experiences in four Latin-American (LA) countries (Mexico, Peru, Guatemala, and Panama) [14] reported treatment modification in adults with acute leukemia in 40.8% of cases; the main reason being logistical issues related to unavailability of beds and lack of personnel. In our center, the most frequent barriers to continuity of care were chemotherapy stock-outs, unavailability of inpatient beds, and lack of financial resources. Adherence to our institutional treatment protocol was lower during the consolidation and intermediate maintenance phases, which was associated with a shortage of Cytarabine and Methotrexate, medications typically administered during these phases. Unavailability of inpatient beds in our center was overcome by providing ambulatory treatment. Specifically, when the treatment delay was estimated to be higher than five days, one of the strategies we implemented for low and intermediate-risk patients was to provide six hours of methotrexate infusion as outpatients [13].

We found some differences in the incidence, severity, and mortality rate associated to COVID-19. The incidence of COVID-19 in our series was 24.7%, with a mortality rate of 4.5%, and classification criteria for severe or critical illness in 18% of cases. Another LA cohort [14] reported that 13.1% of patients developed COVID-19, with a mortality rate of 37% in contrast with an experience at the "Instituto Mexicano del Seguro Social" in Mexico, which reported a 58% incidence of COVID-19, with no associated mortality [15]. The global registry of Covid-19 in pediatric cancer reported the clinical outcomes of 1500 patients. They reported that 19% of them met criteria for critical or severe disease and a related mortality rate of 3.8%; also reporting that in 55% of these children a significant modification occurred in the chemotherapy regimen [16]. Also, in our group, 42% patients were hospitalized for at least 72 hours, while Millen et al. [17] reported 15% of hospitalizations, and Boulad et al. reported 5% [18]. However, these studies included solid tumors, adult patients and tested asymptomatic patients. In contrast, we tested only symptomatic patients; thus, we could have missed some patients with mild disease.

Additionally, induction mortality was higher than that reported in the two years before the COVID-19 pandemic in our center (14.8% versus 4%), which was likely associated with limited availability of medical care and delay in diagnosis [19,20].

The true long-term impact of COVID-19 is currently unknown; however, the documentation and follow-up of outcomes and therapy modifications across different centers will help inform the development and implementation of better strategies to safeguard continuity of care for pediatric cancer patients.

**5.Conclusion**

In conclusion, adaptations made to the treatment protocols and the additional support interventions in our center allowed the continuity of treatment for >80% of ALL patients. However, our rate of abandonment to treatment and mortality during induction increased, reflecting the challenges to access health services that have been prevalent during the COVID-19 pandemic in Mexico. Each center should tailor modifications of treatment protocols and strategies for minimizing the risk of infection, providing a safe environment, and overcoming the lack of available beds and shortage of chemotherapy to safeguard the care of ALL patients based on their local needs and capacity.

**Acknowledgments:** We thank the MAS group (Mexico in Alliance with St. Jude) and the IHI (Institute for Healthcare Improvement) for their accompaniment and guidance in the implementation of the cancer does not wait project.

**Conflict of Interest**: This manuscript is original, it has not been published before, that no conflicts of interest are associated with this publication, and no financial support has influenced the outcome of this work.

**Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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| Table 1 | Operational changes during the COVID-19 pandemic for ALL patients treated in the Hematology Department of the Dr. José E. González University Hospital of the Universidad Autónoma de Nuevo León, Monterrey, México. |
| Table 2 | Pediatric ALL patient characteristics and treatment outcomes. |
| Table 3 | Overview of the characteristics of SARS-CoV2 positive patients. |