Impact of the COVID-19 pandemic on children with cancer. Mortality according to the three waves. A report from the Argentine National Pediatric Cancer Registry (ROHA-NET)

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Abstract

Background and Aims: Worldwide, the incidence of COVID-19 is lower in children than in adults and symptoms are less severe. So far, few studies from Latin America have been published on the behavior of COVID-19 in children with cancer. **Purpose**: To characterize the epidemiology, clinical course, morbidity, and mortality in children with cancer and COVID-19. **Methods:** All patients registered in the Argentine National Pediatric Cancer Registry (ROHA) with diagnosis of SARS-CoV-2 between December 4, 2020, and May 3, 2022 were included. Variables analyzed were: sex, age at COVID-19 diagnosis, clinical presentation at diagnosis, symptom severity, tumor type, intensive care requirement, specific treatment for COVID-19, vital status, and cause of death. Mortality was analyzed comparing the three main waves. **Results:** Overall, 888 children with cancer and COVID-19 infection were registered (484 females); 437 (49.2%) had leukemia, followed by central nervous system tumors (CNS-T) 120 (13.5%). Of the children, 57.2% (n=508) were symptomatic; 75% were febrile, and 37% (n=210) had neutropenia;

17.1% (n=152) were diagnosed within one month of cancer diagnosis. A total of 154 children had severe or critical symptoms (17%). In this study, 112 deaths were reported, 105 (94%) due to disease progression, sepsis, comorbidities, or treatment complications. Seven patients (0.8%) died from COVID-19, all diagnosed with leukemia/lymphoma. No association of deaths was found between the three waves analyzed. **Conclusions:** Based on the ROHA data, we may conclude that in pediatric cancer patients, contrary to what was initially expected, morbidity and mortality due to COVID-19 were not increased.

Introduction

On March 11th, 2020, the World Health Organization declared the outbreak of COVID-19, caused by the SARS-CoV-2 virus a pandemic. On April 12th, 2020, the first case in a pediatric patient with cancer in Argentina was diagnosed. The COVID-19 pandemic has presented a global challenge for the care of children with cancer.[1]

Early reports of the effects of the pandemic on the management of pediatric cancer patients showed that care was affected worldwide, but most notably in low- and middle-income countries.[2,3,4]These initial reports warned about the possibility of a higher incidence and more severe COVID-19 disease among cancer patients due to their immunocompromised status. Nevertheless, subsequent studies showed that pediatric oncology patients infected with SARS-CoV-2 were not at increased risk of severe disease.[5,6]Indeed, most of the children and adolescents were asymptomatic or the clinical course was generally mild[7–9], with few complications[10,11]and little need for intensive care and mechanical ventilatory support.[7,12]

Since the beginning of the pandemic, the management of COVID-19 in patients in general and cancer patients in particular has gone through different stages resulting in modifications in the medical behavior. Children with cancer have always been of particular concern because of their susceptibility to opportunistic infections due to both disease and treatment-related immune alterations. Different international studies have shown that leukemia is one of the most frequent hematology-oncology diseases associated with SARS-CoV-2 infection.[5,7,9,13,14]The reported COVID-19-related mortality rate in pediatric patients with cancer ranges from 0.6% to 4.08%.[7,9,15,16]

The impact of the pandemic on the continuity of cancer treatment has been a concern for physicians caring for children and adolescents with cancer. The pandemic significantly affected pediatric oncology services around the world, resulting in delays in diagnosis, clinical management, and chemo- and radiotherapy treatments. These adversities were most marked in low- and middle-income countries.[2,3,4,7,8]However, once the initial difficulties were resolved, cancer treatment could be continued safely in most patients.[14,17,18,19,20,21]

It was necessary to take proactive and flexible measures in the pediatric hematology-oncology units (PHOUs) to quickly adapt the model of patient care, implement supervision of personal protective equipment (PPE) to protect patients and health care personnel in order to ensure the safety of care.[1]

In Argentina, studies evaluating the effect of the COVID-19 pandemic in children with cancer are scarce. Better knowledge of the characteristics of affected patients using local data is a priority for the management of these patients. The aim of this study was to describe the clinical characteristics, treatment, and outcome of children with cancer included in a population-based cancer registry with SARS-CoV-2 infection.

Methods

Study design

A descriptive, observational, longitudinal study was conducted based on data from the Argentine National Pediatric Cancer Registry (ROHA).

Setting

Argentina extends over 2.8 million square kilometers. It has 24 political units: 23 provinces and Buenos Aires city, the Federal District. Its population is mainly urban (90%); 46% of the population is distributed over the Federal District and the province of Buenos Aires. Political units are commonly grouped into five

major geographical areas ("regions"), as shown on the map (Fig. 1). In 2010, the population 0-19 years of age consisted of 13.8 million children with the following distribution: 61% in the central region (CEN), 14% in the northwest (NW), 11% in the northeast (NE), 8% in the Cuyo region (CUY), and 6% in the region of Patagonia (RP).[22]Of all the children with cancer, 83% receive free healthcare in public centers. Throughout the country, there are 37 private and public PHOUs where partial or complete treatment is provided; six of these units are provincial referral centers with different care levels. More than 40% of the children are assisted at the national public referral center.

The ROHA is part of the National Cancer Institute of the Ministry of Health within the National Program for the Comprehensive Care of Children and Adolescents with Cancer (PROCUINCA). The data used by the ROHA are provided by different sources; most of the cases are reported by different PHOUs throughout the country. In addition, the ROHA receives information from 12 population-based cancer registries that are not exclusively pediatric.

Data collection

For each patient, the following data are collected in the ROHA: name and surname, identification number, date of birth, sex, province of residence, address, tumor histology, location, stage, type of treatment, relapse, and status.

At the onset of the pandemic, an epidemiological registry of cancer patients with SARS-CoV-2 infection was included in the ROHA. Data were collected on date of symptom onset, date of reverse transcription polymerase chain reaction (RT-PCR), clinical manifestation, concomitant infections, hospital admission or intensive care requirement, laboratory studies, status, and date of death.

Inclusion criteria

The cases included in this study were identified in the ROHA. A case was defined as any patient under 19 years of age with a diagnosis of malignant tumor and SARS-CoV-2 disease confirmed by RT-PCR between April 12, 2020 (epidemiological week [EW] 16) and March 5, 2022 (epidemiological week 9) and resident in Argentina at the time of diagnosis.

Exclusion criteria

Patients with SARS-CoV-2 infection more than 5 years after cancer diagnosis were excluded from the study.

Variables

The following variables were considered in the analysis: sex, age at COVID-19 diagnosis, clinical manifestations, type of tumor according to the International Classification of Childhood Cancer - third edition (ICCC-3), requirement for intensive care, specific treatment for COVID-19, and status.

Tumors was coded according to the International Classification of Diseases for Oncology - third edition (ICD-O-3) and the ICCC-3.

Disease severity was defined according to the internationally used clinical classification into 5 degrees of severity: 1) Asymptomatic: no symptoms but a positive COVID-19 test, 2) Mild: outpatient management, gastrointestinal symptoms, upper respiratory tract infection, 3) Moderate: lower respiratory tract involvement, e.g. pneumonia, 4) Severe: oxygen requirement, intensive care unit admission without the need for mechanical ventilation (MV), multisystemic inflammatory syndrome, febrile neutropenia, respiratory distress syndrome, dehydration, and 5) Critical: acute respiratory distress syndrome, respiratory failure requiring MV, shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, or acute kidney injury.[5,23–25]

Contagion waves were defined to compare indicators of COVID-19 mortality in the group of patients diagnosed with leukemia or lymphoma. The case fatality rate was calculated as the ratio of deaths to the total number of cases with leukemia or lymphoma.

To establish the time span of each wave, the curve of confirmed cases was defined according to the date of PCR testing. The start, peak, and end of the curves were determined. The first wave occurred from April 24 (EW 17) to November 18 (EW 47), 2020, with a peak in EW 40; the second wave occurred from December 1 (EW 49), 2020, to October 13 (EW 41), 2021, with a peak in EW 23; and the third wave occurred from December 6 (EW 49), 2021, to February 25 (EW 8), 2022, with a peak in EW 3.

Statistical analysis

A descriptive analysis was performed. Continuous variables are reported as mean and standard deviation or median and range according to their distribution, while categorical variables are presented as counts and percentages. An Excel spreadsheet and STATA version 13 statistical software were used. For the analysis of COVID-19-related mortality in patients diagnosed with leukemia or lymphoma according to the previously defined waves, proportions were compared using the Chi-squared test. Infostat statistical software was used.

Results

A total of 888 pediatric oncology patients were identified to have SARS-CoV-2 infection by RT-PCR testing and were registered in the ROHA between April 12, 2020 (EW 16) and March 5, 2022 (EW 9).

In Argentina, there have been three important COVID-19 waves since the beginning of the pandemic; the first in EW 40 of 2020 with 21 cases/week, the second in EW 23 of 2021 with 18 cases/week, and the third and largest in EW 3 of 2022 with 68 cases/week (Fig. 2).

Median age of the patients at COVID-19 diagnosis was 7 years (range, 3 months to 19 years); 55% were male. Most of the confirmed cases (31%) were patients between 5 and 9 years old (n=275), followed by patients between 1 and 4 years old (29%; n=260). Twenty-three patients under 1 year of age were reported, of whom 12 had retinoblastoma, seven leukemia, two hepatoblastoma, one neuroblastoma, and one glioma.

The majority of SARS-CoV-2-positive children with cancer had leukemia (n=437), followed by central nervous system tumor (n=120), which accounted for 63% of the total number of patients.

At diagnosis, 42% (n=371) of the patients were asymptomatic. Of those symptomatic patients (n=508), 75% had fever (n=381) lasting less than 3 days in 74% of the cases. Table 1 shows the symptoms observed according to frequency. Considering the WHO classification, the majority of the cases were mild (n=333; 37.5%). Of 210 patients with neutropenia (less than 1000 neutrophils), 59% had fever (n=124).

Seventeen percent of the patients were diagnosed with COVID-19 within the first month at cancer diagnosis. Very few patients (2.5%) received specific treatment for the disease (Table 1).

A total of 112 cancer patients with a history of SARS-CoV-2 infection died, 51% of whom had leukemia/lymphoma. The most frequent cause of death was disease progression (61%) and in only seven (6%) children COVID-19 was the cause of death (Table 2).

Of the total number of patients with leukemia or lymphoma (n=526), one patient died of COVID-19 in the first wave (0.6%), four in the second (2.2%), and two in the third (1.1%). In statistical analysis the comparison of these rates yielded a value of 1.87 (p 0.39) (Fig. 2 and Table 3).

Discussion

Since the first SARS-CoV-2-positive case in March 2020, 8 935 746 cases have been confirmed in Argentina. Of these, 8% (720,147) were patients between 0 and 19 years of age[26] and 0.1% (n= 888) were pediatric patients with concomitant oncological disease, who mostly presented with mild clinical manifestations or asymptomatic disease. The low incidence rate in our study is similar to that reported in other studies[27,7]but slightly higher than that estimated for the general pediatric population.[8]This low incidence could be related to the early implementation of social distancing and prevention measures,[11] but may also suggest underreporting, given that children predominantly have mild or asymptomatic forms of COVID-19.[27]

Almost 60% of the children that tested positive for SARS-CoV-2 had leukemia or lymphoma, followed by central nervous system tumors in 13.5%, which is consistent with the distribution of cancer diagnoses in the general pediatric population. In addition, the distribution of diagnoses according to the ICCC-3 in children with SARS-CoV-2 infection was similar to that reported in previous series.[5,7,8,10,14,17,28]

In our series, 41.1% of patients were asymptomatic at the time of COVID-19 diagnosis. This is twice the rate published for the general population of patients under 18 years of age in Argentina.[29]This difference may be explained by the greater number of tests performed in cancer patients as a result of screening prior to admissions, procedures, and transfers.[30]

In the majority of patients, clinical manifestations consisted of mild respiratory symptoms with minimal requirement for hospital admission and not leading to an increase in COVID-19-related morbidity or mortality, coinciding with reports from other countries.[12,31]The symptoms most frequently observed were fever and cough, similar to those reported by other authors both in general pediatric population and in the pediatric population with cancer.[2,5,7,8,10,12,17,28,32]

Although these children are immunocompromised with greater susceptibility to infection, unlike what was initially thought for adults with cancer,[33]more than 70% of children with cancer and SARS-CoV-2 infection evolved favorably and remained asymptomatic or developed mild disease. Only 3 % of cases presented critical disease, consistent with those reported in other pediatric series.[6,11,17,28]

Madhusoodhan et al. found a higher rate of asymptomatic patients than in the general pediatric population in the same geographic region.[7]Similar to other series, our evaluation showed that only a small number of patients who were asymptomatic at diagnosis developed symptoms later. Although in our study mortality was high compared to previously published series.[7,15,18,28,32]when the causes of death in our population were analyzed, 88% were found to be due to progression of the underlying disease or to disease-associated complications[2,7,14]and not attributable to SARS-CoV-2. There was also no difference in COVID-19-related mortality (n=7) in children with leukemia or lymphoma when comparing the three waves, despite different circulating strains.

One of the major interrogatives during the pandemic was whether immunosuppressive treatment should be continued in patients with cancer and SARS-CoV-2 infection. In the first months of the pandemic, recommendations were developed to guide treating physicians in the management of cancer therapies. Different studies show that initially it was decided to discontinue or modify chemotherapies, immunotherapies, surgeries, and radiation therapies, motivated by uncertainty regarding outcome and prognosis of SARS-CoV-2 infections in cancer patients.[2,3,8,17,20,21]Due to a lack of data on treatment discontinuation or modification in our study, we cannot be sure if the same occurred in Argentina.

One of the strengths of our study is that ROHA has national coverage of more than 90% of pediatric cancer patients by including all PHOUs in the country. The creation of the epidemiological registry of patients with SARS-CoV-2 infection in the registry allowed for the dynamic and almost real-time reporting of positive cases. Based on this information, weekly epidemiological reports were prepared and sent back to each institution resulting in data-driven decision-making in the face of this new disease.

It should be noted that the unexpected outbreak of COVID-19 confronted us with a general population, including pediatric cancer patients and their families that had to comply with isolation protocols and restrictions and warranted the implementation of healthcare measures to combat the virus. Although changes in the management over time led to some delays, most patients were able to safely continue their treatment even during the most complicated moments of the pandemic.[14,17,18,19,21]

Future studies will be necessary to know the true impact of SARS-CoV-2 on the oncological disease of these patients.

Conclusion In conclusion, based on our data we may infer that the impact of SARS-CoV-2 in pediatric patients was low in terms of incidence and mortality exclusively attributed to SARS-CoV-2. The clinical course of COVID-19 was mild in the majority of cases.

The PHOU, which adapted to the epidemiological situation in each jurisdiction, continued to care for their patients. In all cases, changes in the hospital care model were reported.

The pediatric oncology units, adapted to the epidemiological reality of each jurisdiction, continued to assist their patients. In all cases, modifications in care attention model at the hospital were reported.

Based on the experience gained, which demonstrated the favorable evolution and the absence of severe complications in most cases of SARS-Cov2 in pediatric cancer patients and the increased risk associated with inadequate oncological management, the interruption of the treatments was limited to the small number of critically ill patients.

As lessons learned, we should include better preparation of health services to deal with infections, improved communication between centers and networking, as well as the use of telemedicine as an element of training that we should incorporate and continue to strengthen beyond the end of the pandemic.

Finally, it would be important to highlight the impact on the physical and psychological health of healthcare personnel, as well as the deaths caused by SARS-CoV-2. Social distancing, hand hygiene, greater awareness of infections, and the mandatory use of masks, which lead to a decrease in infections, were reflected in a decrease of non-covid-related infectious-contagious complications.

Based on the ROHA data, we may conclude that in pediatric oncology patients, contrary to what was initially expected, morbidity and mortality were not increased.

Conflict of Interest statement

The manuscript has not been submitted elsewhere and has not conflict of interest.

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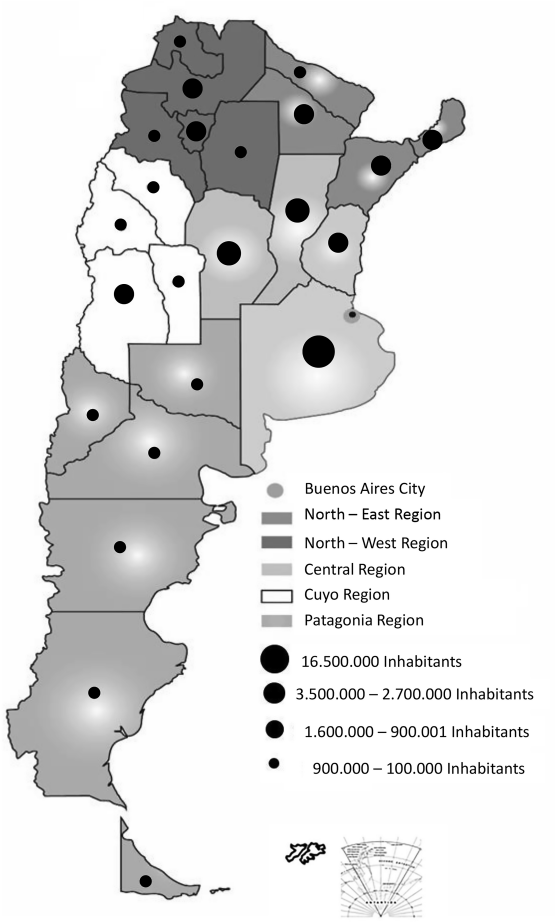
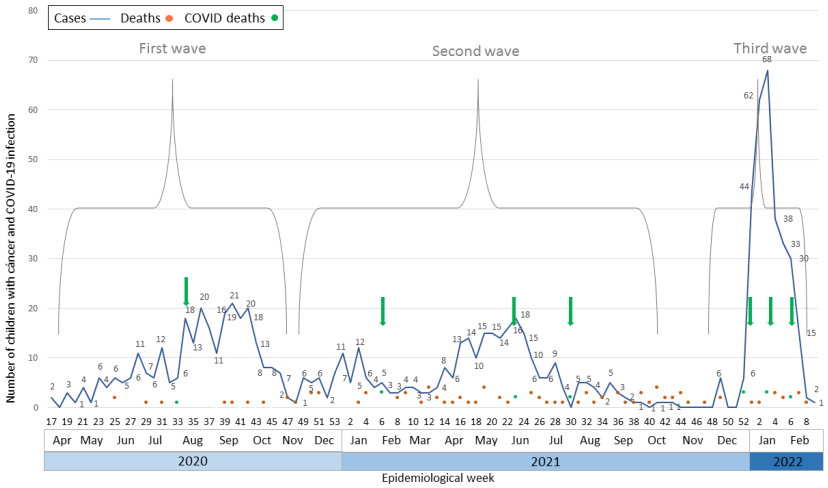
Legends

Figure 1. Map of Argentina. Geographic regions and range of inhabitants by province. Source: ROHA – National Office of Population Census

Figure 2. Number of confirmed SARS-CoV-2 infections and mortality in children with cancer according to Epidemiological Week. Argentina, 2020-22





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