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COVID-19: Consequences for Children With Cancer in Turkey and Globally

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INTRODUCTION

The current outbreak of COVID-19 that was first reported from Wuhan, China, on December 31, 2019 was declared a pandemic on March 11, 2020 by the World Health Organization (WHO).[1] The first case in Turkey was diagnosed on that same day. In mid-May, 2020, Turkey was among the 10 countries with the highest number of COVID-19 cases.[2]

As of April 16, 2021, there are a total of 138 688 383 confirmed cases of COVID-19 and 2 978 935 deaths reported to WHO globally.[1] In Turkey, 4 086 957 cases of COVID-19, and 35 031 deaths have been reported.[2]

Adults with cancer are reported to have a higher risk for COVID-19, and more severe disease and mortality than the general population[3]. In the USA, 26% of patients with cancer who contracted the disease have died from the virus, while 1.8% of the population with COVID-19 have died.[4]

Although children with COVID-19 are reported to have milder disease and good prognosis as compared with adults, immunosuppressive diseases including cancer, immunosuppressive medications, and stem cell transplantation (SCT) have effects on humoral, cell-mediated immunity and neutrophil function, increasing the risk of severe infections and complications caused by viral agents.[5] This manuscript reviews several themes, including the current situation among children with cancer in Turkey and globally, consequences of the COVID-19 pandemic such as the interruption in several health services and the significant slowdown of many others, and reduced funding for research in cancer.

COVID-19 and Children With Cancer in Turkey and Globally

Data specifically addressing COVID-19 and children with cancer are increasing, albeit still limited in comparison to data on adults. The pediatric oncology community responded quickly and organically to the pandemic by creating a global observatory and virtual resource center through a partnership between the International Society of Pediatric Oncology (SIOP) and St. Jude Global.[6,7,8] In that resource, virtual meetings addressing updates of the challenges posed by the pandemic, case discussions, policies for patient treatment, and a global registry of children with cancer and COVID-19 infection were launched. As of April 8, 2021, there were 1642 children with cancer and laboratory-confirmed COVID-19 infection reported from 48 countries.[9]Although, children seem to be at a lower risk for COVID-19 than adults,[3–5] children with cancer are reported to have more critical disease and a higher mortality than children without a cancer diagnosis.[10]

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While COVID-19 incidence is difficult to report due to differences in testing capacity and reporting practices, cohorts and case series from various regions of the world have reported test positivity in pediatric patients with cancer as 1-9%, higher than in the general pediatric population in most of the respective settings.[11-14] Out of 200 pediatric patients on anticancer therapy tested for SARS-CoV-2, 9 (4.5%)[14] were found to be positive for the infection, which was higher than the incidence in the general pediatric population (2%).[15]

In Turkey, children were reported to comprise 7.2% of all cases with COVID-19. In June 2020, the death rate for COVID-19 in all ages was reported as 2.57% in Turkey, and 0.19% of all COVID-19 deaths were of children.[16]

In Turkey, about 2500 children are diagnosed with cancer each year.[17] Children with cancer constituted 0.35% of the total pediatric population with COVID-19 in Turkey. In the first wave (March-May 2020), most (60%) children with COVID-19 were diagnosed in Istanbul, which is the most populated city in Turkey.[10] Likewise, most patients (55%) with COVID-19 at all ages in Turkey were diagnosed in Istanbul.[18] However, as the pandemic continued, the cases were seen in all regions of Turkey, as has been the case in all the world.

In a report from 6 onco-hematologic centers in Italy, where 286 children were tested with polymerase chain reaction, 5.6% (12/212) of asymptomatic cases were found to be positive, whereas 12% (9/74) of those who had symptoms or history of contact were positive, and 2/21 had severe/critical disease.[19]

In a study from Memorial Sloan Kettering Cancer Center in New York, 178 children with cancer and 335 caregivers were tested for SARS-CoV-2 by PCR. The rate of positivity was 29.3% in symptomatic children, it was only 2.5% in asymptomatic patients and with no known exposure. Among asymptomatic and unexposed caregivers, 14.7% tested positive for SARS-CoV-2, emphasizing the importance of testing the asymptomatic caregivers also.[12]

In pediatric cancer studies, history of contact in the family has been reported. In the nationwide study from Turkey, 47% of the children with cancer and COVID-19 had a history of contact in the family.[10]

Although children with COVID-19 in general have mostly asymptomatic/mild disease, studies from national, multicenter, and multinational series of children with cancer report higher incidence of severe and critical disease. In the nationwide study in Turkey conducted between March 11, 2020 and May 31, 2020, 22% of the 51 pediatric cancer cases with COVID-19 had severe/critical disease, 18% needed care in the intensive care unit, and the mortality rate was 1.9%[10]. In the Global COVID-19 in Childhood Cancer Registry (GCCCR), 18.6% of the 1645 patients had severe/critical disease, and death occurred in 5.7% in the whole cohort, with death attributed to COVID-19 in 3.41%.[9]

In many centers, 14-20% of children with COVID-19 who were hospitalized or needed ICU care were reported to have a hematologic/oncologic disorder as an underlying medical condition.[20,21] In most pediatric series, leukemias/lymphomas constitute 47-60% of all cases.[9,10] In the Turkish nationwide study, 61% of the children with cancer and COVID-19 had hematopoietic malignancies. Similarly, in the case series reported from Madrid (73%) and Italy (48%), many patients had hematological malignancies.[9,11,13,22,23] The reason may be that hematopoietic malignancies experience prolonged neutropenia and immunosuppression and these children may be more susceptible to COVID-19 infection.

COVID-19 causes multiple organ involvement due to widespread distribution of angiotensin-converting enzyme-2, the functional receptor for SARS-CoV-2 in multiple organs.[11,19] The most frequent presenting signs in symptomatic children with cancer are fever and cough. The respiratory system is affected the most, followed by the gastrointestinal system, the central nervous and musculoskeletal systems, and skin.[9,10,24] Thoracic tomography findings in affected patients consist of diffuse or patchy pneumonic consolidation and ground glass opacities. Pleural effusion and findings attributed to acute respiratory distress syndrome may also be observed.[25] In the nationwide study in Turkey, COVID-19 pneumonia was detected in 26 of 51 (50.9%) patients.[10] In the GCCCR, 41.9% had abnormal imaging findings attributed to COVID-19.[9]

Prognostic factors for severe/critical disease and need of ICU have been reported as having a hematological malignancy, having had an SCT, a mixed infection, and abnormal computed tomography (CT) findings.[9,10] Age, gender, elevated C-reactive protein, elevated D-dimer, being neutropenic, and having relapsed/refractory disease were not found significant for critical disease in the Turkish series.[10]

In many pediatric cancer series, 30-50% of the cases had febrile neutropenia.[10-12,14] Since differential diagnosis between COVID-19 and other infections is difficult during neutropenia, we suggest that children with cancer and febrile neutropenia should be tested for COVID-19.

By the end of April 2020 and the beginning of May, several scientific societies reported a new clinical presentation related to SARS-CoV-2 infection.[26] This syndrome, known as multisystem inflammatory syndrome associated with COVID-19(MIS-C), is characterized by fever, abdominal pain, gastrointestinal and cutaneous symptoms, and hemodynamic alterations. As described in these reports, MIS-C has similar features to those of Kawasaki disease, toxic shock syndrome, bacterial sepsis, and macrophage-activation syndrome. To date, several publications have reported clusters of patients with differing severity.[26,27,28]

It is hard to speculate which drugs are best for the disease as the search for the "standard of care" drugs are still under debate globally. National and international guides for management are frequently being revised.[1,2,29] Treatment used to date has consisted of hydroxychloroquine, azithromycin, antivirals either as a single agent or in combination, and in severe cases, use of convalescent plasma, mesenchymal stem cells, anti-interleukin-6, and anti-interleukin-1 have been reported.[9,10,30,31] The evaluation and sharing of national/multinational data that includes all children with cancer/SCT and COVID-19 within a time frame, without any selection bias, and accumulation

of international data shall lead to a better understanding of the disease, treatment, and risk factors to guide health care professionals.

Consequences of COVID-19 on Healthcare Systems and Research

The COVID-19 pandemic has interrupted several health services and caused a significant slowdown of many others. However, infection with the SARS-CoV-2 virus itself is not the only threat to children with cancer. Pediatric oncology relies on prompt evaluation and diagnosis, referral to tertiary centers, multidisciplinary multimodal treatment, including but not limited to, chemotherapy, radiotherapy, surgery, and access to supportive care, all of which have been affected to variable extents in many regions in the world, both in high and low-middle income countries.

The interruption and delay in treatment for children with cancer due to COVID-19 is a major problem, especially in children who are at the first months of treatment and have not achieved remission yet. Treatment was delayed in 62.7% of the patients and delayed with a median of 15 (3-45) days in the nationwide study in Turkey. Furthermore 11% of these patients were just at diagnosis.[10,32] In the GCCCR, treatment alterations (chemotherapy delay or dose reduction, surgery or radiation delay) were encountered in 47.5% of the patients.[9]

In a report from 2 academic institutions in California, 64% of the 55 patients who underwent active cancer management had significant changes in management, primarily consisting of delays. Median delay was 21 days (5-112 days).[33]

The early impact of COVID-19 pandemic in the care of children with cancer in Latin America was reported. In that survey of 453 pediatric oncologists in 20 countries, it was shown that the care of pediatric oncology patients was impacted (chemotherapy shortages, limited bed availability, access to radiotherapy, etc.) early in the pandemic and that impact was significantly higher in countries with lower health care expenditures and higher rates of COVID-19 infections. There was also an association between the type of hospital at which the children were treated, since cancer centers had a higher impact than pediatric hospitals.[34] A similar picture was reported from 34 pediatric oncology units within the Pediatric Oncology East and Mediterranean (POEM) collaborative group, from the Middle East, North Africa, and West Asia. There it was reported that almost all centers applied guidelines to optimize resource utilization and safety, including delaying off-treatment visits, rotating and reducing staff, and implementing social distancing, hand hygiene measures, and personal protective equipment (PPE) use.[35] Essential treatments, including chemotherapy, surgery, and radiation therapy were delayed in 29-44% of centers, and 24% of centers restricted acceptance of new patients. Clinical care delivery was reported as negatively affected in 28% of centers. More than 70% of centers reported shortages in blood products, and 47-62% reported interruptions in surgery and radiation as well as medication shortages. However, bed availability was affected in < 30% of centers, reflecting the low rates of COVID-19 hospitalizations in the corresponding countries at the time of the survey.[35]

The COVIMPACT Study collected data by a cross-sectional survey of more than 300 clinicians from 213 institutions in 79 countries from June 22, 2020 to August 21, 2020, and confirmed the major impact of the COVID-19 pandemic on pediatric cancer care globally. Most hospitals (83%) were in low- and middle-income countries (LMICs) and the vast majority (88%) were able to test for COVID-19.[36] Totally 78% of institutions surveyed reported a significant impact on pediatric cancer care and 15 hospitals (7%) reported complete closure of pediatric hematology-oncology services. Almost half (43%) made fewer new cancer diagnoses than expected, while around one-third noted a rise in the number of patients abandoning treatment. The survey concluded that institutions around the world are impacted by the pandemic, but particularly in LMICs where even before the pandemic, they had to deal with fewer resources and less access to care for children with cancer.[36]

Wide-ranging impacts were identified worldwide, including reductions in available clinical staff, pediatric cancer beds, and PPE. However, the results suggest the effects in LMICs were more pronounced, with changes to chemotherapy due to treatment agent shortages, treatment abandonment, and disruptions to radiotherapy among issues more frequently reported.[36]

In many centers, the main measures that were adapted include the creation of COVID-19 and non-COVID-19 patient care pathways, the use of PPE both for the healthcare staff and patients and caregivers, social distancing, and the prohibition of access to visitors, teachers, and volunteers.[10,19]

The COVID-19 pandemic has posed serious impacts on economic systems. Many parents/caregivers of children with cancer have lost their jobs, and this has increased the difficulties in their families. While only 1.2% of the population in Turkey are healthcare professionals, 6.5% of the COVID-19 infections have been documented in healthcare professionals.[37] This has led to anxiety among healthcare workers who are working with so much dedication at the frontline. Many healthcare workers have not been able to be with their children, families or parents, for a prolonged time, in trying to protect them from an unintentional COVID-19 infection. It has been reported that during pandemics, anxiety, depression, post-traumatic stress, and burnout syndrome are prevalent in healthcare professionals and that women and nurses are the most affected.[38]

The pandemic has impacted patients with cancer, not only in causing morbidity and mortality, but also in the reduction of the scientific advancement of early diagnosis, treatment, and cure. Research funding has decreased.[39,40] Although the funding from the federal government has not abated, the American Cancer Society predicts a $200 million reduction in philanthropy,[39] Great Britain's shortfall is $150 million,[40] and Canada's is $100 million, plus European Union support has been reduced by 30%—approximately $365 million—with predictions of a $9.5 billion shortfall in the next 6 years.[39,40]

The safest and most controlled way to effectively and sustainably prevent COVID-19 in a society is to have an effective and safe vaccine and to successfully vaccinate the majority of the population.[41]

CONCLUSION

In conclusion, children with cancer are at higher risk for severe/critical COVID-19 in comparison to children in the general population. Children with hematological malignancies, those who have had SCT, and those who have mixed infections seem to be at a higher risk. The COVID-19 pandemic has caused an interruption in several health services and the significant slowdown of many others, and has reduced funding for research in cancer.

Whether the negative impact of the COVID-19 pandemic on healthcare services will affect survival rates of children with cancer globally in the coming years should be monitored by epidemiological research, and actions should be planned urgently for prevention and recovery.

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