Impact of COVID-19 Pandemic on Delays in Diagnosis and Treatment: Outcomes in Pediatric Malignant Solid Tumors

COVİD-19 Pandemisinin Teşhis ve Tedavi Gecikmesine Etkisi: Çocukluk Çağı Maliyn Solid Tümör Sonuçları

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ABSTRACT

Objective: The restricted access to healthcare during the coronavirus disease 2019 (COVID-19) pandemic has been particularly problematic for cancer patients. Although childhood cancers are highly curable, disruptions in diagnosis and treatment obviously lead to poor results. In the present study, we investigate the effects of the delays in the diagnosis and the treatment of those with cancer during the pandemic, as well as the clinical course and outcomes of cancer patients diagnosed with COVID-19 during the pandemic.

Material and Methods: An 18-question survey was applied in the pediatric oncology clinic to garner data from newly diagnosed patients on the duration of complaints, delays due to hospital refusals and delays in diagnostic examinations. Patients under treatment, on the other hand, provided information on any interruptions in their chemotherapy treatments (whether caused by the patient or the clinician). The data of patients infected with COVID-19 during cancer treatment were collected from their medical files.

Results: The cancer diagnosis was delayed by a median of 60 (14-150) days in 13 patients due to late presentation to the hospital or the refusal of hospitals to accept patients due to overcrowding. Furthermore, the chemotherapy treatments of 9 patients were delayed by a median of 15 (10–60) days due to exposure to COVID-19 infection (in the patient or a family member). A total of 58 of the patients contracted COVID-19 at different stages of their anticancer treatment, and almost all recovered from COVID-19 with mild symptoms.

Conclusion: Restrictions during the pandemic led to delays in the diagnosis and treatment of pediatric solid tumors. In pediatric patients with cancer who contract COVID-19, their anticancer treatments should be continued based on an evaluation of their clinical status.

Key Words: Cancer, Children, COVID-19

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ÖZ

Amaç: Koronavirüs hastalığı 2019 (COVİD-19) salgını sırasında sağlık hizmetlerine erişimin kısıtlanması, kanserli hastalar için önemli bir sorundur. Çocukluk çağı kanserleri yüksek oranda tedavi edilebilse de tanı ve tedavi aksamalarının kötü sonuçlara yol açacağı aşikardır. Çalışmamızda yeni tanı konulan ve tedavi gören çocukların kısıtlamalardan etkilenip etkilenmediğini ve kanser tedavisi sırasında COVİD-19 tanısı alan hastaların klinik seyir ve sonuçlarını araştırdık.

Gereç ve Yöntemler: Hasta ebeveynlerine 18 sorudan oluşan bir anket uyguladık. Kanser tedavisi sırasında COVİD-19 tanısı alan hastaların dosyaları taranarak veriler kaydedildi.

Bulgular: Hastaların 35'i yeni tanı grubunda, 55'i ise tedavisi devam eden gruptaydı. Yeni tanı alan hastaların 13'ü (%38) hastaneye geç başvurduğu için kanser tanısı gecikti. Kemoterapi alan hastaların 9'unda (%16) tedavide gecikme yaşandı. Elli sekiz hasta, kanser tedavisinin farklı aşamalarında COVİD-19 enfeksiyonu geçirdi. Hastaların tamamına yakını hafif semptomlarla COVİD-19'dan iyileşti.

Sonuç: Salgını kontrol altına almak için sıkı önlemler alınması gerekirken, kanser gibi ağır kritik hastalığı olan hastalar dikkatle değerlendirilmeli ve hayati sonuçlar doğurabilecek tedavi gecikmelerinden kaçınılmalıdır. Koronavirüs hastalığı 2019 ile enfekte olan kanserli çocuk hastalarda, hastanın klinik durumu değerlendirilerek kanser tedavisine devam edilmesi düşünülmelidir.

Anahtar Sözcükler: Kanser, Çocuk, COVİD-19

INTRODUCTION

The new coronavirus disease (COVID-19), first reported in Wuhan in December 2019, spread rapidly around the world and developed into a global crisis (1). As of November 27, 2022, a total of 641.494.322 confirmed cases of COVID-19 and 6.63 million deaths had been reported to the World Health Organization (WHO) globally (2). The first case in Türkiye was identified in March 2020, and the country would soon be reporting some of the highest numbers in the world with 17,042,722 cases of COVID-19 and 101.492 deaths reported (3).

Strict social distancing measures were implemented around the globe to curtail the spread of the disease, leading to billions of people isolating themselves at home, while heavy restrictions were placed on travel between countries and cities, and educational and business premises were closed. In hospitals, as the highest-risk environments, stringent measures were put in place to protect the health both of the patients and the healthcare staff. These included strict restrictions on hospital visits by non-emergency patients and postponed elective surgeries, all of which were taken to reduce the density of patients in hospitals, to facilitate social distancing and to make more room for COVID-19 patients. The important issues that needed to be resolved at the height of the pandemic were the postponement of the treatments of cases with special needs/serious illnesses, and the difficulties encountered by non-COVID-19 patients in gaining access to healthcare services.

Childhood cancers are highly curable with early diagnosis and appropriate treatment, however, delays in diagnosis and in the timely provision of lifesaving treatments can lead to the disease progressing to an advanced stage, and missed chances of a cure. A small number of studies to date have investigated the clinical course and outcomes of COVID-19 in pediatric patients, including those with cancer, and the effect of unexpected disruptions and uncertainties in access to healthcare on the care of pediatric oncology patients (4-6). The present study investigates the effects of the COVID-19 pandemic on the diagnosis, treatment and outcomes of children with cancer.

MATERIALS and METHODS

Children with cancer receiving chemotherapy at the Pediatric Oncology Department of Ankara City Hospital of the Ministry of Health and those diagnosed with cancer after March 11, 2020 were included in the study. Patients who had completed their chemotherapy courses were excluded from the study. An 18-question survey was applied to the parents during outpatient clinic visits between March and September 2020, in full compliance with the restrictions applied during the lockdown period.

Survey Organization

The 18-question survey applied to the respondents (parents of patients) garnered data on any delays experienced in the diagnosis of COVID-19 or cancer. The parents of newly diagnosed patients were asked how many days after their first complaint they were admitted to the hospital, whether they delayed presenting to the hospital due to fears of contracting COVID-19, whether they had been turned away by the hospital, whether there were any delays in radiological examinations, whether the results had been reported late, and whether biopsy or pathology results were delayed. They were also asked whether they had applied to our clinic late, or whether the start of the first treatment (chemotherapy) was delayed. The response options were "yes" or "no", and if they answered "yes", the duration of the delay was inquired in days. Delays beyond the expected date in each stage were defined in days, such as for radiological imaging, the reporting of results, taking biopsy samples and obtaining pathology results, and the respondents were asked whether the delay had been due to their own concerns or the restrictions applied by the hospital. They were also asked whether they had developed symptoms, or been diagnosed or hospitalized with COVID-19, whether their chemotherapy had been delayed due to a COVID-19 infection

and whether they had undergone chemotherapy in their home town to avoid attending the clinic.

Patients with COVID-19 infection

The patient medical files and laboratory records of all pediatric patients treated for cancer between March and June 2022 were analyzed for information on any COVID-19 infection. The severity of any COVID-19 infection was classified according to the US National Institutes of Health (NIH) guidelines as asymptomatic, mild, moderate or severe disease.

Patients in our department are tested for the SARS-CoV-2 through nasopharyngeal and oropharyngeal swabs using the reverse transcriptase polymerase chain reaction (RT-PCR) method before surgery, other procedures and admission. Patients who presented with febrile neutropenia were subjected to a PCR test, and they were followed up in the isolated ward until the results were obtained.

The study was approved by both the Turkish Ministry of Health and the ethics committee of Ankara City Hospital, and was carried out in accordance with the Declaration of Helsinki principles and all applicable regulations (19.08.2020/E1-20-1013).

Statistics

The statistical analysis of the study was carried out using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.). The normality of continuous variables was evaluated with a Shapiro-Wilk test, and since the data were not normally distributed, median (minimum-maximum) values were presented. Categorical variables were summarized with frequency (percentage) values.

RESULT

A total of 310 patients were hospitalized in our 45-bed oncology ward and 800 patients were followed up in the outpatient clinic between 11 March and 15 September, 2020, and 90 parents of patients whose treatment was continuing or who had been newly diagnosed with cancer were surveyed.

Delayed cancer diagnosis due to COVID-19

The median age of the 90 patients (38 female, 52 male) whose parents were surveyed was 11 (0.5–19) years, and 35 had been newly diagnosed and 55 were continuing chemotherapy after being diagnosed before the pandemic was declared. The primary diagnosis of the patients showed heterogeneity, with the most common being Ewing's sarcoma (16%) and Hodgkin lymphoma (15%) (Table I).

The cancer diagnosis was delayed in 13 of 35 newly diagnosed patients, with a median delay in 13 patients of 60 (14–150) days, all 13 of whom had delayed visiting the hospital due to fear of exposure to COVID-19. Although eight of these 13 patients attended hospital later, they were not admitted, three of whom visited the hospital 5 months after the first onset of complaints, one after 3 months, three after 2 months and six after 1 month. Of the 35 patients, the imaging of eight (23%) was delayed, and the biopsies of four (12%) patients were delayed for a month. Only five (14%) of the 35 patients reported visiting the clinic late, and none stated that the start of their oncology treatment was delayed.

Table I: Characteristics of 90 patients who answered the questionnaire

	New diagnosed, n=35 (%)	Under treatment, n=55 (%)
Gender		
Male	26 (74)	26 (47)
Female	9 (26)	29 (53)
Age		
Median (range)	12 (1-19)	11 (0.5-18)
Primary diagnosis		
Ewing's Sarcoma		14 (25)
Neuroblastoma	2 (6)	8 (15)
Hodgkin's Lymphoma	6 (17)	7 (13)
CNS Tumors	2 (6)	7 (13)
Soft tissue sarcoma	6 (17)	6 (11)
Non-Hodgkin's Lymphoma	8 (23)	4 (7)
Osteosarcoma	5 (14)	3 (5)
Other	6 (17)	6 (11)
Symptom of COVID-19		
No	28 (80)	43 (78)
Yes	7 (20)	12 (22)
COVID-19 positive		
No	28 (80)	44 (80)
Yes	7 (20)	11 (20)
Diagnosis delay/CT delay		
No	22 (62)	46 (84)
Yes	13 (38)	9 (16)
Telemedicine use		
No	15 (43)	16 (35)
Yes	20 (57)	36 (65)

CNS: *Central nervous system,* ***CT:*** *Chemotherapy*

One adolescent male patient with a vertebral fracture whose complaints included inability to walk and urinary incontinence was not admitted to the hospital as his respiratory symptoms suggested COVID-19, but was admitted to our clinic after lockdown was lifted with paraplegia, and was diagnosed with advanced stage rhabdomyosarcoma metastatic to both the lungs and bones. A Somalian male patient had been diagnosed with nasopharyngeal carcinoma in his hometown, but was not treated, and could travel to Türkiye only 6 months after his complaints started due to the travel restrictions in place. He was critically ill at the time of admission due to advanced-stage metastatic disease and respiratory failure and died in the 10th month of hospitalization.

Delayed cancer treatment due to COVID-19

Of the 55 patients whose chemotherapy treatments were continuing, nine delayed their hospital treatments due to a fear

Table II: Characteristics of patients with COVID-19

	n=58 (%)
Median age (range)(years)	12 (1-18)
Sex	
Male	33 (57)
Female	25(43)
Underlying cancer	
Bone tumors	15 (26)
Lymphomas (HL, NHL)	12 (22)
Brain tumors	11 (19)
Neuroblastoma	8 (14)
Other tumors	11 (19)
Disease status	
Active disease	52 (90)
Undergoing treatment but in remission	6 (10)
Diagnosis	
PCR, clinic positivity	30 (52)
PCR, screening before procedures and admission	28 (48)
Contact history	12 (21)
Symptoms and findings	
Fever	25 (45)
Cough	8 (15)
Dyspnea	4 (7)
Disease severity	
Asymptomatic	27 (47)
Mild	25 (43)
Moderate	3 (5)
Severe	3 (5)
Length of PCR positivity (median, range) (days)	15 (3-75)
Outcome	
Recovery	55 (95)
Death	3 (5)

HL: *Hodgkin's Lymphoma,* ***NHL:*** *Non-Hodgkin's Lymphoma,* ***PCR:*** *Polymerase chain reaction*

of exposure to COVID-19 in six patients and COVID-19 infection in the family in the three other patients. The median duration of delay in these 55 patients was 15 days (10–60 days).

All but two patients had undergone antineoplastic treatment within the last month. A patient with nasopharyngeal carcinoma and one with anaplastic large cell lymphoma tested positive for COVID-19 immediately after diagnosis before starting their chemotherapy treatment. Since the clinical course of the COVID-19 infection could not be followed in these two patients, their chemotherapies were begun only after a negative PCR test.

The primary surgery of one adolescent boy with Ewing sarcoma with no COVID-19 diagnosis was delayed for 2 months due to the restrictions in place within the surgical departments, and his tumor progressed.

A female patient with chromosome breakage syndrome and three different cancers (Wilms tumor, high-grade glioma and hepatocellular carcinoma) tested positive in a PCR test for COVID-19 in the first month of her allogenic stem cell transplantation treatment, and recovered within two weeks with mild symptoms and without specific antiviral therapy, but died 4 months later from brain metastasis.

A male Somalian patient with advanced-stage nasopharyngeal carcinoma whose COVID-19 PCR positivity persisted for 2.5 months underwent a single course of chemotherapy during the PCR test positivity period as his clinical condition was good except for a fever lasting for 3 days. No complications other than neutropenic fever developed after chemotherapy, but the patient ultimately died due to progressive cancer.

Patients who contracted COVID-19

During the first 2 years of the pandemic, 58 patients with cancer in the present study contracted COVID-19, the characteristics of whom are presented in Table II. At the time of their COVID-19 diagnosis, 53 patients were receiving intravenous chemotherapy, two patients were receiving maintenance therapy (T-lymphoblastic lymphoma and neuroblastoma), one patient was receiving radiotherapy and two patients were receiving targeted therapy (Sorafenib). The chemotherapy courses were continued during active infection in four (7%) patients, but were interrupted in the other patients. The median duration of PCR positivity was 14 (3–75) days, 29 patients (50%) were symptomatic, with the most common symptoms being fever (86%) and cough (30%), and 21 (36%) of the patients required hospitalization for reasons other than COVID-19, primarily febrile neutropenia. None of the patients received COVID-19-directed therapy. Of the 58 patients who contracted COVID-19, four (7%) required intensive care, due to diffuse lung metastasis of osteosarcoma in one and extensive lung involvement of Langerhans cell histiocytosis in another, in both of whom COVID-19 aggravated the pulmonary findings, while one required intensive care due to progressive glioma and another due to progressive nasopharyngeal carcinoma, both of whom were identified with severe pulmonary involvement due to COVID-19. Aside from the patient with osteosarcoma, no intubation was required in these patients.

All of the COVID-19-positive patients had relatively mild disease, with almost 90% being hospitalized for the close monitoring of chemotherapy complications, and all but three recovered without complications. The patient with progressive osteosarcoma and diffuse lung metastases tested positive on day one of their treatment for respiratory distress in the intensive care unit, and died on the second day. In the other two patients who died, the cause of death was not COVID-19 but the progression of their primary cancer.

Of the 90 patients, 56 (62%) reported receiving their blood and radiological test results through telemedicine. Only five patients opted to undergo chemotherapy in their home town rather than coming to Ankara.

DISCUSSION

It was found in the present study that the COVID-19 pandemic had led newly diagnosed cancer patients and their families to ignore serious complaints and to delay presentation to the hospital, and further, that the treatments of patients undergoing chemotherapy were sometimes delayed by COVID-19 infections, either in the patient or a family member, and the restrictions in place.

Restrictions on access to healthcare and delays in cancer diagnoses due to COVID-19 have been reported in various studies to date, affecting both children and adults (6-11). More specifically, there have been case series published reporting diagnosis and treatment delays in pediatric solid tumors due to the COVID-19 pandemic. In one such series, Offenbacher et al. reported that diagnoses of pediatric solid tumors have decreased during the COVID-19 pandemic, and patients tend to be admitted with more advanced stages of the disease.(12) Dvori et al. reported on 17 pediatric patients with solid tumors whose diagnosis and treatment for cancer were delayed by up to 8 months (13). The findings of these studies suggest that the detrimental effects of delaying the diagnosis and treatment of cancer may actually outweigh the risks associated with the COVID-19 pandemic.

In Türkiye, the first case of COVID-19 was reported on March 11, 2020, after which the number of reported cases and deaths witnessed a rapid increase. At the beginning of April 2020, strict restrictions on hospital visits and travel were imposed by the Turkish government, instilling a state of panic in the public, and leading to a reluctance to attend hospitals. Furthermore, many hospitals adopted a policy of not accepting patients with mild symptoms, and patients were advised not to come to the hospital unless absolutely necessary, although whether such restrictions would lead to a delay in the diagnosis of cancer patients was raised as a matter of concern.

Our results reveal that around one-third of parents delayed presenting to hospital with their children, even after they developed severe symptoms. One of the most striking examples of this involved a female patient with widespread metastatic osteosarcoma and with giant masses and severe pain in her leg whose family delayed visiting a doctor for 2 months for fear of infection. Another such example involved a young male patient with rhabdomyosarcoma who did not complete the last three cycles of chemotherapy, and who subsequently presented with severe neurological deficits and brain metastases in the third month of the pandemic and was started on radio-chemotherapy as a matter of urgency. We believe that the progression of the disease to an advanced stage or recurrence can certainly be attributed to such delays by parents. The median delay time in our series was 30 days (10–150), and most delays were due to the parents' concerns. One of the patients whose diagnosis was delayed was from Somalia while the other three were Syrian, which reflects the general patient composition of our hospital, which frequently accepts foreign patients and refugees.

The results of this study reveal that the fear of exposure to COVID-19 among families and the limited access to healthcare services led to significant delays in the diagnosis and treatment of cancer. In a nationwide study from Türkiye, delays in diagnosis and treatment were reported in 62.7% of patients, with a median delay of 15 (3–45) days (14). In one study, eight patients with hematological malignancies were reported to present to hospital 21–45 days after the first appearance of symptoms (9) In a study involving 12 patients by Lazzerini et al. (15), one of the two acute leukemia patients in the series was admitted to the emergency department after 7 days of high fever, while the other presented with severe anemia and respiratory distress. Of the 12 patients in the study, four ultimately died, and all 12 parents reported avoiding the hospital for fear of infection, similar to those in the present study.

In an international Pediatric Oncology East and Mediterranean (POEM) group study of 34 healthcare facilities in 19 countries, including three centers in Türkiye, restrictions on the acceptance of new pediatric oncology patients were reported by eight centers and delays in chemotherapy by 10 centers (16). The study also reported that 91% of the participating centers had placed restrictions on off-treatment visits, which was similar to the policy applied in our center, where long-term restrictions were applied to off-treatment visits to minimize their number. In contrast, most of the patients whose treatment had recently been completed continued to attend routine check-ups. As the pediatric hematology oncology clinic with the largest bed capacity in Europe, we continued to accept a large number of patients during the COVID-19 pandemic, including new oncology patients, unlike in other hospitals, and applied strict measures to reduce the spread of infections, such as allowing only one patient in each room, limiting parental access to pediatric wards to 1 parent only, and restricting changes in caregivers. Face masks were mandatory for all patients, caregivers and hospital staff, elevators were assigned for exclusive use by pediatric oncology staff and the playroom was closed. Outpatients were encouraged to use telemedicine to obtain the results of blood tests to reduce the number of people waiting, and 56 (62%) of the patients used telemedicine effectively. Patients whose treatments had been completed were advised to postpone routine check-ups unless they had any specific complaints, which led to a significant decrease in the number of patients in the outpatient clinic. No modifications were made to treatment doses or durations, and all myelosuppressive treatments were continued as planned. We also maintained tumor boards through teleconferencing.

In the present study, a high level of chemotherapy compliance (82%) was observed in patients whose treatments were continuing, and nearly all chemotherapy delays were due to COVID-19 infections. The treatment of only one case was discontinued for two weeks due to their contact with a COVID-

19-positive family member. Beypinar et al. (17) reported that in 108 adult cancer patients, delays in treatment for no reason during the COVID-19 pandemic were significantly higher than during the pre-COVID-19 period, with 51% of patients delaying their treatment without reason, although none had contracted a COVID-19 infection. In a study by Kebudi et al. (18) in Türkiye, chemotherapy was interrupted in 32 of 51 children with cancer and stem cell recipients with positive COVID-19 test results, with a median delay of 15 days reported. We believe this difference between pediatric and adult patients to be due to the fact that the treatment of children is under the control of their parents. Furthermore, the fact that cancer patients and their parents were already accustomed to such precautions as the use of masks, hygiene and social distancing during chemotherapy may have made it easier for them to adapt to the requirements of the pandemic.

While there were few studies published related to COVID-19 in pediatric cancer patients prior to mid-2020, this situation changed rapidly in the following months. In a study from China involving 171 children with COVID-19, it was reported that the disease had a milder prognosis in children than in adults (5). Among these patients, the single case with leukemia was one of only three patients in the entire group requiring mechanical ventilation support. In a study conducted in Italy, five pediatric cancer patients were reported with COVID-19, all of whom had mild symptoms and self-limited disease (19). The reason for the mild course of the disease in immunosuppressed children is still unknown. The mild course of COVID-19 in 58 patients in our study group is consistent with the findings of existing literature, and the deaths of all three patients who died were not attributable to COVID-19, but to the progression of the tumor. Our data show that among the children with no significant concomitant disease other than cancer, COVID-19 did not have serious consequences, and it was shown that myelosuppressive treatments can be continued in asymptomatic patients with careful, patient-specific evaluation.

Our study has several limitations, the most important of which are its retrospective design and the limited number of cases. Due to the small number of COVID-19-positive patients, it is difficult to comment on the course of the infection in pediatric oncology patients, so large prospective studies are needed. Furthermore, we did not have the opportunity to determine whether the delays in diagnosis were attributable to a fear of viral infection or a denial of symptoms. The majority of the patients in the study were from outside Ankara, and some had even come from abroad for treatment. Although the distance to our center from their home town may have affected the results, there is insufficient data to measure any influence on the results. Despite these limitations, we believe that the presented results contribute to literature by showing the social and physical effects of the COVID-19 pandemic on pediatric oncology patients and their parents and health professionals, while also providing information about the course of COVID-19 in immunosuppressed children undergoing chemotherapy.

CONCLUSION

The restrictions applied during the pandemic led to delays in the diagnosis and treatment of pediatric solid tumors. Delays in the diagnosis of cancer can be far more costly than the consequences of COVID-19 infection, as the disease may progress beyond a stage that can be cured in some patients. The continuation of the anticancer treatments of pediatric cancer patients who contract COVID-19 should be considered based on an evaluation of the clinical status of the patient.

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