Cerrahpaşa Med J 2023; 47(3): 318-321 ORIGINAL ARTICLE

The Investigation of Symptoms and Therapy Delay in Children with Cancer During the Coronavirus 2019 Pandemic: A Single-Center Experience

Yasin Yilmaz, Gülşah Tanyildiz, Sifa Sahin, Cansu Ceren Eryilmaz, Mustafa Bilici, Serap Karaman, Deniz Tugcu, Aysegul Unuvar, Zeynep Karakas

Division of Pediatric Hematology and Oncology, Department of Pediatrics, Istanbul University Istanbul Faculty of Medicine, İstanbul, Turkey

Cite this article as: Yilmaz Y, Tanyildiz G, Sahin S, et al. The investigation of symptoms and therapy delay in children with cancer during the coronavirus 2019 pandemic: A single-center experience. *Cerrahpaşa Med J.* 2023;47(3):318-321.

Abstract

Objective: The coronavirus 2019 pandemic had a worldwide effect on people as well as on pediatric patients with cancer. This effect also caused cancer therapy plan alterations. In this study, we aimed to investigate pediatric patients with cancer who were diagnosed as having coronavirus 2019 infections and the alterations in treatment plans.

Methods: Pediatric patients with cancer who were followed up in Istanbul Medical Faculty Pediatric Hematology and Oncology Outpatient Clinic and were diagnosed as having coronavirus 2019 between March 2020 and March 2022 were retrospectively analyzed.

Results: A total of 28 patients were diagnosed as having a coronavirus 2019 infection. Forty-three percent of the patients had leukemia, and 57% had solid tumors. More than half (58%) of the patients had mild coronavirus 2019 symptoms. Sixteen (57%) patients had a therapy delay because of coronavirus 2019 infections. The mean therapy delay day was 5.8 ± 2.9 (median: 5 days). Hematologic malignancy (leukemia) had a delay rate of 33% in therapy, and it was 75% in solid tumors.

Conclusion: The coronavirus 2019 pandemic affected all people as well as pediatric patients with cancer. The rate of delay in therapy was 57% in our overall pediatric cancer population. The prevention of patients against virus, vaccination of parents, and review of therapy plans might be scheduled in cancer centers.

Keywords: COVID-19 pandemic, cancer, pediatric patients, therapy delay

Introduction

People all over the world have been affected by the coronavirus 2019 (COVID-19) pandemic, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It started in China in December 2019 and was accepted as a pandemic by the World Health Organization (WHO) in March 2020.[2] According to data reported by the WHO on October 24, 2022, there have been 624 235 272 confirmed cases of COVID-19, including 6 555 270 deaths. As of October 18, 2022, a total of 12 814 704 622 vaccine doses have been administered.[3]

The pandemic affected healthy people and patients alike. It caused a crisis in daily life and all societies.[4] From nutrition to mental health, all medicine and social science areas developed programs against the pandemic.[5] One of the most vulnerable groups, pediatric patients with cancer, was also adversely affected by the pandemic. Some published papers revealed that pediatric patients were less affected than adult patients.[6] On the other hand, their underlying disease put them at severe risk. A large cancer study showed that patients with hematologic cancer, lung cancer, or metastatic cancer had severe outcomes during the pandemic.[7]

Another important issue is therapy delay in patients with cancer. Studies related to therapy delay (chemotherapy, surgery, radiotherapy, and transplant) reported up to 70% of therapy delay rate.[8] A national study showed a median of 14 days in treatment delays.[9] In this study, we aimed to investigate the severity of COVID-19 symptoms and therapy delay in pediatric hematology and oncology patients in a university hospital in Turkey.

Received: January 24, 2023 **Accepted:** March 27, 2023
Publication Date: November 30, 2023
Corresponding author: Yasin Yilmaz, Division of Pediatric Hematology and Oncology, Department of Pediatrics, Istanbul University Istanbul Faculty of Medicine, İstanbul, Turkey
e-mail: dryasinyilmaz@gmail.com
DOI: 10.5152/cjm.2023.23008

Methods

Participants

Thirty-two pediatric cancer patients from Istanbul Faculty of Medicine Pediatric Hematology and Oncology Clinic had COVID-19 infections. As 4 of them were reinfected with the virus, we only recruited the rest of them into study. Thus, 28 patients were enrolled in the study; 6 were girls. The mean age of the patients was 9.2 ± 5.6 years. The patients were divided into diagnosis groups: 43% had leukemia and the others had solid tumors [11% had lymphoma, 7% had central nervous system (CNS) tumors, and 39% had other cancer types (neuroblastoma, bone tumors, soft tissue tumors, Wilms tumor, and hepatoblastoma)] (Table 1).

Thirty-nine percent of patients received radiotherapy, 39% underwent surgery, and all patients received chemotherapy. More

Table 1. Sociodemographic and Clinical Data of Patients

Characteristics	Value
Gender (female/male)	6/22
Age (mean ± SD)	9.2 ± 5.6 years
Age of diagnosis (mean ± SD)	6.7 ± 5.2 years
Disease duration (mean ± SD)	2.5 ± 3.3 years
Diagnosis	
Leukemia	(n = 12) 43%
Lymphoma	(n = 3) 11%
CNS tumor	(n = 2) 7%
Other solid Tm	(n = 11) 39%
Disease status	
Remission	(n = 15) 54%
Partial remission	(n = 6) 21%
Progression	(n = 2) 7%
Relapsed	(n = 5) 18%
COVID-19 Symptom Severity	
Asymptomatic	(n = 5) 18%
Mild	(n = 16) 58%
Moderate	(n = 3) 11%
Severe	(n = 1) 4%
Critical	(n = 3) 11%

COVID-19, coronavirus 2019.

than half (54%) of the patients were in remission, 21% were in partial remission, 7% were in progression according to each chemotherapy protocol guidelines, and 18% of them relapsed.

Ethical Approval

Ethical approval for the study was obtained from the local ethics board (2020/971). Informed consent was obtained from all patients.

Statistics

The Statistical Package for Social Sciences version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) program was used for statistical analysis. A descriptive analysis of quantitative variables was performed. For the evaluation of categorical variables, the Chi-square test was performed. The Mann–Whitney *U*-test was used to make comparisons between 2 groups of variables. Spearman analysis was performed for correlations. A *P* value of < .05 was considered significant.

Results

Twenty-eight children with cancer were infected with the COVID-19 virus. More than half (58%) of the patients had mild COVID symptoms. The mean age of cancer diagnosis was 6.7 ± 5.2 years and the mean duration of disease was 2.5 ± 3.3 years (Table 1).

One in 5 patients (18%) was asymptomatic, more than half of patients (58%) had mild symptoms, 11% had moderate symptoms, 4% had severe symptoms, and 11% had critical (intensive care unit need) symptoms according to COVID-19 severity criteria (Dong et al. 2020). The vaccination rate among the parents was 77% for mothers and 82% for fathers.

Laboratory tests were performed on the first day of COVID-19 infection. The median level of white blood cells was 5400/mm^3, for neutrophils it was 4200/mm^3, lymphocytes were 850/mm^3, hemoglobin was 10.9 g/dL, platelets was 264.500/mm^3, immunoglobulin G was 537, C-reactive protein (CRP) was 6.0 mg/L, procalcitonin was 0.1 ng/mL, D-dimer was 457 mcq/L, fibrinogen was 319 mg/dL, and ferritin was 256 ng/mL.

There were 16 patients (57%) whose therapy was postponed due to COVID-19 infection. The mean therapy delay day was 5.8 ± 2.9 (min 2-max 12; median 5) days. The therapy delay duration did not differ between leukemia and solid tumors. Hematologic malignancy (leukemia) had a 33% rate of delay in therapy, whereas it was 75% in solid tumors (P = .02). The therapy delay rate was 54% in the mild/moderate COVID symptoms group, whereas it was 75% in the severe/critical group (P = .43) (Table 2).

The chemotherapy delay duration was significantly correlated with serum ferritin level levels (P = .004, r = 0.65). By contrast, the relationship between thrombocyte levels and chemotherapy delay duration was negatively significant (P = .04, r = −0.45). Delay duration was not correlated with age, age at diagnosis, and disease duration.

The median chemotherapy delay duration was 6 days in patients who underwent surgery, whereas it was 4 days in patients who did not undergo surgery (P = .35). The median chemotherapy delay duration was 4 days in the remission group (remission plus partial remission) and 5 days in the progressive group (progression plus relapsed) (P = .78). Two patients relapsed after COVID infection, and the mean duration between infection and relapse was 93 (median 93) days. Both of these patients had leukemia.

Table 2. Therapy Delay According to Clinical Characteristics

Characteristics (n = 16)	Delay Ratio	χ^2 and P of (delay ratio)	Delay in Days (Median)	P of (Delay in Days)
Malignancy		χ^2 = 4.8, P = .02		P = .85
Leukemia (n = 4)	33%		5 days	
Solid tumor (n = 12)	75%		5 days	
Disease status		χ^2 = 0.7, P = .37		P = .78
Remission/partial remission (n = 13)	62%		4 days	
Progression/relapsed (n = 3)	43%		5 days	
COVID-19 symptom severity		χ^2 = 0.6, P = .43		P = .58
Mild/moderate (n = 13)	54%		5 days	
Severe/critical (n = 3)	75%		4 days	

Discussion

The COVID-19 pandemic affected children with cancer, and many infected patients in the world did not receive chemotherapy or radiotherapy because of uncertainty. Most cancer institutions and experts tried to establish algorithms for guidance on decisions about reconstructing cancer therapy.[10-13] These algorithms and triage were mainly based on unexpected mortality and morbidity rates of patients with cancer during the pandemic.[14,15] Therefore, studies and analyses from all over the world suggested that intentional delaying of chemotherapy for stable cancer should be considered until any significant COVID symptoms had resolved.[13,16,17]

In this study, we retrospectively investigated the COVID symptoms and pandemic-related therapy delay in children with cancer. More than half (58%) of the patients had mild COVID symptoms (fever, cough, sore throat, runny nose, and sneezing). The chemotherapy of more than half (57%) of the patients was postponed because of COVID-19 infection. The mean therapy delay was 5.8 (median: 8) days. Children with leukemia had a 33% rate of delay in therapy, whereas it was 75% in those with solid tumors.

There are several papers about therapy delays in patients with cancer. Madhusoodhan et al[8] investigated children with cancer during the pandemic, showing that almost half of all patients (45%) had mild COVID symptoms. Similar to our results, 67% of patients had postponed therapy during COVID infection. Their[8] study included 13 institutions, and they revealed that 54% of institutions reported delays in chemotherapy, 46% delays in surgery, and 30% delays in transplants.

WęcławekTompol et al[9] investigated the impact of COVID-19 on pediatric patients with cancer. They found that 58% of patients had delayed chemotherapy due to COVID-19 infections. Moreover, they indicated that the median therapy interruption was 14 days. Santoro et al[18] retrospectively analyzed cancer surgery delays globally. They emphasized that 70% of reported cases had cancer surgery delays. The delay was 5 to 8 weeks longer compared with pre-pandemic era.

During the pandemic, large registries were established and tried to provide the necessary documents and reports about COVID-19 infections for children with cancer. One was the Pediatric Oncology COVID-19 Case Report (POCC)[19] and another is the Global Registry (Global Registry of COVID-19 in Pediatric Cancer) (Global 2022) founded by St. Jude Children's Research Hospital and International Society of Paediatric Oncology (SIOP).[20] According to their actual data, POCC reported that chemotherapy was delayed in 37% of patients with hematologic malignancies and 25% of patients with solid tumors. The Global Registry reported a delay of chemotherapy in 38.9% of patients. Children with cancer mostly had mild COVID symptoms (38.2%) according to data from the Global Registry. The POCC data showed that the chemotherapy delay rate was 37% in September 2022, whereas it was 50% in December 2020.

A prospective cohort study conducted by Mullangi et al[21] investigated therapy delays in adult patients with cancer. They found rates of 46% in chemotherapy delays, 47% for radiotherapy delays, and 71% for surgery delays. This study was performed in 60 academic and community medical practices in the United States of America. The rates of therapy delay were highly increased in the surgery plan. Hematological malignancy and metastatic disease were associated with chemotherapy delays. Hammad et al[22] revealed a rate of 59% of chemotherapy delays in pediatric patients with cancer. The median chemotherapy delay was 21 days. Another study[23] showed a rate of 40% therapy delays in pediatric oncology patients.

Conclusion

In this study, we investigated the impact of COVID-19 infections on the treatment plans of pediatric patients with cancer. Our results were similar to or slightly higher than the literature. When new data about the advantages and disadvantages of chemotherapy during COVID were released, centers were more encouraged to give anticancer therapy. After March 2022, when our COVID registry closed, we also minimized the therapy delay algorithms. Vaccination of parents might be more emphasized during a pandemic. Although the COVID pandemic gradually loses its efficiency on population, more studies on infectious disease outbreaks and cancer treatment are needed for further treatment plans.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Istanbul University Istanbul Medical Faculty (Approval no: 971, Date: 17/07/2020).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.Y., G.T.; Design – Y.Y., G.T.; Supervision – Z.K.; Resources – S.S., C.C.E., M.B.; Materials – C.C.E., M.B.; Data Collection and/or Processing – Y.Y., C.C.E., S.S., M.B.; Analysis and/or Interpretation – Y.Y., S.K.; Literature Search – A.U., D.T.; Writing Manuscript – Y.Y., G.T.; Critical Review – D.T., A.U., Z.K., S.K.

Acknowledgement: We thank Mr. David Chapman for the very kind revision of our manuscript in terms of English language.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

1. Chams N, Chams S, Badran R, et al. COVID-19: a multidisciplinary review. *Front Public Health*. 2020;8:383. [CrossRef]
2. Du Z, Wang L, Cauchemez S, et al. Risk for transportation of coronavirus disease from Wuhan to other cities in China. *Emerg Infect Dis*. 2020;26(5):1049-1052. [CrossRef]
3. World Health Organization. *Coronavirus (COVID-19) Dashboard*. Available at: https://cOVID19.who.int (last available 25.10.2022).
4. Ataman K. From risk society to crisis society: impact of COVID-19 pandemic on our lives. *J Adv Res Health Sci*. 2021;4(suppl1): 105-111.
5. Onyeaka H, Anumudu CK, Al-Sharify ZT, Egele-Godswill E, Mbaegbu P. COVID-19 pandemic: a review of the global lockdown and its far-reaching effects. *Sci Prog*. 2021;104(2):368504211019854. [CrossRef]
6. Bellino S, Punzo O, Rota MC, et al. COVID-19 disease severity risk factors for pediatric patients in Italy. *Pediatrics*. 2020;146(4): e2020009399. [CrossRef]
7. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov*. 2020;10(6):783-791. [CrossRef]
8. Madhusoodhan PP, Pierro J, Musante J, et al. Characterization of COVID-19 disease in pediatric oncology patients: the New York-New Jersey regional experience. *Pediatr Blood Cancer*. 2021;68(3):e28843. [CrossRef]
9. Węcławek-Tompol J, Zakrzewska Z, Gryniewicz-Kwiatkowska O, et al. COVID-19 in pediatric patients with cancer is associated with treatment interruptions but not with short-term mortality: a Polish national study. *J Hematol Oncol*. 2021;14(1):163. [CrossRef]
10. Kebudi R. COVID-19 pandemia: global consequences for oncology. *J Adv Res Health Sci*. 2020;3(suppl1):99-105.
11. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP,

COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. *Pediatr Blood Cancer*. 2020;67(7):e28409. [CrossRef]
12. Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: cancer care in the time of COVID-19. *Ann Intern Med*. 2020;172(11):756-758. [CrossRef]
13. National Institute for Health and Care Excellence. COVID-19 rapid guidelines: delivery of systemic anticancer treatments. *National Institute for Health and Care Excellence* 2020. https://www.nice.org.uk/guidance/ng161/resources/cOVID19-rapidguideline-delivery-of-systemic-anticancer-treatmentspdf-66141895710661 Accessed November 5, 2022.
14. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907-1918. [CrossRef]
15. Al-Quteimat OM, Amer AM. The impact of the COVID-19 pandemic on cancer patients. *Am J Clin Oncol*. 2020;43(6):452-455. [CrossRef]
16. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337. [CrossRef]
17. Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. *Nat Cancer*. 2020;1(6):565-567. [CrossRef]
18. Santoro GA, Grossi U, Murad-Regadas S, et al. DElayed COloRectal cancer care during COVID-19 Pandemic (DECOR-19): global perspective from an international survey. *Surgery*. 2021;169(4):796-807. [CrossRef]
19. Johnston EE, Levine J, Kahn A, et al. Reports & updates - institute for cancer outcomes and survivorship | UAB [internet]. The POCC report: the pediatric oncology COVID-19 case report; 2022. Available at: https://www.uab.edu/medicine/icos/icos-research/the-pocc-report/reports-updates.
20. COVID-19 and childhood cancer registry [internet]. *St. Jude Global*. Available at: https://global.stjude.org/en-us/global-cOVID-19observatory-and-resource-center-for-childhood-cancer/registry.html.
21. Mullangi S, Aviki EM, Chen Y, Robson M, Hershman DL. Factors associated with cancer treatment delay among patients diagnosed with COVID-19. *JAMA Netw Open*. 2022;5(7):e2224296. [CrossRef]
22. Hammad M, Shalaby L, Sidhom I, et al. Management and Outcome of coronavirus disease 2019 (COVID-19) in Pediatric patients with cancer: a Single Centre Experience from a Developing country. *Clin Lymphoma Myeloma Leuk*. 2021;21(11):e853-e864. [CrossRef]
23. Raza MR, Maqsood S, Rana ZA, et al. Impact of COVID-19 on the children with cancer in six pediatric oncology units (POUs) of Pakistan-A multi-center study. *Cancer Investig*. 2022;40(5):401-405. [CrossRef]