COVID-19 infection in pediatric patients treated for cancer

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Abstract

Background COVID-19, the novel coronavirus, has caused a global pandemic affecting millions of people around the world. Risk factors for critical disease in adults are advanced age and underlying medical comorbidities, including cancer. Data are sparse on the effect of COVID-19 infection on pediatric patients with cancer during their active antineoplastic therapy. The optimal management of antineoplastic treatment during COVID-19 infection in this unique population is controversial.

Aim To describe the severity and clinical course of COVID-19 infection in pediatric patients with cancer during active antineoplastic treatment and to study their course of treatment.

Methods Clinical and laboratory data were collected from medical files of patients diagnosed with COVID-19, confirmed by polymerase chain reaction (PCR), who received active antineoplastic treatment between March 2020 and May 2021 in a large tertiary pediatric medical center.

Results Eighteen patients with diverse pediatric cancers are described. They were infected with COVID-19 at different stages of their antineoplastic treatment regimen. Eight had an asymptomatic COVID-19 infection, nine had mild symptoms, and one had severe disease. All of them recovered from COVID-19 infection. Two patients experienced delays in their antineoplastic treatment; none of the other patients had delays or interruptions, including patients who were symptomatic for COVID-19.

Conclusion In pediatric patients with cancer who test positive for COVID-19, yet are asymptomatic or have mild symptoms, the continuance of antineoplastic therapy may be considered.

Keywords COVID-19 · Pediatric patients · Cancer · Antineoplastic therapy

Introduction

At the end of 2019, a novel coronavirus (COVID-19) was identified as the cause of a cluster of respiratory diseases resulting in an epidemic throughout the world. The virus is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection, through mild respiratory symptoms to severe disease, presenting with dyspnea and hypoxia, and a potential deterioration to respiratory failure, shock, multi-organ dysfunction, and fatal illness [2]. The most critical or fatal disease occurs predominantly in hospitalized adults with advanced age or with certain underlying medical comorbidities including cancer [3–6]. Adult oncological patients infected with COVID-19 often have severe disease [7–9]. However, in pediatric patients with cancer, the impact of chemotherapy administration at the time of COVID-19 infection is yet to be determined. Due to their immunocompromised state, children undergoing cancer-directed therapy have been surmised to be at a higher risk for COVID-19-associated complications and fatalities; however, data to support this are lacking [10].

Here, we present a series of eighteen pediatric patients with COVID-19 infection during active antineoplastic treatment for diverse diagnoses in a tertiary medical center in Israel. Our data suggest that chemotherapy may be compatible with COVID-19 infection in pediatric oncology patients.
**Methods**

We surveyed all pediatric patients treated for cancer from March 2020 to May 2021 in the largest tertiary pediatric medical center in Israel. The diagnosis of SARS-CoV-2 was based on a positive polymerase chain reaction (PCR) test from a nasopharyngeal swab, regardless of symptoms. Of note, in accordance with institutional policy, all admitted patients were routinely tested for SARS-CoV-2 during this period, regardless of the reason for their hospitalization. Data were collected from patients’ medical files, including clinical and laboratory parameters. COVID-19 was categorized according to the US National Institutes of Health (NIH) classification severity index: asymptomatic, mild, moderate, or severe disease [11].

The study protocol was approved by our institutional review board (0914–20-RMS).

**Results**

Eighteen pediatric patients with cancer who tested positive for SARS-CoV-2 were admitted for antineoplastic treatment during the study period: eight females and ten males. They represent 6.4(424,438),(511,450)% of the 280 children who were newly diagnosed and treated for cancer in our medical center during the 14-month study period. The median age at SARS-CoV-2 diagnosis was 11.7 years (range 1.8–18 years) (Table 1). The most common underlying malignancy was acute lymphoblastic leukemia (n = 10; 56%). Other underlying malignancies included Burkitt lymphoma (n = 2), low-grade glioma (n = 2), Hodgkin lymphoma (n = 1), Ewing sarcoma (n = 1), high-grade glioma (n = 1), and Langerhans cell histiocytosis (n = 1). Twelve patients were diagnosed with COVID-19 while receiving intravenous chemotherapy (one was also receiving radiotherapy), four were diagnosed during maintenance therapy for acute lymphoblastic leukemia (oral methotrexate/mercaptopurine), one patient was diagnosed while receiving combined oral chemotherapy and biological agents (BRAF inhibitors) and one patient was receiving radiotherapy only (Table 1). None of the patients had received the SARS-CoV-2 vaccine, which had not yet been approved for the pediatric population at the time of our study.

COVID-19 infection was classified as asymptomatic in eight patients (44%) and mild in nine (50%); only one patient had severe disease, with a severe respiratory presentation (described below). Presenting symptoms included fever in six patients (33%) and rhinorrhea in three (17%); Only one patient had significant respiratory distress secondary to COVID-19 infection; all the other patients had normal oxygen saturations and did not require oxygen support.

All the patients were admitted to isolated rooms designated for the treatment of COVID-19 patients. The median length of hospital stay was three days (range 1–40). The duration of hospitalization was not extended for any of the patients due to the COVID19- infection; the patients remained in the hospital as required for the administration of their chemotherapeutic regimens. Three patients were treated with antibiotics due to fever at presentation, discontinued upon receiving negative culture results (Table 1). Six patients were not admitted to the hospital and continued treatment as outpatients. None of the patients received COVID-19-specific therapy. The median duration of COVID-19 PCR positivity among hospitalized patients was 40 days (range 9–130 days). None of the patients experienced antineoplastic treatment delays due to COVID-19 infection.

A negative correlation was demonstrated between lymphocyte counts and the duration of COVID-19 PCR positivity, with a trend towards statistical significance. The mean lymphocyte count of 11 patients, treated with active intravenous chemotherapy, was 0.66 ± 0.48 × 10^9/L and the meantime to negative PCR was 52 ± 42.6 days. This compared to 1.44 ± 1.16 × 10^9/L and 21.9 ± 7.6 days for those who received oral chemotherapy or other treatment (P = 0.085) (Fig. 1).

The single incidence of severe COVID-19 occurred in a 15-year-old female (patient number 13, Table 1). She was admitted to the intensive care unit with shortness of breath and low blood pressure. Emergency electrocardiogram and echocardiography performed in the resuscitation room upon arrival demonstrated severe pericardial and pleural effusion. Emergency pericardiocentesis was performed, with drainage of 900 ml of serous fluid and immediate clinical improvement. COVID-19 infection was diagnosed following routine PCR examination at admission. Abdominal and chest CT scan demonstrated a mediastinal mass with superior vena cava syndrome, main bronchus stenosis, and pericardial effusion. Pericardial effusion analysis established a diagnosis of Burkitt lymphoma. When stabilized, the patient was transferred to a department dedicated to treating patients with COVID-19, where she received two cycles of induction chemotherapy (based on Inter-B-NHL Ritux 2010 protocol [12], NCT01516580) and remained an inpatient for 40 days. During her hospital stay, she was respiratory stable; her lowest saturation index was 94%, with no need of oxygen support. Her COVID-19 infection was classified as severe due to severe grunting and dyspnea upon admission. Throughout her hospitalization, she remained COVID-19 positive, as confirmed by both PCR and cell culture.
| Patient | Sex (M/F) | Age (years) | Underlying malignancy | Phase of antineoplastic therapy | Length of admission (days) | Time to negative COVID PCR (days) | COVID-19 severity* | Symptoms | Lowest \(O_2\) saturation (%) | Effect of COVID-19 infection on therapeutic continuum |
|---------|-----------|-------------|------------------------|---------------------------------|---------------------------|----------------------------------|-------------------|----------|-----------------------------|-----------------------------------------------|
| 1       | F         | 5.5         | ALL                    | Consolidation (AIEOP—BFM 2017, NCT03643276) | 5                          | 9                                | Asymptomatic      | None     | 100                          | None                                          |
| 2       | F         | 12.5        | ALL                    | Consolidation (AIEOP—BFM 2017, NCT03643276) | 3                          | 61                               | Asymptomatic      | None     | 98                          | None                                          |
| 3       | M         | 16          | ALL                    | Consolidation (AIEOP—BFM 2017, NCT03643276) | 5                          | 130                              | Asymptomatic      | None     | 99                          | None                                          |
| 4       | M         | 9.4         | ALL                    | Maintenance (AIEOP—BFM 2017, NCT03643276)    | -                          | 37                               | Asymptomatic      | None     | 100                         | None                                          |
| 5       | F         | 9.5         | ALL                    | Consolidation (AIEOP—BFM 2017, NCT03643276) | 5                          | 13                               | Mild              | Fever, rhinorrhea | 99 | None                         |
| 6       | F         | 11          | ALL                    | Consolidation (AIEOP—BFM 2017, NCT03643276) | 1                          | 118                              | Mild              | Abdominal pain    | 100 | None                         |
| 7       | F         | 5.9         | ALL                    | Maintenance (AIEOP—BFM 2017, NCT03643276)    | -                          | 17                               | Mild              | Rhinorrhea        | 100 | None                         |
| 8       | M         | 16          | ALL                    | Maintenance (AIEOP—BFM 2017, NCT03643276)    | 3                          | 21                               | Mild              | Fever              | 99 | None                         |
| 9       | M         | 10.5        | ALL                    | Induction (AIEOP—BFM 2017, NCT03643276)       | 14                         | 33                               | Mild              | Fever              | 98 | None                         |
| 10      | M         | 14.8        | ALL                    | Maintenance (AIEOP—BFM 2017, NCT03643276)    | –                          | 19                               | Mild              | Fever, cough       | 99 | None                         |
According to the US National Institute of Health

**Table 1** (continued)

| Patient | Sex (M/F) | Age (years) | Underlying malignancy | Phase of antineoplastic therapy | Length of admission (days) | Time to negative COVID PCR (days) | COVID-19 severity* | Symptoms | Lowest O₂ saturation (%) | Effect of COVID-19 infection on therapeutic continuum |
|---------|-----------|-------------|-----------------------|---------------------------------|---------------------------|----------------------------------|-------------------|----------|---------------------------|------------------------------------------------------|
| 11      | M         | 7.5         | Hodgkin lymphoma      | Consolidation (NCT01516580)    | 1                         | 34                               | Mild              | Rhinorrhea | 99                        | None                                                 |
| 12      | M         | 17.5        | Burkitt lymphoma (recurrent) | Consolidation (NCT01516580)    | 3                         | 51                               | Asymptomatic       | None      | 98                        | None                                                 |
| 13      | F         | 15          | Burkitt lymphoma      | Induction (NCT01516580)        | 40                        | 87                               | Severe            | Grunting  | 94                        | None                                                 |
| 14      | M         | 6           | Low grade glioma      | Maintenance [31]                | 1                         | 26                               | Mild              | None      | 99                        | None                                                 |
| 15      | M         | 13          | High grade glioma     | Adjuvant radiotherapy          | –                         | 19                               | Asymptomatic       | None      | 100                       | None                                                 |
| 16      | F         | 18          | Grade II glioma       | Biologic treatment [32] and adjuvant chemotherapy | –                         | 14                               | Asymptomatic       | None      | 98                        | None                                                 |
| 17      | M         | 18.5        | Ewing sarcoma         | Consolidation and radiotherapy (COG -NCT00006734) | 1                         | 18                               | Asymptomatic       | None      | 100                       | None                                                 |
| 18      | F         | 1.8         | Langerhans cell histiocyctis | Stratum II (LCH-IV, NCT02205762) | -                         | 16                               | Mild              | Fever     | 99                        | None                                                 |

* According to the US National Institute of Health

ALL acute lymphoblastic leukemia, **AIEOP** Association Italiana di Ematologia Oncologia, **BFM** Berlin, Frankfurt, Muenster, **LCH** Langerhans cell histiocytosis, **COG** Children Oncology Group
Discussion

We report a series of 18 pediatric oncological patients who were positive for COVID-19 at our center during the period of March 2020–May 2021. We found that COVID-19 infection had little or no impact on the course of active antineoplastic treatment and the therapeutic continuum in our patients. Active antineoplastic treatment did not have any apparent effect on COVID-19 severity status or the development of chemotherapy complications in our patients with COVID-19.

Several reports have concluded that adults with cancer are particularly vulnerable to SARS-CoV-2 infection, and especially to severe COVID-19. This is evident by an increased number of hospital admissions, more admissions to the intensive care unit, and a greater need for supplemental oxygen and mechanical ventilation. Among adults, independent risk factors identified for severe COVID-19 infection include increased age, male sex, and chronic comorbidities, including obesity and cancer [3, 4, 7]. In adults with cancer, smoking status, multiple comorbidities, low-performance status, and active cancer treatment have been associated with severe COVID-19 infection [8, 13]. Adults with cancer have also tended to develop COVID-19-related complications [8] and to have poorer outcomes than the general population [13, 14], including increased 30-day all-cause mortality [7].

Children were found to be less affected by SARS-CoV-2 than adults, and account for 1–8% of confirmed incidences of COVID-19. When affected, children usually have a milder disease [11, 13–16].

Several previous reports have suggested that pediatric patients with cancer, infected with COVID-19, are at an increased risk of severe disease due to their underlying malignancy and treatment effect, similar to adults with cancer [16]. Pediatric patients with cancer who test positively for COVID-19 have been reported to require intensive care admission and to have unfavorable outcomes [17, 18]. Continued chemotherapy during COVID-19 infection has been reported to result in dismal outcomes [17, 18].

In contrast to the above, others have argued that COVID-19 has minimal effect on pediatric cancer patients, and that those affected are mostly asymptomatic or with only mild disease [19–21]. Madhusoodhan et al. [10], who described pediatric patients with cancer during active therapy, concluded that they appear to have a higher risk of severe disease and a greater need of critical care support compared to the general pediatric population. However, this risk may be lower than initially perceived and is far lower than that observed in adult oncology patients. Similarly, in their cohort of pediatric hematology and oncology patients, Gampel et al. [22] described relatively mild COVID-19 (male patients had a slightly more severe clinical course). The children were treated as outpatients, without the need for respiratory support. In light of the uncertainties regarding the impact of COVID-19 on oncology patients, delays have been commonly reported: in cancer diagnoses, due to fear of exposure by patients, parents,

![Graph showing the duration of positive COVID-19 PCR according to lymphocyte count in pediatric patients treated for cancer.](image)

**Fig. 1** The duration of positive COVID-19 PCR according to lymphocyte count, in pediatric patients treated for cancer. Each dot represents the data of a single patient. Seven were treated with active intravenous chemotherapy (yellow dots) and 11 received other treatments (blue dots). PCR polymerase chain reaction, COVID-19 Coronavirus disease

**Abbreviation:** PCR – polymerase chain reaction, COVID-19 – Coronavirus disease
and physicians; and in therapy of diagnosed patients [10, 22–24].

The majority of our patients with cancer who were positive for COVID-19 had underlying hematological malignancies and were diagnosed with COVID-19 during the induction or consolidation phases of therapy, which consist of intensive antineoplastic treatment.

We noticed a negative correlation between lymphocyte counts and the duration of COVID-19 PCR positivity. However, in several patients, the duration of COVID-19 PCR positivity was shorter than 20 days, despite low (<0.5×10^9/L) lymphocyte counts. Evidently, other factors contribute to the duration of COVID-19 PCR positivity.

Only one patient was considered to have a severe COVID-19 infection (US NIH classification severity index [11]), based on dyspnea and desaturation at presentation. We suspect that this patient’s extensive mediastinal mass was the main cause of her symptoms, rather than COVID-19, and that none of our patients actually had COVID-19 disease more severe than mild. In two patients, chemotherapy was delayed due to fever, which was attributed to either COVID-19 infection or to another viral infection.

Adherence to chemotherapeutic protocols and receiving treatment in due time is of utmost importance for the overall prognosis of pediatric cancers. This explains overall prognosis of pediatric cancers. This explains the treating oncologists’ decisions in all the described patients to continue antineoplastic treatment regimens, generally without delay. All the patients received their intended treatment without complications secondary to either antineoplastic treatment or COVID-19 infection.

Interestingly, the median duration of positive COVID-19 PCR in our cohort was 40 days (range 9–130 days). In comparison, median durations between 8 and 19.5 days have been reported for viral shedding of respiratory specimens in several papers on pediatric populations [25–27]. The difference may be explained by our patients’ depressed immune system, resulting from their underlying malignancies and the antineoplastic treatment they received. Notably, in patients with low lymphocyte counts, the duration of SARS-CoV-2 PCR positivity was longer, as described earlier [28, 29]. Nonetheless, most of our patients had asymptomatic or mild disease, and all recovered from COVID-19. Positive COVID-19 viral PCR is an important tool for diagnosing COVID-19; however, our results support the view that treatment should not be delayed until attaining PCR negativity [15, 24, 30].

Our study has several limitations, such as a small sample size, with a preponderance for hematological malignancies. Only two patients were receiving induction therapy at the time of COVID-19 diagnosis. Nevertheless, our work provides an important representation of the pediatric hematology-oncology population during the COVID-19 era and provides valuable data regarding their treatment.

Conclusions

Our pediatric patients with cancer who were positive for COVID-19 but were asymptomatic or had mild COVID-19 symptoms did not experience exacerbation of COVID-19 symptoms as a result of active antineoplastic treatment. Our findings suggest that uninterrupted continuance of antineoplastic therapy may be considered in pediatric patients with cancer who are COVID-19-positive, and asymptomatic or with mild COVID-19 symptoms.

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