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Retrospective Study

Manifestations of COVID-19 infection in children having malignancy: A single centre experience in Jordan

COVID-19 in pediatric patients with malignancy

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11

Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. All countries are following the guidelines and the recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of cases of COVID-19. Few data are available regarding the clinical course, the severity of the disease and mode of treatment in children with malignancy and COVID-19.

AIM

To evaluate the treatment plan and the outcome of children who have malignancy and developed COVID-19.

METHODS

A retrospective study of the medical files of patients who have malignancy and developed COVID-19 in the period between July 2020 and June 2021 was performed.

The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan and outcome. Eligible patients were patients who had malignancy and tested positive for COVID-19 on reverse transcription polymerase chain reaction.

RESULTS

A total of 40 patients who had malignancy developed COVID-19 during the period from July 1, 2020 to June 1, 2021. Primary diseases for them were as the following: 34 patients (85%) had hematological malignancies (30 of them had acute lymphoblastic leukemia, 2 of them had acute myeloblastic leukemia, and 2 of them had Hodgkin lymphoma), while 6 of our patients (15%) had solid tumors (2 of them had neuroblastoma, 2 of them had rhabdomyosarcoma, and 2 of them had central nervous system tumors). 12 of our patients (30%) didn't need hospitalization and they underwent home isolation only, while 28 patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 patients were admitted in the pediatric intensive care unit).

CONCLUSION

COVID-19 with malignancy in the pediatric age group has a benign course and doesn't increase the risk of having severe infection compared to other children.

Key Words: COVID-19; Malignancy; Disease severity score; Children

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Core Tip: Corona virus disease 2019 (COVID-19) is causing a global health crisis since the end of 2019. This retrospective study describe the manifestation of COVID-19 in our

oncology patients who were treated in Queen Rania Children's Hospital in the period between July 2021 and June 2021 focusing on the initial presentation, clinical course and the management plan and comparing these results with the international data worldwide trying to reach the optimal way ¹⁷ for the care of oncology patients during the COVID-19 crisis.

INTRODUCTION

12 Coronavirus disease 2019 (COVID-19) has brought about a global health crisis since late 2019^[1]. As there were more than 2 million cases of COVID-19 worldwide, the World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020^[2,3]. By June 1, 2021, a total of 170448610 cases of COVID-19, including 3663570 deaths, had been reported worldwide. In Jordan, a total of 737284 cases of COVID-19 and 9472 deaths had been reported by June 1, 2021^[4].

The incubation period of the virus is between 2 and 14 d with an average of 5 d^[5,6]. The main routes of transmission of the virus are droplets and close contact^[7]. COVID-19 has affected all age groups. The pediatric population accounts for only 3%-5% of total cases^[8]. Oncology patients generally shed respiratory viruses for longer than immunocompetent people and this is mostly true for COVID-19 as well^[9]. In children, most cases of COVID-19 are asymptomatic, and most studies have revealed that children have less severe symptoms in comparison to adults^[10-12]. On the other hand, some patients develop life threatening complications like acute respiratory distress syndrome, thrombosis and multi organ failure^[13-15]. Children who have malignancy are frequently immunocompromised because of the therapy they receive, putting them at high risk for severe infections which are the major cause of mortality in these patients^[16-18]. However, there is growing evidence that the mortality rate in pediatric cancer patients with COVID-19 is extremely low^[19,20]. The international pediatric oncology community acted quickly to the COVID-19 pandemic and made many recommendations to decrease the risk of infection in pediatric cancer patients^[21,22].

21 This study aimed to analyze and evaluate the treatment plans and outcomes of children who have malignancy and developed COVID-19 in Queen Rania Children's Hospital (QRCH) and to compare our results with the international results.

1 MATERIALS AND METHODS

This retrospective study was approved by the Ethical Committee of the Jordanian Medical Services. The medical records of the patients who had malignancy and tested

positive for COVID-19 were conducted at QRCH in Amman, Jordan, during the period between July 2020 and June 2021.

All pediatric oncology patients under 14 years old who had received anticancer treatment and were diagnosed with COVID-19 by polymerase chain reaction (PCR) nasopharyngeal swab were eligible for this study.

The primary end point was death, discharge from hospital, or end of active care for COVID-19 for patients who needed further treatment of their primary disease in hospital, or 14 d after initial diagnosis of COVID-19 in patients who didn't need hospitalization.

Data were collected on primary disease, age, white blood cell count, absolute neutrophil count, lymphocyte count, place of admission, clinical status on admission, mode of treatment, radiological findings, and outcome.

PCR for COVID-19 was done for symptomatic patients, patients who had close contact with a confirmed case of COVID-19, and before any admission to the hospital, as our hospital guidelines recommend doing PCR for COVID-19 for any patient who needs admission, whatever the cause for admission.

Detailed clinical histories including primary disease, status of the disease, comorbidities and detailed chemotherapy history were taken from all of our patients. We also performed full physical examinations, investigations and chest X-rays, and, if indicated, a high-resolution chest computed tomography (CT) scan was performed. After getting all of these data, researchers assigned patients a "disease severity score" categorizing the severity of their disease into the following categories: asymptomatic, mild, moderate and severe disease (as described in Table 1).

For patients who needed an admission, they were admitted in an isolation room in a specialized ward in the hospital (COVID-19 ward). When they met the criteria for discharge, they were discharged home with precautions and remained in home isolation until 14 d from the day of their COVID-19 diagnosis.

COVID-19 recovery was defined by the disappearance of the clinical symptoms in symptomatic patients or 14 d from the diagnosis of COVID-19 in asymptomatic patients.

RESULTS

Around 400 oncology patients were seen in QRCH during the study period between July 2020 and June 2021. A total of 40 oncology patients tested positive for COVID-19 during the same period. 24 patients (60%) were males while 16 patients (40%) were females. 28 patients were below the age of 6 years; they account for the majority of our patients in this study (70%). 5 patients (12.5%) were between the ages of 6-12 years while 7 patients (17.5%) were between the ages of 12-14 years. Hematological malignancies were the predominant primary disease in this study, as they account for around (85%) of the cases. The patients' characteristics are summarized in Table 2.

Upon presentation, full investigations were done for the patients in addition to chest X-rays. A high-resolution chest CT scan was done if there were any chest X-ray abnormalities or if there were moderate to severe respiratory symptoms. Only 10 patients required a chest CT scan. Laboratory and radiological findings are summarized in Table 3.

According to the disease severity score, 10 patients (25%) were asymptomatic, 20 patients (50%) had mild symptoms, and 8 patients (20%) had moderate symptoms while just 2 patients (5%) had severe symptoms. Of these patients, 12 patients (30%) were kept in home isolation while 28 patients were treated in hospital, where 26 patients (65%) were treated in the COVID-19 ward and 2 patients (5%) were treated in the pediatric intensive care unit (PICU). The solid tumor patients were asymptomatic or had mild symptoms, while the moderate and severe symptoms were found only in patients with hematological malignancies; however, some patients who had hematological malignancies were asymptomatic or had mild symptoms. The hospital management was case by case and the treatment plan was composed of intravenous (IV) antibiotics, azithromycin, dexamethasone, oxygen support, intravenous immunoglobulin (IVIG) for

patients with hypogammaglobulinemia, and vitamins. Details about the clinical course of COVID-19 are summarized in Table 4.

DISCUSSION

Few data are available worldwide regarding the effect of COVID-19 on pediatric oncology patients; however, multiple studies were published discussing the COVID-19 clinical course in these patients. In our centre, we reported that 10% of our oncology patients developed COVID-19 during the period between July 2020 and June 2021. This percentage of COVID-19 infection in oncology patients was higher than what was reported in the general pediatric population in Jordan in the same period, which was around 5%-6%^[4]. This increase in the percentage of COVID-19 among our oncology patients can be explained by the frequent testing of these patients for COVID-19 even if they were asymptomatic, as they required recurrent admissions to the hospital for different reasons including chemotherapy, fever, blood and platelet transfusions and surgeries; screening for COVID-19 was done before each admission as part of our hospital protocol regarding admissions during the era of COVID-19. However, this was not the case for the normal pediatric patients. The screening for COVID-19 was not done for healthy children who didn't need hospital admission unless they were symptomatic or in close contact with a confirmed COVID-19 case.

The median age for our oncology patients at the time of COVID-19 diagnosis was 5 years (range between 1.5 and 13.5 years). This is similar to what was reported by Millen *et al*^[23] in a study done in the United Kingdom involving 54 patients under the age of 16 years with malignancy. The median age in our study was less than what was reported by Al Odda *et al*^[24] in a study done in al Sulaimani-Kurdisan involving 54 malignancy patients and what was reported by Dong *et al*^[25] in a Chinese study involving 2143 patients having malignancy, as the median age for these 2 studies was 7 years. We also reported that the majority of our patients were less than 6 years (70%), followed by patients who were more than 12 years (17.5%). These results are the same as what was reported by Navaeian *et al*^[26] in a study done in Iran among 20 oncology patients.

In our study, 24 patients were males (60%), while 16 patients were females (40%). This male predominance was reported in a study done in our centre about patients who underwent hematopoietic stem cell transplantation and had COVID-19 infection post-transplant; all of them were males^[27]. Madhusoodhan *et al*^[28] also reported male predominance in a multicentre retrospective study involving 578 pediatric oncology patients in the New York-New Jersey region; 70% of their patients were males.

The majority of our cases had hematological malignancies (85%); 30 patients (75%) had acute lymphocytic leukemia (ALL), 2 patients (5%) had acute myeloid leukemia (AML), and 2 patients had Hodgkin lymphoma. Solid tumors accounted for a smaller percentage (20%) of the cases. Similar results were reported by most of the international studies done worldwide^[10,20,29,30]. This predomination of hematological malignancies among oncology patients who had COVID-19 can be explained by the fact that hematological malignancies are the most common malignancies in pediatric age groups, and they require longer duration of treatment, especially for ALL patients. Furthermore, the hematological malignancies themselves and the chemotherapy used for the treatment of these types of malignancies have a greater effect on T lymphocytes function compared to solid tumors^[31,32].

Regarding our patients, fever was the most common presenting symptom, as 24 patients (60%) had a temperature higher than 37.8 axillary at the time of the COVID-19 test. All of these patients were admitted to the COVID-19 ward in our hospital and were treated with IV antibiotics, as bacterial infection cannot be ruled out and has to be covered by IV antibiotics, especially in neutropenic patients.

Most of the international studies also reported that fever was the most common presenting symptom of COVID-19 in oncology patients^[33,34].

Most of our patients had mild symptoms (50%), while just 2 patients (5%) had severe symptoms. The moderate and severe symptoms were found exclusively in patients who had hematological malignancies, while the patients who had solid tumors were asymptomatic or had mild symptoms. This can be explained by the fact that the hematological malignancies themselves and the chemotherapy used for the treatment of

these types of malignancies have a greater effect on T lymphocytes function compared to solid tumors^[31,32], in addition to the role of ¹granulocyte-colony stimulating factor (G-CSF) administration after completing chemotherapy in solid tumor patients, which prevents the development of severe neutropenia.

Asymptomatic patients and patients with mild symptoms except fever were discharged home with instructions for strict home isolation and they were followed by video and phone calls.

¹⁹The patients with severe symptoms were treated in the PICU as they required the use of continuous positive airway pressure (C-PAP) to maintain O₂ saturation of more than 94%. The primary disease for these 2 patients with severe symptoms was ALL. Both of them were in remission and they were in the consolidation phase of their treatment; however, these 2 patients had severe neutropenia at the time of COVID-19 infection. The treatment plan for these 2 patients was IVIG, dexamethasone, azithromycin, and IV antibiotics in addition to the C-PAP, which was needed for 2 days for the first patient and for 3 days for the second patient. Gradual improvement in the clinical status was noticed for both of them and they were discharged home without any complications after around 2 wk of admission. As the severe neutropenia might have played a major role in developing severe symptoms of COVID-19 in these 2 patients, modifications of the chemotherapy doses for all of our patients in the hospital were made to prevent severe bone marrow suppression, especially severe neutropenia; furthermore, we administered the G-CSF 48 h after finishing the chemotherapy protocol for non-hematological malignancies to perform a bone marrow rescue.

Patients with moderate symptoms were admitted to the COVID-19 ward and they received dexamethasone and azithromycin. IV antibiotics were also given for patients with fever. IVIG was given for patients with secondary hypogammaglobulinemia which may have occurred due to chemotherapy; only 9 of our patients (22.5%) received IVIG.

These results are similar to what was reported by Millen *et al*^[23], who reported that 6.6% of their oncology patients had severe symptoms of COVID-19. On the other hand,

our results are higher than what was reported by Madhusoodhan *et al*^[28], as they reported that only 17 out of 578 oncology patients (3%) developed severe symptoms of COVID-19.

However, studies done about COVID-19 in the general pediatric population showed similar rates of severe symptoms of COVID-19 among children who tested positive for COVID-19. Bellino *et al*^[35] reported in a study done in Italy that 4.3% of patients who had COVID-19 developed severe symptoms. Also, Meena *et al*^[36] reported in their systematic review and meta-analysis that 4% of pediatric patients who had COVID-19 developed severe symptoms.

These similar results of severe symptoms of COVID-19 among oncology patients compared to the general pediatric population suggest that, even though the oncology patients have more risk factors for developing severe symptoms of COVID-19, children with malignancy who have COVID-19 are not at greater risk of having severe symptoms of COVID-19.

Not one of our patients died or developed any of the chronic complications of COVID-19, including multisystem inflammatory syndrome in children, after recovering from the infection. These results may be explained by the role of chemotherapy-related immune suppression in the protection against the development of cytokines release storm^[37]. The mortality rate in our study is comparable to the overall death rate reported by Verity *et al*^[38], as the estimated rate in their study was 0.66 % and declined to 0.0016% in children under the age of 9 years.

For all of our patients who tested positive for COVID-19, chemotherapy was withheld for at least 10 days, even in asymptomatic patients. We didn't notice any increase in the malignancy-related morbidity nor mortality due this delay of chemotherapy.

On the other hand, we did not notice any increase in the incidence of any malignancy groups during the COVID-19 era, which indicates that the virus is not an oncogenic virus, at least in the short term.

As there is a risk of exposure to COVID-19 in both the community and the hospital settings, resulting in extreme anxiety in the families of patients with malignancies,

standard precautions for basic and respiratory hygiene must be strictly applied to reduce the risk of transmission of COVID-19.

Limitations of this study included the small number of cases, as this study includes just one institution's experience in a short period of time. Another limitation of this study was the short follow-up period of these patients, which prevented us from detecting the possible long-term complications.

CONCLUSION

Patients with malignancies are more prone to becoming infected with COVID-19, especially patients with hematological malignancies. However, these patients are not more prone to developing severe symptoms of COVID-19 in comparison to children in general. Furthermore, mortality and morbidity due to COVID-19 infection are not increased in patients with malignancies.

Therefore, chemotherapy should be continued for ²patients with cancer during the era of COVID-19, provided that the WHO recommendations are strictly applied and provided that your patients are not severely suppressed and have tested negative for COVID-19. However, prevention of severe neutropenia by giving G-CSF as a bone marrow rescue is mandatory to prevent the ¹moderate to severe symptoms of COVID-19 in malignancy patients.

ARTICLE HIGHLIGHTS

Research background

¹⁰The coronavirus disease 2019 (COVID-19) has been the cause of ¹a global health crisis since the end of 2019. All countries are following the guidelines and the recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of cases of COVID-19. Few data are available regarding the clinical course, the severity of the disease and mode of treatment in children with malignancy and COVID-19.

Research motivation

COVID-19 is making a big problem worldwide, with few data available about this new health crisis. Patients with comorbidities are more susceptible to have COVID-19 complications, especially oncology patients who are receiving different modalities of treatment making them immunocompromised most of the time. We would like to share our experience in these patients to compare it with the published data worldwide.

Research objectives

¹ The main objective of this research is to evaluate the outcome of oncology patients who develop COVID-19 and to compare it with the results of normal population in the same age group and to compare the outcome among different malignancy groups. Also we compare our patients' outcome with the international data published worldwide to distribute our experience and try to improve our management plan for these patients to provide the best care for them during this health crisis.

Research methods

⁹ A retrospective review of the medical files of patients who have malignancy and developed COVID-19 in the period between July 2020 and June 2021 was performed. The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan and outcome. Eligible patients were patients who had malignancy and ⁴ tested positive for COVID-19 on reverse transcription polymerase chain reaction.

Research results

A total of 40 patients who had malignancy developed COVID-19 during the period from July 1, 2020 to June 1, 2021. Primary diseases for them were as the following: 34 patients (85%) had hematological malignancies (30 of them had ⁸ acute lymphoblastic leukemia, 2 of them had acute myeloblastic leukemia, and 2 of them had Hodgkin lymphoma), while 6 of our patients (15%) had solid tumors (2 of them had

neuroblastoma, 2 of them had rhabdomyosarcoma, and 2 of them had central nervous system tumors). 12 of our patients (30%) didn't need hospitalization and they underwent home isolation only, while 28 patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 patients were admitted in the pediatric intensive care unit).

Research conclusions

COVID-19 with malignancy in the pediatric age group has a benign course and doesn't increase the risk of having severe infection compared to other children.

Research perspectives

It will help us to distribute our experience worldwide and to give an idea about what is going on in the developing countries during this health crisis especially in oncology patients who needs special care.

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