Chapter

Management of Covid-19 Disease in Pediatric Oncology Patients

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Abstract

Pediatric cancer patients are immunocompromised, and the risks are higher in this population. Confirmed cases are defined as PCR (polymerase chain reaction) positive patients. The severity of infection is divided into four groups: asymptomatic/mild, moderate, severe, and critical, based on the clinical, laboratory, and radiological features. In the pediatric population, the COVID-19 disease has a mild course. Chemotherapy courses can be interrupted according to the symptoms and severity of the disease. Azithromycin, antivirals are used as a single agent or in combination. In critical patients, convalescent plasma, mesenchymal stem cells, tocilizumab, and granulocyte transfusions are administered. In recent studies, having hematological malignancy, stem cell transplantation, a mixed infection, and abnormal computerized tomography findings increase the severity of the disease and the need for an intensive care unit. Therefore, the patients and their families should be aware of a higher risk of severe forms than immunocompetent children.

Keywords: chemotherapy, COVID-19, immunocompromised, immunotherapy, pediatric oncology

1. Introduction

Coronaviruses are zoonotic RNA viruses. SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the novel coronavirus, belongs to the Betacoranovirus subgroup [1]. SARS-CoV-2's incidence in children varies (China: 2-12.3%, Italy: 1.2%, USA: 5%). The infection in pediatric cases is asymptomatic or mild. The median incubation period is 5-7 days. The primary source of transmission is respiratory droplets and direct contact. The primary tool for diagnosis is a real-time polymerase chain reaction test (RT-PCR) on samples. Eighty percent of children had household contact; ten percent were asymptomatic, fifty percent had a fever. Other symptoms are cough, respiratory distress, fatigue, myalgias, vomiting, diarrhea, anosmia, ageusia, sore throat. Children generally recover in 1-2 weeks. The case fatality rate in children is zero percent [2]. This benign course of the disease is related to the immune preparedness of children to a new pathogen. Immunologic mechanisms are also different in children compared with adults [3, 4]. Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare postinfectious complication of SARS-CoV-2 infections; it is RT-PCR negative for SARS-CoV-2 virus but antibody positive [5].

Cancer treatment includes various immunosuppressive drugs [6]. It is well known that immunocompromised children have higher mortality and morbidity rates than the healthy population due to viral respiratory infections [7]. In the

pediatric oncology setting, the mortality rate in COVID-19 is reported up to 4% [8]. In COVID-19 relevant areas, the virus transmission rate is low in children with cancer. Cancer diagnosis, treatment, palliative care, hospital visits are interrupted because of the pandemic. Another concern is delayed cancer diagnosis, chemotherapy shortages, decreased availability of surgery, radiotherapy, supportive treatment, inadequate personal productive equipment, and drugs, especially in low-middle income countries [9, 10]. The most common cancer in the pediatric population is acute leukemia. In industrialized countries, the incidence of acute leukemia is a 40-60 age-standardized rate per million, one-third of all childhood cancers. Brain and spinal tumors are the second; lymphomas are the third most common tumors in industrialized countries [11]. Therefore, urgent treatment is critical and life-saving, especially in leukemia and lymphoma induction therapy [12]. Here we present an explanatory review of different approaches and experiences in this unique population.

2. SARS-CoV-2 infection in pediatric oncology

The incidence of COVID-19 among cancer patients varies %1 to 7% [13–15]. In SARS-CoV-2 Infection, cancer patients' hospitalization rate is four times more than the healthy population [16]. Madhusoodhan et al. reported that mortality and morbidity rates in COVID-19 positive children with cancer were higher than the average population. The most common underlying malignancy was acute lymphoblastic leukemia (ALL) (53%). Severe infection and critical support need rates are also higher. Among hospitalized patients with cancer, oxygen support and intensive care unit (ICU) admission rates were significantly higher than the non-cancer group. Sixty-seven percent of positive cases' chemotherapy courses were interrupted between 2 and 78 days. Forty-six percent delays in surgery, thirty percent delays in transplant were noted. The mortality rate was 4.1%, not solely associated with the COVID-19 disease [17].

2.1 Risk of SARS-CoV2 infection in children with cancer

Cancer patients are immunocompromised due to tumor growth and treatment. Chemotherapy reduces immunoglobulin levels and causes qualitative and quantitative T cell dysfunction. Immunocompromised patients have a higher risk of developing severe disease. Therefore, the leading practices are basic hygiene rules, avoiding crowded places, and possible infection and handwashing situations [18]. Patients with cancer have a higher risk of symptomatic or severe COVID-19 disease. Chemotherapy, surgery in the last month, and immunotherapy administration increase COVID-19 disease severity and associated deaths. However, radiotherapy was not associated with adverse outcomes. Developing symptoms are rapidly, and hospitalization rates and duration were higher in cancer patients. Cancer survivors' signs are more extreme than the average because immune recovery is not completed [19]. In one study, male sex, older age; obesity rates were slightly higher in severe COVID-19 cases with cancer [17]. The United States Centers for Disease Control and Prevention published the risk factors for the severity of COVID-19. Medical complexity, genetic, chronic health conditions, and immunosuppression are presented as possible severity risk factors [18].

2.2 Variants of COVID-19

The mutations in the SARS-CoV2 genome may change its phenotype (transmissibility, virulence). Alfa (B.1.1.7 lineage) variant (20I/501Y.V1) has increased

transmission compared with previous strains. Some studies suggest this variant is also associated with severity. Delta (B.1.617.2 lineage), first identified in India, is more transmissible and has more hospitalization rates than the alfa variant. Vaccine effectiveness is also altered in this variant but is high in preventing hospitalization and severe disease. Beta (B.1.351 variant) was identified first in South Africa; vaccine effectiveness may be reduced with this mutation. Gama (P.1 lineage) variant may increase transmissibility. Epsilon variants (B.1.427 and B..1.429) are associated with higher viral mRNA levels on nasal swabs [20].

2.3 Clinical presentation

Clinical features are mild in neonates and children worldwide. However, fever, respiratory symptoms, gastrointestinal symptoms, and neurologic manifestations are observed among COVID-19 cases. The severity of the disease is divided into five groups (asymptomatic, mild, moderate, severe, critical) [21]. Covid toes are described as reddish nodules in distal digits in children and adolescents. The other dermatologic manifestations are morbilliform rah, livedo reticularis-like vascular lesions, and urticarial [22]. Multisystem Inflammatory Syndrome In Children (MIS-C) is a past-infection complication of COVID-19 infection. MIS-C features are persistent fever >38°C, history of SARS-CoV2 disease, at least two of the following symptoms (rash, gastrointestinal, edema of the hands and feet, oral mucosa changes, conjunctivitis, lymphadenopathy, and neurologic symptoms). Arrhythmias and ventricular dysfunction are other presentations of MIS-C [23].

2.4 Diagnosis

Whole-genome sequencing led to finding newer genes for RT-PCR. RT-PCR test on upper and lower respiratory secretions is routinely used for diagnosis. This test should be repeated in clinically suspected cases. Gaita samples can also be positive by RT-PCR. Serology is essential for the previous infection for SARS-CoV2 and common coronaviruses. Laboratory findings may be lymphopenia, thrombocytopenia, neutropenia. In severe cases, lactate dehydrogenase, coagulation parameters, and D-dimers are elevated. C.T. (computerized tomography) findings include multiple patchy, nodular, ground-glass, or reticular opacities and infiltrations [24].

2.4.1 Testing of patients with cancer

Symptoms of COVID-19 (fever, cough, dyspnea, diarrhea, etc.) and suspected exposure are essential for testing cancer patients. According to IDSA (Infectious Diseases Society of America) guidelines, the first higher priority includes unexplained viral pneumonia or respiratory failure in critically ill patients in ICU. Also, fever or lower respiratory tract illness in immunosuppressed, older, or have underlying chronic health conditions is an indication. The other symptoms in the first higher priority are fever or lower respiratory tract illness in patients with COVID-19 contact within 14 days or in health care workers, public health care workers, and other essential leaders. Non-ICU hospitalized patients with unexplained fever, and lower tract illness are in the second level of priority. The third priority consists of outpatients with criteria of influenza testing (chronic diseases and immunocompromising conditions), pregnant women, and children with similar risk factors. Public health and infectious diseases authorities' decisions are the fourth priority [25]. Before cytotoxic chemotherapy, solid organ and stem cell transplantation, cellular immunotherapy, or high-dose corticosteroids, SARS-CoV2 RNA testing is recommended in several guidelines [26].

2.5 Treatment and outcome of SARS-CoV2 infection in children with cancer

2.5.1 Guideline recommendations for children

Treatment recommendations of COVID-19 for childhood cancer are the same with children without cancer. Supportive treatment (hydration, nutrition, oxygen supplementation) is essential in COVID-19 treatment. In the COVID-19 treatment guidelines panel, remdesivir is recommended for hospitalized children ≥12 years with risk factors of severe disease and increasing demand for oxygen. In addition, this panel recommends dexamethasone for children with high flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation in COVID-19 disease. If dexamethasone is not available, other glucocorticoids can also be given. The dose of dexamethasone is 0.15 mg/kg/dose (maximum 6 mg) for up to ten days. Convalescent plasma is used for mechanical ventilated COVID-19 positive children. Anti-SARS-CoV2 monoclonal antibodies (bamlanivumab plus etesevimab or casarivimab plus imdevimab) studies are insufficient in the pediatric population. However, ≥ 16 aged and hospitalized patients having at least one high risk of severe disease can be consulted for pediatric infectious disease. The safety of baricitinib has not been evaluated in pediatric patients; the data of baricitinib and remdesivir combination is insufficient for hospitalized children who have a contraindication for corticosteroids. The use of tocilizumab for severe pediatric cases has been described; there is inadequate data for recommending tocilizumab in MIS-C or hospitalized children with COVID-19. All of these therapies can be discussed for selected patients [23]. Increased D-dimer and high risk of thrombosis are indications for anticoagulation in childhood cancer with COVID-19 disease [27].

In MIS-C, IVIG (intravenous immunoglobin) and corticosteroids are in the first-line treatment. High-dose IVIG (typically 2 g/kg, based on ideal body weight) is used. In severe cases, low-moderate dose glucocorticosteroids (1-2 mg/kg/day) should be given with IVIG. Interleukin-1 antagonists are given in refractory instances in patients with MIS-C. Features of macrophage activation syndrome or contraindications for glucocorticosteroids are indications of it. Therefore, high-dose steroids are used for refractory patients. Antiplatelet therapy is used at least for weeks after diagnosis. In case of indefinite treatment and documented thrombosis, anticoagulation is recommended [23, 28].

2.5.2 The COVID-19 treatment guideline panel recommendations for adult patients with cancer

Vaccination for COVID-19 is recommended for adults with active cancer and those receiving treatment for cancer. The vaccination should be done at least two weeks before starting chemotherapy. In adults with hematologic malignancies, vaccination should be done after neutrophil recovery for those receiving intensive chemotherapy. Vaccination should be done at least after three months of hematopoietic stem cell transplantation and chimeric T-cell therapy.

For signs and symptoms of COVID-19 and before chemotherapy, radiotherapy, and all invasive procedures, testing with PCR should be performed. Treatment delays for curable cancers like pediatric lymphoblastic leukemia should be avoided. If regimens with similar results are preferable, orally administered drugs or regimens with fewer days should be chosen. Regimens should not be altered even in COVID-19 patients with cancer. In radiotherapy guidelines, the daily dose by a fraction is increased to lower the days of treatment. For patients with febrile neutropenia, a PCR test for COVID-19 should be performed. National Comprehensive Cancer

Network guidelines should be followed. Treatment of COVID-19 in cancer patients is the same with the general population. Drug interactions are essential [23].

2.5.3 COVID-19 experience in pediatric oncology

Early data from China revealed that children positive for COVID-19 had a low (2.8%) rate of severe disease [29]. However, in COVID-19 positive children, ICU admission rates were 33.2% in the COVID-NET group study and 35% in another study [30, 31]. Furthermore, in a systemic review (June 2020), the survival rate was %100 among children with cancer and COVID-19 [32].

In a multicenter, retrospective study of 578 children with cancer, 98 were positive for COVID-19. Asymptomatic (n = 25), mild (n = 45), moderate (n = 11), severe (n = 17) disease were observed. Twenty-eight were hospitalized, seven needed mechanical ventilation. Hydroxychloroquine (n = 15), azithromycin (n = 15), tocilizumab (n = 5), remdesivir (n = 4) were given [17]. In a systematic review of 204 children with cancer, 96 were hospitalized because of COVID-19 infection. Thirty-two percent had oxygen requirements. Pneumothorax, pleural effusion, pulmonary arterial hypertension, bronchiolitis obliterans, diffuse alveolar hemorrhage, septic shock, and acute respiratory distress syndrome are other complications. Forty-one patients received hydroxychloroquine; nine took steroids, five took lopinavir/ritonavir combination. Azithromycin (n = 4), remdesivir (n = 4), and tocilizumab (n = 3) were used. Twenty-one required intensive care unit admission. Out of 15 deaths, four of them were not related to COVID-19. Thus, the mortality rate was 4.9% [33]. Millen et al. reported 54 positive children of COVID-19 with cancer. The majority (53.7%) of the patients had ALL (acute lymphoblastic leukemia). Four of them had acute myeloid leukemia, five had central nervous system tumors, six had neuroblastoma. None of them died of COVID-19 disease. Twenty-one percent were taking very myelosuppressive chemotherapy; twenty-one were receiving a less intense regimen. Twenty-six had targeted therapies. None received high-dose chemotherapy and stem-cell transplantation within 28 days of this infection [34]. In a resource-limited country, Peru, the epidemiologic data was similar. Among 69 children with cancer, 36 had ALL, 5 had NHL (non-Hodgkin lymphoma), 5 had brain tumors, and COVID 19. Ivermectin, azithromycin, corticosteroids were used for COVID-19 treatment. Unfortunately, seven of them died and, COVID-19 lethality is 10% in this study [35]. Graetz et al. reported that out of 79 countries and 213 centers, 88% had SARS-CoV2 testing opportunities, 43% of centers declined in new cancer diagnosis. Reduction in surgery (72%), chemotherapy changes (57%), disruption in radiotherapy (28%) has been a great deal. In low-middle income countries, unavailability of chemotherapy agents, lag in treatment, and radiotherapy was more common [36].

In another cross-sectional study, 51 children with cancer were examined, and they had COVID-19. Sixty point eight percent had hematologic malignancies; six underwent stem cell transplantation, 17 had moderate or severe disease, nine had a critical illness. Delay in treatment (chemotherapy, radiotherapy, surgery) and reduction in chemotherapy doses were reported in 40-58% of the cases [37]. Kebudi et al. said the mortality rate was 1.9% in COVID-19 infection of pediatric oncology patients. Hematologic malignancies, HSCT, a mixed condition, increased the severity of COVID-19 disease [38]. COVID-19 recommendations are rapidly changing, guidelines of the Ministry of health were used in this study. Recent proposals for immunocompromised children in this guideline are; mild cases with possible worsening respiratory failure should be treated. Here, drug interactions should be carefully examined. These patients older than twelve receive favipiravir with a loading dose of 1600 mgr twice a day, and a maintenance dose of 600 mg,

once a day. Hydroxychloroquine ± azithromycin is deleted currently but previously given in this guideline [39].

2.6 Managing hematologic malignancies in COVID-19 pandemic

European Society for Blood and Marrow Transplantation (EBMT) reported their recommendations (June 2020). Steroids that may cause viral rebounds and adverse events are the main component of acute lymphoblastic leukemia treatment. Dose reduction is not recommended in prophase, induction, and consolidation. Asparaginase has thrombotic complications that are also observed in COVID infections. Treatment delay is not recommended for drugs, blinatumomab or inotuzumab. Tyrosine kinase inhibitors are the mainstay treatment in Philadelphia-positive ALL; this treatment should not be delayed. As well as acute promyelocyte leukemia should be treated immediately. Acute myeloid leukemia with adverse cytogenetic risks and a suitable donor for allogeneic stem cell transplantation needs intensive therapy. Patients with favorable or intermediate-risk factors should also be treated, but some modifications in doses can be preferred after induction. This procedure cannot be postponed for patients with a risk of progression or relapse without allogeneic stem cell transplantation. Controversial indications should be reconsidered [40]. Passamonti et al. reported that outcomes were worse in hematological malignancies with COVID-19. The leading diagnoses with worse survival were acute myeloid leukemia, indolent NHL, aggressive NHL, or plasma cell neoplasms. In addition, the mortality rate of hematological malignancies was four times higher than the general population with COVID-19. This rate was also 41 times higher than the hematologic malignancies without COVID-19. Thus, disease type and status are essential for outcome [41]. Retrospective studies support a mortality rate up to %62 in hematological malignancies with COVID-19. Prolonged persistence of the RNA up to 32.7 days is reported.

Acute leukemias, especially acute myeloid leukemia (AML), myeloproliferative neoplasms, myelodysplastic syndromes, lymphomas, have the worst complications and outcomes. Chemotherapy was not generally associated with worse results. PCR ± C.T. of the chest is recommended before treatment. Induction treatment should not be delayed. In case of a positive test, a multidisciplinary team containing a pediatric hematology-oncologist and pediatric infectious diseases specialists should decide the time of others courses. With a positive test, the period of chemotherapy can be postponed for two weeks. In high-risk AML, allogeneic stem cell transplantation should not be delayed. Recommendations of EBMT should be followed [42]. Tyrosine kinase inhibitors (TKIs) are the mainstay treatment in chronic myeloid leukemia (CML). The cessation of these drugs needs a deep and stable response to treatment and close follow-up. In the COVID-19 pandemic, termination of therapy is not a helpful approach. The interaction of remdesivir with imatinib, dasatinib, and nilotinib is essential. In CML blastic phase, TKIs plus intensive chemotherapy is an urgent treatment [42].

Newly diagnosed aggressive NHL like Burkitt lymphoma and Diffuse large B cell Lymphoma need acute treatment, and delay is inappropriate. DA-EPOCH-R (dose-adjusted etoposide, cyclophosphamide, vincristine, doxorubicin, prednisone) is the standard treatment for PMBCL (primary mediastinal B-cell lymphoma). Because of the severe immunosuppressive effect of this regimen, alternatives are recommended, like R-CHOP with radiotherapy consolidation. RICE (rituximab, ifosfamide, carboplatin, etoposide) can be given as a salvage regimen in a relapsed refractory setting. However, less myelotoxic regimens can be preferred. In Hodgkin lymphoma treatment, bleomycin and checkpoint inhibitors have adverse pulmonary toxicity events. In adults, the omission of bleomycin can

be an option for complete remission after the second course. Guidelines for radiotherapy should be followed [39]. Bendamustine as an option in relapsed refractory patients is associated with mortality in COVID-19 positive lymphomas [43].

2.7 Treatment of brain tumors in COVID-19 pandemic

The mainstay treatment in children is surgery; the delay in treatment leads to neurologic sequela, decreases survival, increases morbidity. Late diagnoses are other challenges. Early intervention is essential [44].

2.8 Treatment of SARS-CoV2 infection for children receiving bone marrow transplantation and current recommendations

Of 318 HSCT receipts with COVID-19 infection, 184 with allogeneic HSCT, 134 with autologous HSCT were included in one study. In the allogeneic HSCT group, fifteen cases were ≤ ten years old; eleven were between 11 and 20 years old. Three patients were ≤ ten years old; none were 11-20 years old in the other group. Therefore, AML, ALL, MDS are the leading diagnoses for allogeneic HSCT. Fifty-five patients had a severe presentation of COVID-19 infection requiring mechanical ventilation. In the allogeneic HSCT group, 42% had a myeloablative regimen, 56% took a reduced-intensity conditioning regimen (RIC), 45% received TBI (total body irradiation) based conditioning regimen. In moderate–severe cases, COVID-19 convalescent plasma remdesivir, tocilizumab, Hydroxychloroquine, azithromycin were commonly used. In addition, Lopinavir, ritonavir, methylprednisolone, oseltamivir, ribavirin, acyclovir, famciclovir, antibacterial agents were also used. After 30 days of transplantation, overall survival was 68% for the allogeneic HSCT group, 67% for autologous HSCT receipts. Male sex, age older than 50, and COVID-19 within 12 months of transplantation was strongly associated with mortality [45].

The COVID-19 Treatment Guidelines include the following recommendations for HSCT and cellular therapy receipts and donors;

- For adults, vaccination for SARS-COV2 is recommended.
- In the presence of signs and symptoms of COVID-19, PCR testing is recommended. If COVID-19 infection is suspected, time donation or transplantation should be re-checked.
- In transplant and cellular therapy patients, COVID-19 treatment should be consulted by a transplantation specialist. In addition, drug interactions of immunosuppressants with other medications should be investigated [23].

3. Covid-19 vaccines in children

BNT162b2 (Pfizer; BioNTech) is the first vaccine approved in children (12-15 years) with 100% efficacy. A trial of this vaccine for six months to eleven years of age is ongoing. Moderna's mRNA-1273 vaccine also has 100% efficacy in adolescents (12-17 years aged). Sinovac's mRNA vaccine is approved in China for children more than three years of age. Protection may be lower against some variants. However, BNT162b2 and AZD122 vaccines have excellent results in reducing hospitalization and severe disease. Phase III trials for beta variants include BNT162b2s01 (Pfizer; BioNTech), Moderna's mRNA-1273.351, and mRNA-1273.211 vaccines [46]. More recent studies revealed that the third dose of vaccine is warranted for active use of

chemotherapy for cancer, hematologic malignancies, hematopoietic stem cell transplantation. Administration of some drugs (rituximab etc.) should be postponed until two-four weeks after vaccination completion if possible [47, 48]. FDA has recently approved BNT162b2 (Pfizer; BioNTech) for individuals aged 16 years and older. It is still under emergency use for children between 12-15 years of age [49].

4. Conclusions

COVID-19 infection is mild in children. However, the outcomes of COVID-19 in children with cancer are worse than the healthy children. Therefore, cancer treatment initiation should not be postponed for curable cancers. Treatment of COVID-19 in children with cancer is the same with healthy children with COVID-19. Therefore, Hydroxychloroquine plus azithromycin is no longer used; in the panel, remdesivir is recommended. In Turkey, favipiravir is used. MIS-C is a critical and late complication of COVID-19. Vaccination is recommended. However, the vaccine studies of COVID 19 in children are not completed [50]. Following the recent guidelines, multidisciplinary teamwork is essential for deciding the management of children with cancer.

Conflict of interest

The authors declare no conflict of interest.

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