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COVID -19 in Children with Cancer: A Review

*Mozhgan Hashemieh[1]

[1]MD, Pediatric Hematologist and Oncologist, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

The World Health Organization (WHO) has announced that COVID -19 is a public health emergency requiring international concern. Child cancer patients are highly vulnerable to this virus during SARS-CoV- 2 outbreak. These children have varying degrees of immunosuppression due to primary illness and also anti-tumor therapy. Although children in comparison to adults have a milder course of COVID -19 infection, pediatric patients with malignancies had a higher risk for severe clinical events due to COVID-19 in comparison to children without cancer. Most neoplasms in pediatric population have an aggressive manner and therefore require prolonged periods of multi agent chemotherapy. In adults with cancer who have stable disease, postponement of therapy ispossible, but in children delay in onset of treatment is not a suitable option. One of the most effective strategies in order to prevent COVID -19 is minimizing the risk of exposure and also extreme isolation. Moreover, in the majority of children with cancer hospital admission is required. At present, there is no specific antiviral treatment for SARS -CoV - 2, hence the increased surveillance and preventive strategies in order to reduce the risk of exposure should be considered. There are many unanswered questions in management of children with cancer who were infected with COVID -19. In this setting, treatment decisions need to be individualized on a case-by-case basis and in order to deliver a suitable treatment, patient stratification is required. Pediatric patients with cancer should receive their anti-cancer treatment in the setting of vigorous screening for SARS -CoV - 2. Further studies are needed to understand the course of COVID -19 infection in children with cancer.

Key Words: Cancer, Children, COVID -19, SARS, MERS.

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Corresponding Author:

Mozhgan Hashemieh, MD, Imam Hossein Medical Center, Shahid Madani Street, Tehran, Iran.

Email: m.hashemieh@sbmu.ac.ir

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1- INTRODUCTION

The 2019 novel coronavirus (2019-nCov) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV- 2) is a new public health problem, which is rapidly spreading from Wuhan city in China to the rest of the world (1, 2). As of March 10, 2020, the COVID -19 had infected more than 110,000 people worldwide and has been responsible for 4,000 deaths worldwide, but the preliminary data on the burden of this virus is limited, in children (3). A recent study of 72,314 cases in China has shown that less than 1% of the patients were younger than 10 years of age (4). Also, the number of children's cases with COVID -19 may increase in future and a lower number of pediatric patients at the beginning of a pandemic does not necessarily mean that children are less susceptible (5). Children, in comparison with adults experience a milder course of SARS- CoV-2 and have better prognosis (6). However, there are a number of subgroups in pediatric population with an increased risk of more severe disease, such as children with cancer (7).

Cancer patients are a highly susceptible group in COVID -19 pandemic, but so far the clinical characteristics of COVID -19 infected cancer cases are largely unknown (8). SARS- CoV-2 among children with cancer might be a much more severe disease in comparison with healthy children (9). Patients with cancer are especially vulnerable to respiratory pathogens and severe pneumonia due to the immunosuppressive situation they have (8). The risk of hospitalization in patients with cancer due to influenza is four-fold and the risk of death is ten times higher compared with general population, especially in patients with hematological malignancy or those manifesting with neutropenia or particularly lymphopenia (10). It is recommended that children with a neoplasm who are receiving anti-cancer treatments should have strict screening for COVID-19 infection and should avoid treatments causing marked immunosuppression in case of COVID-19 co-infection. Regarding increasing number of childhood cancers in all parts of world, there is an urgent need to answer the following questions, including whether COVID-19 infected cancer patients will have dismal prognosis, such as death from the infection or severe pneumonia, and whether cancer patients should receive anti-tumor treatments as usual with previous doses, in epidemic areas. Furthermore, delaying chemotherapy in all children with cancer could not be advised as a reasonable option to reduce the infection risk in the ongoing outbreak (8). Therefore, the aim of this review article was to explore these issues by conducting a comprehensive search about various aspects of childhood cancers in the COVID -19 pandemic and also management of critical COVID-19-infected cancer patients have been discussed.

2- MATERIALS AND METHODS

In this review, an electronic search was performed in databases of Scopus, EMBASE, Cochrane, Web of Science and Medline (via PubMed) with no language or time restrictions (up to August 5, 2020). The single and combination keywords of: "2019 novel coronavirus" OR "2019-nCoV" OR "COVID-19" AND "Childhood Cancer" OR "Neoplasm". The references of all included articles were searched to identify additional studies. The title, abstract and full text of all documents identified using these search criteria were screened by an expert pediatric hematologist and oncologist and those describing children with cancer who were infected with COVID-19 were finally selected. Overall, 188 articles could be originally identified using our search criteria, 167 of which were excluded after title, abstract or full text reading, because

they did not correlate with COVID- 19 in childhood. In this study, all review articles, cohort studies, retrospective analysis and randomized controlled trial about COVID -19 in children with cancer were included. Pilot, preliminary and case report studies were not included due to limited sample size and a higher risk of bias. All studies that were not related to the subject, or were duplicate, were excluded.

3- RESULTS

A total number of 21 studies were finally selected. The results of these studies have been classified in 4 groups: General aspects about COVID -19 in children, susceptibility of children with cancer to COVID -19, the effect of cancer therapy on immune function in childhood neoplasms and treatment of children with cancer in COVID -19 outbreak.

4- Routes of transmission in children with cancer

Children can be infected easily by respiratory droplets containing the virus. Usually infection with corona virus occurs through respiratory route. This virus has animal to person and person to person transmission. Also, in children corona virus can be transmitted by contact with contaminated objects such as toys. COVID-19 has interfamilial transmission especially to elderly and children who are susceptible to this virus (11). Also, one of the most common routes of transmission is nosocomial transmission of SARS-CoV-2. Hospital related transmission could occur among both patients and healthcare workers (8). In a retrospective study on 138 patients it was reported that 41.3% of the patients acquired SARS-CoV-2 infection during hospitalization and 5 of these patients were from the oncology ward (12). If the disease had gone further, without effective and sufficient control, the outbreak might have gone into a new step or explosion stage. In this phase, school transmission could lead to a wider community spread and children can further become the main spreader of COVID-19. Regarding the fact that children often have mild symptoms, many of them could not be diagnosed, especially at early stages (11).

5- Clinical manifestations of COVID -19 in children

The spectrum of clinical manifestation in children is similar to adults. Dong et al. in a large study on 2,143 children with documented disease have shown that the most common symptoms were fever, cough, sore throat, sneezing, myalgia and fatigue. Some children may experience wheezing (13). Other symptoms were gastrointestinal complaints such as vomiting, diarrhea, nausea and abdominal pain (11). According to the disease severity classification used by multiple Chinese publications, severe disease was defined as dyspnea, central cyanosis and oxygen saturation less than 92%. Critical disease was defined as respiratory failure, shock and signs of multi organ failure such as encephalopathy, heart failure, abnormal coagulation and acute renal failure. The prevalence of severe and critical disease is much higher in infants compared with older children (13). However, in children with cancer the symptoms may be atypical and even sometimes subtle. Therefore, heightened awareness is necessary for clinician in order to detect COVID -19 disease in early stages (14). Furthermore, the delay in admission of patients with cancer and COVID -19 may lead to an unfavorable prognosis (8).

6- Susceptibility of children with cancer to COVID -19

Pediatric patients with cancer are regarded as a highly vulnerable group in the current COVID -19 pandemic. These patients are more likely to be infected with this virus due to immunosuppressed state. These children are receiving anti-neoplastic agents which result in weakening of

immune system (15). In patients who have received anti-cancer treatment within 14 days, a more severe impairment in immune system function has been reported (14). Moreover, younger age, presence of an underlying pulmonary disease and a respiratory co-pathogen (particularly respiratory syncytial virus) are associated with increasing severity of lower respiratory tract disease in COVID-19 (16). Many of these patients, especially cases with hematological malignancies such as acute lymphoblastic leukemia (ALL), receive steroids for long periods. Administration of steroids has been considered to diminish virus clearance due to its immunosuppressive effect (8). Children with cancer are often called to go to hospital for diagnostic investigation, treatment modalities and even follow up. Moreover, if these children are infected with COVID -19, their clinical course is more likely to be severe. Furthermore, intensive care units in the majority of hospitals may not be able to provide sufficient care for cancer patients with COVID -19 (15).

6-1. The effect of cancer therapy on immune function in childhood neoplasms

6-1-1. Chemotherapy

It has been well established that corticosteroid and other immunosuppressive drugs have a key role in severe respiratory viral disease (17). Administration of anti-neoplastic agents may lead to a marked damage to hematopoietic cells in bone marrow resulting in neutropenia and thrombocytopenia. However, cancers that invade normal bone marrow such as lymphoma and leukemia can result in neutropenia and thrombocytopenia. During nadir period when their granulocyte numbers are the minimum, cancer patients are highly susceptible to various infections. This nadir commonly occurs 7-12 days after the end of each chemotherapy cycle (18). Lymphopenia is another important risk factor for occurrence of respiratory viral infections especially COVID-19. Furthermore, SARS- CoV-2 virus could directly invade lymphocytes leading to lymphocyte death. Lymphocytes express the COVID -19 receptor ACE 2 (angiotensin converting enzyme 2) and may be a direct target of this virus (19). Lymphopenia could predict the severity of disease and presence of lymphopenia on admission was correlated with ICU admission (20). Among chemotherapeutic agents, cisplatin, cyclophosphamide, fludarabine, methotrexate, and taxes are the most potent agents which cause lymphopenia (21). Also, platelets have an important role in immune system and have viricidal property against some viruses, so thrombocytopenia due to chemotherapy could be a predisposing factor for viral infections (22). Some authorities recommend postponing adjuvant chemotherapy for stable cancer patients particularly in active pandemic area (18).

6-1-2. Radiotherapy

High dose radiation therapy could impair the immune system. Therefore, this modality of treatment is a critical predisposing factor for progression to lower respiratory tract infection. Kim et al. have reported that high dose body irradiation in hematopoietic stem cell transplantation predisposes recipient to respiratory syncytial virus (RSV) (23). External beam radiation could effect on lymphocyte resulting in radiation induced lymphopenia. By using proton beam therapy, stereotactic body radiation or a hypofractionated schedule, the risk of lymphopenia due to radiation decreases (21).

6-1-3. Hematopoietic stem cell transplantation (HSCT)

The highest morbidity and mortality due to viral respiratory infections occurs in recipients of HSCT. This modality of treatment kills the host immune system and replaces it with donors. These patients are particularly prone to different infections such as viral respiratory disease during the first 3 months after transplant and often reconstitution of immune system to baseline occurring up to one year (24, 25). Also, graft versus host disease (GVHD), use of corticosteroids, neutropenia, hypoalbuminemia, lymphopenia, and older age are the most important risk factors for lower respiratory tract infections (26, 27). However younger cancer survivors often have stronger reconstituted immune system in comparison with older survivors (18). Ogimi et al. have shown that infection with human corona virus has been correlated with higher rates of oxygen requirement and also mortality among hematopoietic stem cell recipients (28).

6-1-4. Immune therapy in cancer patients

At present, there are no established guidelines for beginning of immunotherapy during the SARS-CoV-2 infection pandemics. Immune check point inhibitors, T- cell transfer therapy and immune modulating agents have been used in treatment of some types of cancer. Furthermore, the pathogenesis of side effects of this therapy is due to hyper activated T cell response against normal tissues. The main side effects of this modality of treatment include prolonged lymphopenia, thrombocytopenia, and anemia and even increased vascular permeability leading to pleural effusion or pulmonary edema (29). Janus kinase inhibitors (JAK i), and Bruton tyrosine kinase inhibitors which have been administered in specific variants of hematologic malignancies, such as lymphoma and leukemia may result in immune suppression by inhibiting cytokine and growth factor signaling pathways and prevention of lymphocyte maturation (18).

7- Diagnosis

Documented diagnosis is by specific molecular tests on respiratory samples such as nasopharyngeal swab, endotracheal aspirate or bronchoalveolar lavage. Occasionally virus can be isolated from stool or even in severe cases from blood (30). Nucleic acid testing is the principal method of laboratory diagnosis. 2019-nCoV nucleic acid could be detected via RT – PCR (reverse transcription polymerase chain reaction) or by viral gene sequencing on respiratory or blood samples (31). Other laboratory tests are not specific. The white blood cell count is normal or low. Also, if the absolute lymphocyte count was below 1000, the risk of severe disease increases. The platelet count is usually normal or mildly low. The CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate) are often elevated but procalcitonin level is usually normal. Elevation of procalcitonin level may indicate a bacterial co-infection (30). The chest CT features include ground glass opacity and patchy consolidation and the CT findings in cancer children with COVID-19 infection are similar to the features in general population. Also, the presence of patchy consolidation in chest CT scan on admission is a risk factor associated with severe events (8). Shi et al. have shown the timing of emergence of CT features in COVID -19 infection. They have found that the first feature on CT scan is the ground glass opacity, even before the onset of symptoms. This CT finding increases during the two weeks and then diminishes in the third week. In one or two weeks after beginning of symptoms, patchy consolidation appears which can rapidly progress to bilateral extension consolidation with a white lung presentation on CT scan. This stage of CT manifestation is often associated with a dismal prognosis (32).

8- Treatment

Several treatment modalities are currently available for SARS-CoV-2 virus in children with cancer, but up to now, treatment of most patients with COVID-19 focuses on supportive strategies (18). These supportive therapies include administration of sufficient fluid and electrolyte, nutritional support, oxygen supplementation and antibiotics for superimposed infections (33, 34). At present there is no definite and specific antiviral treatment for COVID-19 virus in children (35). Antiviral therapy was obviously administered in severe cases, but data on its efficiency in children with this virus infection are missing (6). Patients with mild infection often recover without any complications at home. The main strategy for this group of patients should be isolation and prevention of virus spread to other persons. Patients with moderate symptoms and pneumonia could be managed with supportive therapy, hydroxychloroquine and azithromycin (18). There is no dosage recommendation for chloroquine diphosphate (CD) in children. The usual dose for adult is 0.5gr twice daily for 7 days and for people with body weight less than 50kg, this dose should be decreased to 0.5gr once daily. However extreme caution should be used during consumption of this drug in children (35). Although in a recent study it has been shown that chloroquine does not have antiviral activity and combination of chloroquine and azithromycin not have any clinical benefit in treatment of hospitalized patient with severe COVID-19 infection (36). Chloroquine diphosphate has some mild side effects such as dizziness, headache and anorexia, but the main adverse reaction is ocular toxicity. If visual abnormality occurs, the administration of this drug should be stopped immediately. Other adverse reactions of chloroquine consist of arrhythmia, drug induced psychosis and leukopenia (35). Remdesivir and lopinavir/ritonavir have been proposed for cases with severe disease. Patients with ARDS (acute respiratory distress syndrome) or those requiring assisted ventilation have been classified in severe group. In patients with cytokine release syndrome who have acute lung injury and high levels of inflammatory markers, tocilizumab is indicated (18).

8-1. Lopinavir/ritonavir (LPVr)

Initially LPVr has been used for treatment of children with HIV infection (37, 38). Also, the positive effects of this drug on SARS and MERS infection have been shown in clinical trials (39, 40). LPVr is available in oral tablet and solution. Oral solution form of this drug is suitable for children with a body surface less than 0.6 m^2. Lopinavir is metabolized by liver, so in patients with severe hepatic insufficiency, this drug is contraindicated. Furthermore, administration of LPVr may lead to first, second and third degree atrioventricular (AV) block. Other common side effects of this drug in children consist of diarrhea, vomiting and rash (35).

8-2. Tocilizumab

Different studies have shown that cytokine storm has a critical role in the pathogenesis of SARS and MERS infection (41). Also, in COVID-19 infection, higher plasma levels of cytokines such as IL-6 (interleukin-6), IL-2, IL-7, IL-10, granulocyte colony stimulating factor (G-CSF), monocyte chemoattractant protein (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1 α) and tumor necrosis factor α (TNF α) have been detected in critically ill patients in ICU. These changes show a cytokine storm in these cases and also have a close relation with severity and prognosis of patients (42, 43). Among these cytokines, IL- 6 might play an important role in the cytokine storm and interference of IL- 6 could be a

valuable therapeutic option for severe cases of COVID-19 (41). Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody which has been used for treatment of rheumatoid arthritis (44, 45). Xu et al. in a study on 21 patients with severe and critical COVID-19 infection have shown that this drug could be an effective therapeutic option (40). Furthermore, some authors recommend that in critically ill patients with elevated IL-6, the repeated dose of tocilizumab could be beneficial (46). Both of these studies have been done on adults, hence the experience with this drug is very limited for children (41, 46).

8-3. Remdesivir

Remdesivir is a pro drug of a nucleotide analogue whose main function is inhibiting viral DNA polymerase. This drug has broad spectrum activity against different viruses, especially filoviruses (Ebola), and corona viruses such as SARS-CoV and MERS-CoV. Grein et al., have used compassionate use of remdesivir for 61 patients with severe COVID -19. These authors have demonstrated clinical improvement in 68% of patients (47). Wang et al. have reported that this drug could inhibit COVID-19 infection strongly even at low micromolar concentration (48). Also, Holshue et al., reported that remdesivir has been effective in treatment of a patient with SARS-CoV-2 infection in United States (49). Remdesivir is currently indicated for patients with severe symptoms such as ARDS and also requiring mechanical ventilation (18).

8-4. Interferon (IFN)

Zhejiang University School of Medicine recommends that the use of nebulized IFN alpha – 2b could be effective in children infected by SARS-CoV-2 (31). IFN-alpha is a broad spectrum antiviral agent with inhibitory properties on viral replication and spread. IFN –alpha is available in spray, gel and injection (35). According to expert's consensus statement, IFN could be used for treatment of COVID -19 in children (50). IFN should be used with caution in children and overdose of this drug could cause bleeding, renal failure and liver enzyme abnormalities (35). Common side effects of IFN consist of low grade fever, and flu-like syndrome. One of the adverse reactions of this drug particularly in combination with ribavirin is growth and development inhibition. IFN-alpha is contraindicated in patients with abnormal liver function tests and those with creatinine clearance below 50ml/min. Moreover, IFN-alpha is contraindicated in children with history of mental illness, aplastic anemia and severe heart disease (35).

8-5. Convalescent plasma

In the refractory severe infections with COVID-19 with worsening of manifestations, the convalescent plasma should be considered (17). The effectiveness of convalescent plasma for treatment of severe cases with COVID-19 has been reported in many publications (51-58). Also the US Food and Drug Administration (FDA) has approved the use of convalescent plasma for critically ill patients (58). Duan et al. in a study on 10 patients with severe COVID-19 have reported that one dose (200 ml) of convalescent plasma could increase or stabilize the neutralizing antibodies at a high level resulting in disappearance of viremia in 7 days. These authors have shown that clinical manifestations and laboratory signs rapidly improved in 3 days. Furthermore, images of chest CT scan in these patients showed varying degree of absorption of lung lesions in 7 days (57). Also, several studies have reported that use of convalescent plasma could result in shorter hospital stay and lower mortality in patients with severe COVID-19. Additionally, no adverse event was observed during or after convalescent plasma therapy (51). Currently, however,

no specific antiviral antibody for SARS-CoV-2 in not available and management of COVID-19 must be focused on prevention, case detection, monitoring and supportive care (59).

4- DISCUSSION

Among children with cancer, COVID-19 might be a much more severe infection in comparison with healthy normal children. This is similar to other corona viruses which cause more severe infection in immunocompromised children (9). Zhang in a study on 44,672 laboratories that confirmed COVID-19 cases in all parts of China, has reported that only 416 (0.9%) were less than 10 years of age and 549 (1.2%) from 10- 20 years (60). Although with increase in the number of infected adults, the rate of this infection in children also increases (11). Also, Kim et al. in a study on patients with cancer have reported that coronavirus pneumonia had a higher mortality rate in cancer cases (61). Moreover, these patients often have prolonged viral shedding (62). However, there are some disagreements about children with cancer in COVID-19 outbreak. In a recent study from China, authors have shown that there was no increase in incidence of COVID-19 infection in cancer patients but cancer patients had a higher incidence of severe events such as respiratory complications necessitating intensive care. Furthermore, patients with cancer when infected with SARS-CoV-2 virus, have a poorer outcome, so the more intensive attention should be paid to these patients, because the condition of these patients could deteriorate rapidly (63). Peng et al. have reported that in Liang's study, the sample size was too small and heterogeneous, so these data are insufficient to conclude that patients with cancer have a higher risk (64). In many pediatric hematology and oncology centers, only for symptomatic children with cancer has the COVID -19 test been done, and there is no recommendation for this test among asymptomatic children, therefore the true rate of infection is not known. The low rate of documented COVID-19 infection among children with cancer is somewhat surprising, because logically pediatric patients with cancer would be at least as vulnerable to COVID-19 infection as their healthy peers. However, it seems that the true risk of severe disease with SARS-CoV-2 in immunocompromised pediatric population with cancer is still unknown (9). Minotti et al. in a systematic review about the COVID-19 infection in children and adults with immunosuppression have concluded that cancer was more often associated with a more severe course, but not necessarily a worse outcome. These authors have shown that immunosuppressed patients have a better prognosis as compared to other comorbidities especially in adults such as diabetes and cardiovascular disorders. In cancer patients, a weaker immune response against COVID-19 may have a potential protective effect leading to a milder course of disease. Indeed, host response is an important factor contributing to disease severity. Dysregulation of immune system or an excessive uncontrolled response are responsible for injury to tissues during the process of infectious diseases such as corona viruses (65). However, data on clinical features and outcome of immunocompromised children with cancer infected with SARS-CoV-2 is little and the majority of published data has been done in adults. Most neoplasms in pediatric population have an aggressive manner and therefore require prolonged periods of multi agent chemotherapy. In adults with cancer who have stable disease, postponement of therapy could be possible, but in children delay in onset of treatment is not a suitable option. One of the most effective strategies in order to prevent COVID-19 is minimizing the risk of exposure and also extreme isolation. However, in majority of children with

cancer hospital admission is required for an appropriate therapy (66).

5- CONCLUSION

Immunocompromised children with cancer have a worse outcome during the COVID -19 infection. At now, there is no specific antiviral treatment for children with COVID -19. Identification of specific risk factors for SARS -COV-2 infection in hospitalized children with hematological neoplasms is not possible. Therefore, increased surveillance and protective strategies such as isolation have been recommended.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1.Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. The Lancet 2020;395(10223):470-73.

2. Hosseinzadeh Shirayeh B, Shojaie L, Maharatfard Jahromy M, Vaziri M, Safavi S, Jafari R, et al. Comparison of Clinical Characteristics of Hospitalized Patients with and without Covid-19 in Mashhad, Iran: A Retrospective, Single-Center Experiences. International Journal of Pediatrics, 2020; 8(12): 12619-628.

3.Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382(17):1663–65.

4.Wu Z, Mc Googan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID -19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention.JAMA.2020;323(13):1239-42.

5. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID -19? J Microbiol Immunol Infect 2020; 2020;53(3):371-72.

6. Ludvigsson JF. Systematic review of COVID -19 in children show milder cases and a better prognosis than adults. Acta Paediatr 2020;109(6):1088-95.

7. Cruz AT, Zeichner SL. COVID -19 in children: initial characterization of the pediatric disease. Pediatrics.2020; e20200834.

8. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID -19 infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020; 31(7):894-901.

9. Hrusak O, Kalina T, Wolf J, Balduzzi A, Provenzi M, Rizzari C, et al. Flash Survey on SARS-CoV-2 Infections in Pediatric Patients on anti-Cancer Treatment. Eur J Cancer 2020; 132:11-16.

10. Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev 2013;2013(10):CD008983.

11. Cao Q, Chen YC, Chen CL, Chiu CH. SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics. J Formos Med Assoc 2020;119(3):670.

12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061-69.

13. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020;145(6): e20200702.

14. Ganatra S, Hammond SP, Nohria A. The Novel Coronavirus Disease (COVID -19) Threat for Patients with Cardiovascular Disease and Cancer. JACC: CardioOncology 2020; 10.1016/j.jaccao.2020.03.001.

15.Cannizzaro R, Puglisi F. COVID -19 and cancer patients: choosing wisely is the key. Dig Liver Dis 2020; 52(6):595-596

16.Ogimi C, Englund JA, Bradford MC, Qin X, Boeckh M, Waghmare A. Characteristics and outcomes of coronavirus infection in children: the role of viral factors and an immunocompromised state. J Pediatric Infect Dis Soc 2019;8(1):21-8.

17. Hijano DR, Maron G, Hayden RT. Respiratory Viral Infections in Patients with

Cancer or Undergoing Hematopoietic Cell Transplant. Front Microbiol 2018; 9:3097.

18. Yeoh CB, Lee KJ, Rieth EF, Mapes R, Tchoudovskaia AV, Fischer GW, et al. COVID-19 in the Cancer Patient. Anesth Analg 2020;10.1213.

19. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020;5(1):1-3.

20. Fan BE, Chong VC, Chan SS, Lim GH, Lim KG, Tan GB, et al. Hematologic parameters in patients with COVID -19 infection. Am J Hematol 2020;95(6): E131-E134.

21. Ménétrier-Caux C, Ray-Coquard I, Blay JY, Caux C. Lymphopenia in Cancer Patients and its Effects on Response to Immunotherapy: an opportunity for combination with Cytokines? J Immunother Cancer 2019;7(1):85.

22. Speth C, Löffler J, Krappmann S, Lass-Flörl C, Rambach G. Platelets as immune cells in infectious diseases. Future Microbiol 2013; 8:1431–51.

23. Kim YJ, Guthrie KA, Waghmare A, Walsh EE, Falsey AR, Kuypers J, et al. Respiratory syncytial virus in hematopoietic cell transplant recipients: factors determining progression to lower respiratory tract disease. J Infect Dis 2014;209(8):1195-204.

24. Fisher BT, Danziger-Isakov L, Sweet LR, Munoz FM, Maron G, Tuomanen E, et al. A multicenter consortium to define the epidemiology and outcomes of inpatient respiratory viral infections in pediatric hematopoietic stem cell transplant recipients. J Pediatric Infect Dis Soc 2018;7(4):275-82.

25. Ogonek J, Kralj Juric M, Ghimire S, Varanasi PR, Holler E, Greinix H, et al. Immune reconstitution after allogeneic hematopoietic stem cell transplantation. Front Immunol 2016; 7:507.

26. Eichenberger E.M, Soave R, Zappetti D, Small C.B, Shore T, van Besien K, et al. Incidence, significance, and persistence of human coronavirus infection in hematopoietic stem cell transplant recipients. Bone Marrow Transplant 2019; 54:1058–66.

27. Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, meta pneumovirus, rhinovirus, and coronavirus. Clin Infect Dis 2013; 56:258–66.

28. Ogimi C, Waghmare AA, Kuypers JM, Xie H, Yeung CC, Leisenring WM, et al. Clinical significance of human coronavirus in bronchoalveolar lavage samples from hematopoietic cell transplant recipients and patients with hematologic malignancies. Clinical Infectious Diseases 2017; 64(11):1532-39.

29. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol 2015;33(18):2092-2099.

30. Singhal T. A review of coronavirus disease-2019 (COVID -19). Indian J Pediatr 2020; 87: 281–86.

31. Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr .2020;16(3):240-46.

32. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID -19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):425-34.

33. Cai J, Xu J, Lin D, Xu L, Qu Z, Zhang Y, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. [Published online ahead of print, 2020 Feb 28]. Clin Infect Dis. 2020; ciaa198.

34. Zimmermann P, Curtis N. Coronavirus infections in children including COVID -19: An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infec. Dis J 2020; 39(5):355.

35. Wang Y, Zhu LQ. Pharmaceutical care recommendations for antiviral treatments in children with coronavirus disease 2019. World J Pediatr 2020; 12:1-4.

36. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID -19 infection. Med Mal Infect 2020:30085-88.

37. Sáez-Llorens X, Violari A, Deetz CO, Rode RA, Gomez P, Handelsman E, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2003; 22(3):216-23.

38.Cvetkovic RS, Goa KL. Lopinavir/ritonavir. Drugs 2003;63(8):769-802.

39. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J 2003; 9: 399–406.

40. Chong YP, Song JY, Seo YB, Choi JP, Shin HS; Rapid Response Team. Antiviral treatment guidelines for Middle East respiratory syndrome. Infect Chemother 2015; 47:212–22.

41. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID -19 patients with tocilizumab. Proc Natl Acad Sci USA 2020;117(20):10970-10975.

42. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223):507-13.

43. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel corona virus in Wuhan, China. Lancet 2020; 395:497-506.

44. Kaly L, Rosner I. Tocilizumab - a novel therapy for non-organ-specific autoimmune diseases. Best Pract Res Clin Rheumatol 2012; 26:157-65.

45. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al.Efficacy and safety of tocilizumab in patients with systemic onset juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008; 371:998-1006.

46. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID -19: A single center experience. J Med Virol 2020;10.1002/jmv.25801.

47. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe COVID -19. N Engl J Med 2020;382(24):2327-36

48. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269-71.

49. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382(10):929-36.

50. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020; 16(3):223-31.

51. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID -19. Lancet Infect Dis 2020;20(4):398-400.

52. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID -19 with convalescent plasma. JAMA 2020;323(16):1582-89.

53. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID -19 patients. Proc Natl Acad Sci U S A 2020;117(17):9490-96.

54. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID -19. J Clin Invest 2020;130(4):1545-48.

55. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID -19. J Clin Invest 2020;130(6):2757-65.

56. Roback JD, Guarner J. Convalescent plasma to treat COVID -19: possibilities and challenges.JAMA.2020;10.1001.

57. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA. 2020;117(17):9490-96.

58. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ 2020; 368:m1256.

59. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf. (Accessed Feb 20, 2020).

60. Zhang YP. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID -19) in China. Chin J Epidemiol 2020; 41:145e51.

61. Kim YJ, Lee ES, Lee YS. High mortality from viral pneumonia in patients with cancer. Infect Dis (Lond) 2019; 51:502–9.

62. Milano F, Campbell A.P, Guthrie K.A, Kuypers J, Englund J.A, Corey L, et al. Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. Blood 2010; 115:2088–94.

63. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21(3):335–37.

64. Peng L, Zagorac S, Stebbing J. Managing patients with cancer in the COVID -19 era. Eur J Cancer 2020; 132:5-7.

65. Minotti C, Tirelli F, Barbieri E, Giaquinto C, Donà D. How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review. J Infect 2020; 81(1):e61-e66.

66. Kotecha RS. Challenges posed by COVID-19 to children with cancer. Lancet Oncol 2020; 21(5): e235.