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CASE SERIES

CANCER AND CHEMOTHERAPY IN PEDIATRIC COVID-19: A CASE SERIES

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ABSTRACT

Objectives: This case series aims to present three cases of pediatric cancer – two acute leukemia and one solid tumor with active COVID-19 infection who underwent chemotherapy

Methodology: Three cases of pediatric cancer who tested positive for SARS-CoV2 are presented. All proceeded with scheduled chemotherapy despite active COVID-19 infection. Two had no post-chemotherapy complications, while one had febrile neutropenia and hospital-acquired pneumonia.

Results: In this case series, COVID-19 infection in pediatric patients with cancer does not appear to be more severe compared with the general population. The severity of signs and symptoms can be attributed to a lower Cycle Threshold (CT) value and a co-infection. COVID-19 infection did not change the course and post-chemotherapy complications in all cases.

Conclusion: Patient demographics, comorbidities and type of malignancy played an essential role in the pre- and post-chemotherapy outcome. Individual patient factors including CT values, comorbidities, co-infections, COVID-19 disease severity classification, and blood count picture are also instrumental in the management and outcome of these cases. Pediatric cancer treatment should be a priority during active COVID-19 infection.

KEYWORDS: *COVID-19, Chemotherapy, Cancer, Children*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

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INTRODUCTION

The COVID-19 pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has quickly changed the course of medicine. Currently, more than 100 million people have been affected globally, with over 4 million deaths. In the Philippines alone, there are more than 1 million positive cases to date.[1] Fewer cases of COVID-19 have been reported in children (age 0-17 years) compared to adults with a milder course.[2] In recent studies, data on children with comorbidities, like cancer, and those with medical complexities, such as neurologic and metabolic conditions, showed that they were more likely to test positive for the disease.[3] Locally, the Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) registry data showed that 7.4% of total pediatric COVID-19 positive patients are those with pediatric hematologic or oncologic disease. Additional data from the St. Jude Global registry for childhood cancer reported a total of 1,700 positive COVID-19 cases among pediatric patients from 49 countries across the globe.

During this pandemic, much attention was brought to delays in accessing timely pediatric care leading to unintended morbidity worldwide.[4] Delays in the diagnosis and treatment of life-threatening diseases, including cancer, have been reported. Intensive care admissions, which could have been prevented, were described due to delays in seeking medical attention. A lot of attention was directed to the implementation of basic guidelines to limit the spread of the virus but not enough focus was placed on the importance of adherence to pediatric cancer treatment and management. This poses a question on how to go about managing COVID-19 positive pediatric cancer patients.

In our institution, guidelines were developed for the treatment of cancer patients due to lack of international or local guidelines.

These cases can become the basis for developing recommendations that balance the risk of delaying chemotherapy during active COVID-19 infection. The risk of continuing chemotherapy despite disease severity especially during periods of immunosuppression can be further analyzed.

This case series presented 3 cases of children with hematologic and oncologic malignancies who underwent chemotherapy during active COVID-19 infection in a tertiary hospital. It highlighted differences in clinical presentation, course, diagnosis, management, and treatment outcomes. Distinctive features such as CT values, comorbidities, co-infections, COVID-19 disease severity classification, and blood count picture that played a role in the patients' overall outcome were emphasized. The importance of continuing pediatric cancer treatment despite active COVID-19 infection was stressed.

PATIENT'S INFORMATION

A descriptive, observational study of three cases of pediatric cancer that underwent chemotherapy despite active COVID-19 infection are presented. An informed consent was obtained from all 3 cases regarding the write up of this case series.

Case One

This is a case of a 2-year-old male, diagnosed with B-cell Acute Lymphoblastic Leukemia (ALL), Standard Risk since February 2021. Induction chemotherapy was started according to the Modified Societe Internationale D'oncologie Pediatrique (SIOP) Pediatric Oncology in Developing Countries (PODC) Graduated Intensity Regimen Low Income Country (LIC) 3 protocol. On his second week of treatment, he underwent mandatory SARS-CoV2 Reverse Transcription Polymerase Chain Reaction (RT-PCR) testing as per institutional protocol, which was positive. He had no known exposure and no other family member tested positive for COVID-19.

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He had no respiratory symptoms prior to, during, and after COVID-19 testing but had decreased appetite and generalized body weakness on review of systems. There was no blurring of vision, bleeding episodes, chest pain, constipation and or diarrhea, changes in urinary habits, vomiting, or seizures. He had pyomyositis of the right leg which presented with pain, limitation of range of motion, muscle tenderness and erythema of overlying skin and was on oral antibiotics prior to this admission. Routine blood tests revealed anemia and thrombocytopenia, which was addressed by transfusion of PRBC and platelet concentrate. Empiric antibiotics for pyomyositis were continued.

The absence of respiratory symptoms, normal routine chest radiograph, resolving pyomysositis, along with stable vital signs, despite a CT value of 33.38, prompted the managing team to pursue scheduled chemotherapy on the 6th day of his COVID-19 illness. He remained stable during and post-chemotherapy. Blood counts remained normal and he remained asymptomatic throughout his hospitalization. A repeat SARS-CoV2 RT-PCR taken 12 days from the 1st test (9th day of hospitalization) was negative and he was sent home and cleared for community integration.

Table 1. Diagnostic Profile and COVID-19 Status of Case One

SARS-CoV-2 Status (Pre-Chemotherapy)	COVID-19 Asymptomatic
Diagnostic Tests Pre-Chemotherapy	
Hgb (g/dl)	127
WBC x 10^9 /L	2.60
Neutrophils	0.12
Lymphocytes	0.82
Platelet Count x 10^9/L	75
Absolute Neutrophil Count	1003.1
Chest Radiograph	Normal
CT-Value	FAM: 33.38 HEX: 34.15
SARS-CoV-2 Status (Post-Chemotherapy)	COVID-19 Asymptomatic
Diagnostic Tests Post-Chemotherapy	
Hgb (g/dl)	130
WBC x 10^9 /L	2.83
Neutrophils	0.13
Lymphocytes	0.86
Platelet Count x 10^9/L	50
Absolute Neutrophil Count	1003.7
Chest Radiograph	Normal
Complications Post-Chemotherapy	None
SARS-CoV-2 Status (on Discharge)	Recovered
SARS-CoV-2 Status (on Follow-up)	No reinfection to date

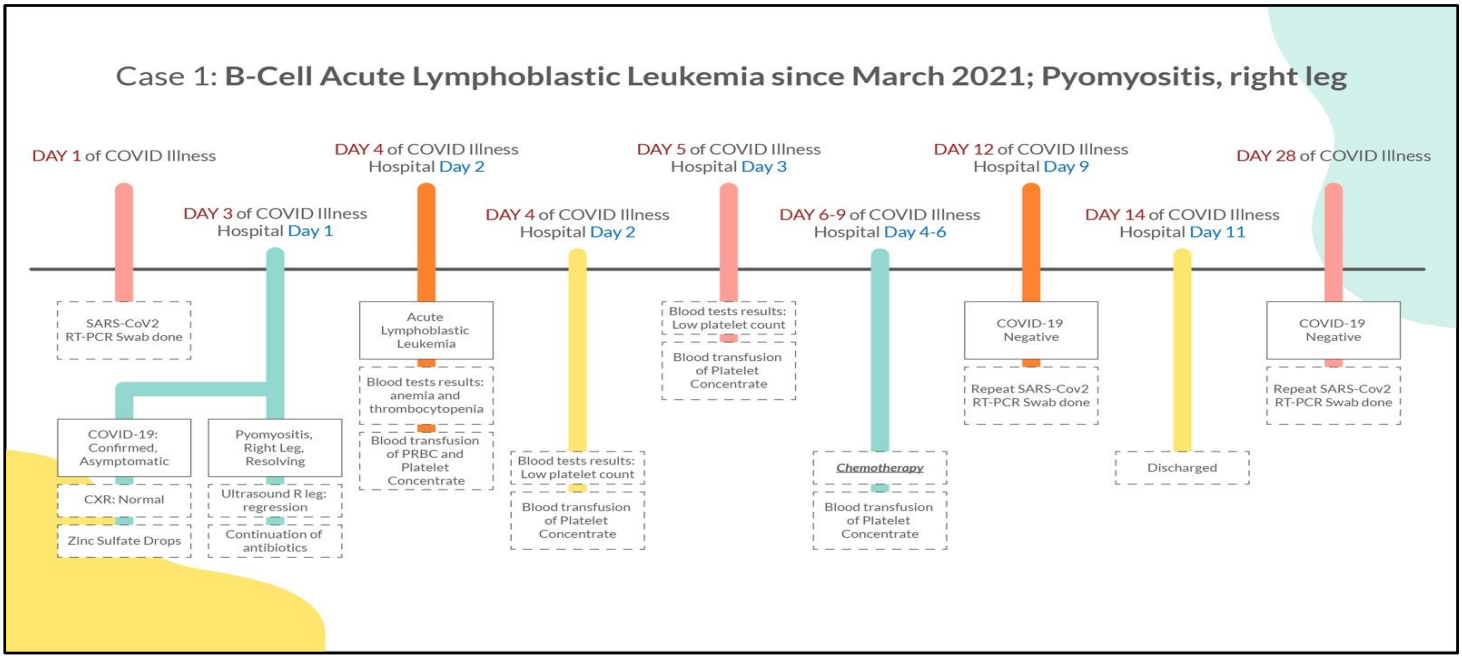

Figure 1. Timeline of Events and Course of Case One

Case Two

This is a case of a 3-year-old male diagnosed with B-cell Acute Lymphoblastic Leukemia, Standard Risk since April 2020. He was initiated on modified BFM/pre-B cell Children's Cancer Group (CCG) protocol and had his chemotherapy 2 weeks prior to this admission.

Five days prior to his scheduled fifth cycle of maintenance chemotherapy, he developed intermittent fever, with decreased appetite, oral intake, and activity which prompted consult at the Emergency Room. He had no known exposure to a COVID confirmed case; however, due to the presence of fever in this patient, and on following institutional protocols, SARS-CoV2 RT-PCR testing was done on admission.

On review of systems, he had generalized body weakness. There were no rashes, no blurring of vision, cough and colds, bleeding episodes, chest pain, changes in bowel and bladder habits, vomiting, or seizures. Physical examination showed that he had stable vital signs, with findings of pallor and non-tender lymphadenopathies on the occipital area. At that time, he had no respiratory findings and no retractions. His clinical signs and symptoms were attributed to a systemic viral infection (SVI) to consider dengue fever versus febrile neutropenia. His complete blood count revealed anemia, leukopenia, and thrombocytopenia. Dengue serology was positive for Immunoglobulin M (IgM) antibodies and negative for Immunoglobulin G (IgG). Dengue nonstructural protein 1 antigen (NS1) was also negative. He underwent mandatory SARS-CoV2 RT-PCR testing which revealed a positive result. The patient had no known exposures but his mother tested positive for COVID-19 as well.

Patient was started on empiric antibiotics for febrile neutropenia. In addition, platelet concentrate and PRBC transfusions were given. Serial CBC monitoring was continued and adequate hydration was maintained.

The improving trend of his blood picture, absence of respiratory symptoms, normal chest radiograph, and stable vital signs prompted the managing team to continue with his scheduled chemotherapy despite active COVID-19 with a low CT value (21.89) and the presence of dengue fever.

He had recurrence of febrile episodes two days post-chemotherapy and febrile neutropenia was again entertained. Work-up for sepsis was done revealing unremarkable results, but due to the low absolute neutrophil count (ANC), empiric antibiotics were continued. On the 12th hospital day, he had occasional dry cough with recurrence of intermittent fever and decreased appetite. Chest x-ray revealed pneumonia. Patient was managed as a case of healthcare-associated pneumonia and antibiotics were shifted to Piperacillin-Tazobactam.

On the 19th hospital day, he had worsening cough with fever despite antibiotic therapy. Repeat chest x-ray showed progression of pneumonia. Patient had persistently low ANC hence Fluconazole and Vancomycin were added to the treatment regimen. Gradual improvement was noted and on the 26th hospital day, 30 days after the onset of signs and symptoms, repeat RT-PCR test was negative. He was sent home improved on the 33rd hospital day. He remained COVID-19 negative on repeat SARS-CoV2 RT-PCR testing on follow-up, 41 days after his first COVID-19 diagnosis.

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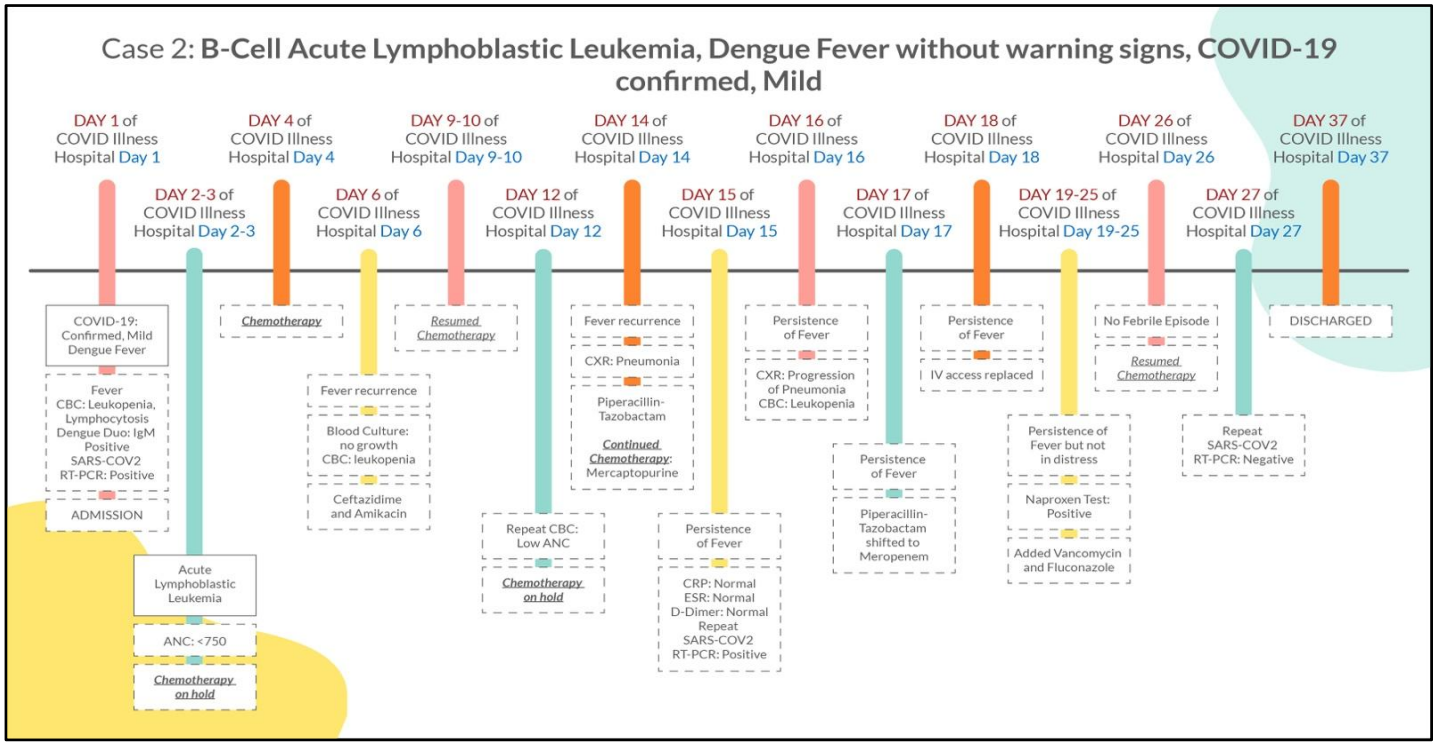

Figure 2. Timeline of Events and Course of Case Two

Table 2. Diagnostic Profile and COVID-19 Status of Case Two

SARS-CoV-2 Status (Pre-Chemotherapy)	COVID-19 Mild
Diagnostic Tests Pre-Chemotherapy	
Hgb (g/dl)	102
WBC x 10^9 /L	1.27
Neutrophils	0.41
Lymphocytes	0.40
Platelet Count x 10^9/L	374
Absolute Neutrophil Count	1005.1
Chest Radiograph	Pneumonia
CT-Value	FAM: 21.89 ROX: 17.92
SARS-CoV-2 Status (Post-Chemotherapy)	COVID-19 Moderate
Diagnostic Tests Post-Chemotherapy	
Hgb (g/dl)	120
WBC x 10^9 /L	2.59
Neutrophils	0.12
Lymphocytes	0.67
Platelet Count x 10^9/L	274
Absolute Neutrophil Count	310.8
Chest Radiograph	Pneumonia, with progression
Complications Post-Chemotherapy	Febrile Neutropenia, Healthcare-Associated Pneumonia
SARS-CoV-2 Status (on Discharge)	Recovered
SARS-CoV-2 Status (on Follow-up)	No reinfection to date

Case Three

This is case of a 7-year-old female diagnosed with Osteosarcoma of the right distal tibia last September 2020. She was started on European Osteosarcoma Intergroup (EOI) chemotherapy protocol in October of 2020 and is already on her 7th cycle, 2 weeks prior to this admission. She had above the knee amputation in December 2020 after four cycles of chemotherapy. She was also diagnosed with Pulmonary Tuberculosis (TB) in February 2020 and is on her 4th month of anti-TB therapy during this admission.

On her 8th cycle of maintenance chemotherapy, she underwent mandatory SARS-CoV2 RT-PCR testing per institutional protocol, which was positive. She was asymptomatic with no respiratory symptoms prior to, during, and after COVID-19 testing. She had no known exposures and no other family member had COVID-19 infection. On review of systems, there were no recent weight changes, anorexia, or growth delay and the rest of the organ systems were unremarkable. She had stable vital signs and physical examination was normal. Complete blood count was done with unremarkable results.

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The COVID-19 PCR had a high CT value of 23.17, but she was clinically stable with normal baseline laboratory results so the managing team proceeded with the scheduled chemotherapy. She remained asymptomatic post-chemotherapy with normal laboratory tests. She was able to complete the 5-day chemotherapy course without any complications. She was discharged and home isolation was continued for 5 more days. She remained asymptomatic on follow up 16 days after her COVID-19 infection.

Table 3. Diagnostic Profile and COVID-19 Status of Case Three

SARS-CoV-2 Status (Pre-Chemotherapy)	COVID-19 Asymptomatic
Diagnostic Tests Pre-Chemotherapy	
Hgb (g/dl)	119
WBC x 10^9 /L	3
Neutrophils	0.50
Lymphocytes	0.39
Platelet Count x 10^9/L	188
Absolute Neutrophil Count	1500
Chest Radiograph	Normal
CT-Value	FAM: 23.17 ROX: 17.04
SARS-CoV-2 Status (Post-Chemotherapy)	COVID-19 Asymptomatic
Diagnostic Tests Post-Chemotherapy	
Hgb (g/dl)	110
WBC x 10^9 /L	4.62
Neutrophils	0.86
Lymphocytes	0.12
Platelet Count x 10^9/L	213
Absolute Neutrophil Count	3973.2
Chest Radiograph	Normal
Complications Post-Chemotherapy	None
SARS-CoV-2 Status (on Discharge)	Home Isolation completed (recovered)
SARS-CoV-2 Status (on Follow-up)	No reinfection to date

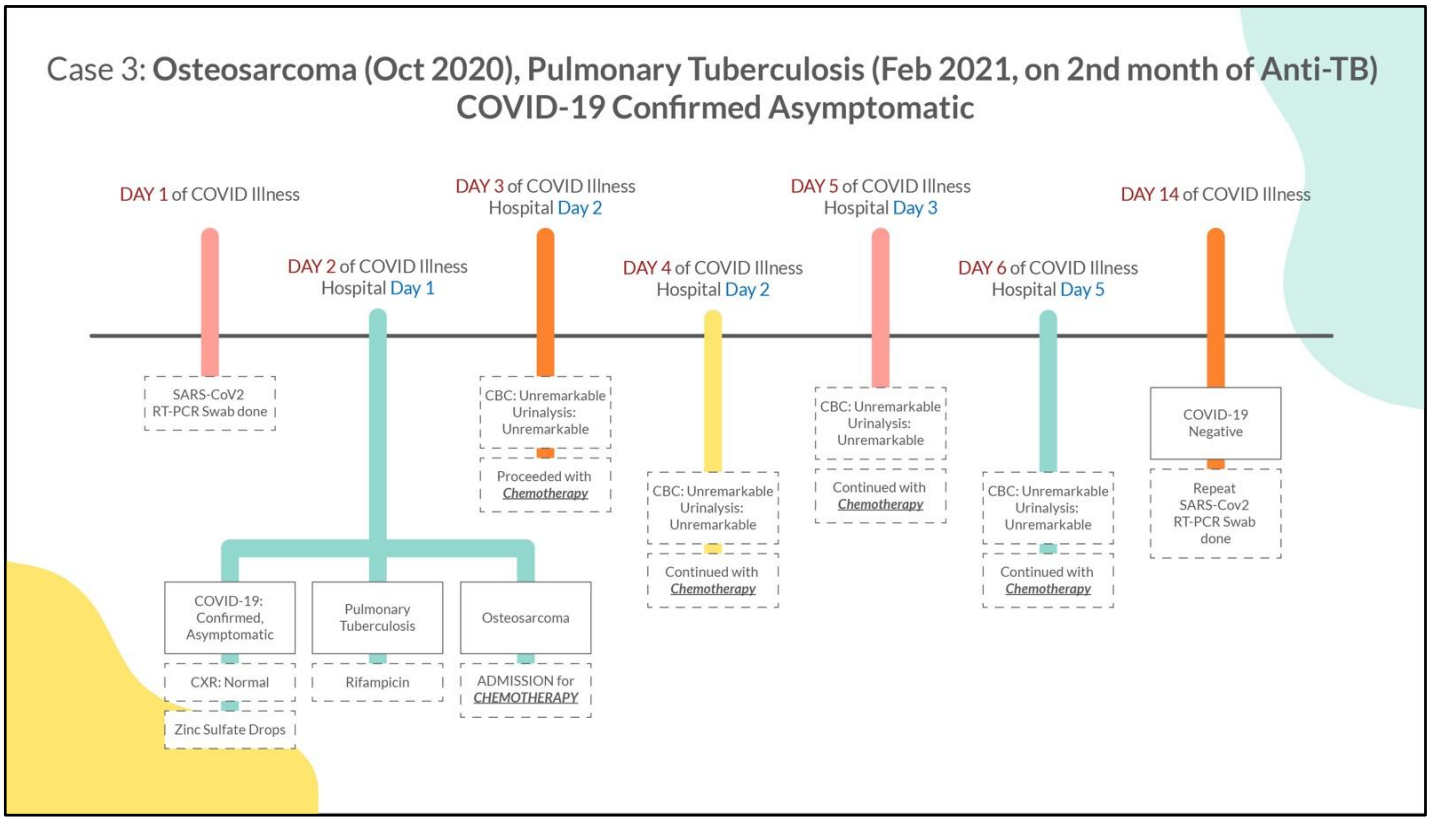

Figure 3. Timeline of Events and Course of Case Three

DISCUSSION

Childhood cancer, although rare, is the second leading cause of death among children. Leukemia is the most common, representing about 28% of childhood cancers, closely followed by brain tumors, lymphomas, and bone cancers.[5] Locally, the Department of Health reports that 50% of all new cancers in children each year are leukemia (September 2020).[6] The Philippine Pediatric Society (PPS) Registry recorded 3,283 patients with ALL and 2,234 patients with osteosarcoma or bone and articular malignancy from 2015 to 2021.[7]

The incidence of COVID-19 among patients with cancer seems higher relative to the general population with the highest risk noted among those with hematologic and lung cancers.[8] Signs and symptoms of COVID-19 were reported to be mild in small surveys of children who developed COVID-19 while receiving immunosuppressive medications for kidney disease or inflammatory bowel disease.[9] In a study from a single institution in New York City, among 178 children with cancer, only 1 in 10 COVID-19 positive patients required admission for symptoms related to COVID-19.[10] Locally, in a tertiary hospital in Northern Luzon, of 207 children who tested positive for COVID-19, only 4.8% were children with malignancies. In this study, none of the 3 cases were admitted for symptoms related to COVID-19, and COVID-19 was just an incidental diagnosis during their admission. All three cases did not present with respiratory symptoms and only one presented with non-specific symptoms of fever and anorexia which could be attributed to COVID-19 and a concomitant dengue infection.

In a study by Westblade, *et al*. among 3,000 hospitalized patients with COVID-19, the viral load, measured through CT values, was highly predictive of morbidity and mortality in patients with or without cancer.[11]

Viral load on admission was an independent predictor of in-hospital mortality among patients with active cancer, with increasing viral load equating to increasing morbidity and mortality. A positive RT-PCR result may have variable CT levels from <24 to ≤32. Lower CT levels are associated with severe COVID-19 with complications and disease progression.[12,13] Cases 1 and 3 had asymptomatic COVID-19, with cycle threshold values of 33.58 and 23.17, respectively; while case 2 had a CT value of 21.89. A lower CT value correlates with a high viral load which could have accounted for his symptoms.

The Centers for Disease Control and Prevention (CDC) considers that cancer represents an established or potential risk for severe COVID-19.[14] However, not all data are consistent across studies.[15-17] Case 2 had a more progressive disease, initially presenting with fever (mild disease) later on evolving to moderate COVID-19 with fever and dry cough, crackles and chest x-ray findings of pneumonia. Case 1 and 3 had localized disease - pyomyositis on the right leg and pulmonary tuberculosis, respectively, and were asymptomatic throughout the COVID-19 illness.

Variations in clinical course may be attributed to the underlying characteristics of cancer populations in these studies, such as cancer type and chemotherapy protocol received. Other factors, including lower socioeconomic status, poorly controlled comorbidities, and older age are also associated with a worse prognosis, which influence mortality rates in patients with cancer and COVID-19.[18-20] Since comorbidities in all 3 cases were adequately addressed, this contributed to a milder course with better prognosis for all patients.

In limited studies conducted in countries like Europe and the US that touched on chemotherapy strategies, the population ranged from 2 to 18 years old (median of 12.8 years) with male predominance (70%).[22,23]

The most common underlying diagnosis was ALL (53%) and most had a newly diagnosed disease, with a minority having relapse/refractory cancer (75% vs. 25%). Majority had no reported comorbidities. The studies reported that approximately half (46%) of patients received mildly immunosuppressive chemotherapy, whereas 21% received moderately immunosuppressive treatment and 33% received severely immunosuppressive treatment. There appeared to be no correlation between COVID-19 severity with degree of chemotherapy-induced immuno-suppression. Only a minority of asymptomatic patients who underwent immunosuppressive treatment developed COVID-19 symptoms and most had mild illness.[22,23] In the 3 cases presented, all received immunosuppressive treatment during active COVID-19 infection and cases 1 and 3 remained to be classified as mild COVID-19. Only case 2 progressed from mild to moderate COVID-19 post chemotherapy which may be due to multiple factors, primarily his co-infections.

The reports registered in the Philippines reflect the global report, where 1-9 year old males are affected. ALL remains to be the most common diagnosis with ANC counts of >1000. Most are classified as asymptomatic or mild and most of them did not require hospitalization or treatment.[24] These data are comparable with the cases presented.

Lymphopenia has recurrently been discussed as a risk factor for severe disease in COVID-19 in adults. Kainth, *et al.* found a tendency for elevated total white blood cell counts in more severe pediatric cases, but not lymphopenia.[25] Additionally, in a systematic review of 7780 children with COVID-19, Hoang, *et al.* described an overall normal white blood cell count, with mild neutropenia and an elevated lymphocyte count.[26]

The development of lymphopenia in pediatric oncology patients may have implications for subsequent therapy, particularly immunotherapy. In some studies, COVID-19 positive cancer patients showed a reduced platelet count, but this was mostly ascribed as a chemotherapy-induced complication. Lymphopenia, C-Reactive Protein (CRP), and other lab parameters, such as LDH and ferritin, might support the diagnosis but might not predict the outcome of COVID-19 in cancer patients as they frequently have chemotherapy-induced cytopenias and acute phase reactants are frequently elevated.[27,28] Similarly, all 3 cases presented with leukopenia on admission while acute phase reactants were not obtained in this series.

A study by Jee, *et al.* disproved reports that suggested a high incidence of severe or critical illness (38.8%) in patients with cancer and COVID-19.[28] The study showed that patients treated with cytotoxic chemotherapy between 14 to 90 days before SARS-CoV-2 test positivity did not have an increased hazard ratio for the composite endpoint, ICU admission or death in separate analyses. This finding was further supported in a subgroup analysis and multiple sensitivity analyses that found no effect of chemotherapy on COVID-19-associated mortality in patients with cancer in various countries. All the three cases presented in this series were given chemotherapy within 14 days of active SARS-CoV-2 infection but none of them were admitted to the ICU and post-chemotherapy outcomes were favorable. In contrast, findings from China suggested worse outcomes with chemotherapy with severe COVID-19 as endpoint.

The pandemic paved the way for a rapid global response from the international childhood cancer community to provide rational solutions for problems in the care of children with cancer, regardless of where a child may live.

It is international consensus that, wherever possible, children presenting with a likely diagnosis of cancer during this pandemic undergo clinical assessment and appropriate investigations to establish a diagnosis and be offered effective therapy while mitigating the risk of exposure to COVID-19.[29-31] They further recommended that the standards of care for diagnosis, treatment, and supportive management not be compromised or electively modified during the pandemic, if at all possible. Lastly, all elements of cancer treatment should continue without modification unless resources become overwhelmed.

In pediatric patients with ALL, the major threat may be COVID-19-related interruption of treatment, or in some settings, treatment non-completion. The principal child cancer organizations (SIOP, SIOP-E, COG, SIOP-PODC, International Society of Paediatric Surgical Oncology (IPSO), Pediatric Radiation Oncology Society (PROS), International Children's Palliative Care Network (ICPCN) and St. Jude Global) recommend that children presenting with ALL undergo full investigation to establish diagnosis and risk stratification and commence treatment. They do not recommend any elective modification of maintenance chemotherapy, but in high COVID-19 prevalence regions, clinic visits should be minimized by extended dispensing of maintenance chemotherapy supported by virtual contact for clinical review. Supporting the family in this way may ensure treatment compliance and avoid treatment abandonment.

The Pediatric Hematology and Oncology Society of the Philippines has also sought the expertise of other societies outside the country on specific solutions to address our country's constantly changing health system. Suggestions include a separate COVID-19 in-patient facility for continued chemotherapy in most hospitals.

Patients should continue to receive chemotherapy in the COVID ward as per schedule and as clinically indicated.[32-35] It also includes screening for COVID-19 in patients prior to admission, outpatient chemotherapy, procedures requiring sedation, and screening in those who are symptomatic or have a history of travel and exposure. Imaging such as a chest x-ray or CT scan is done only to patients who develop respiratory symptoms or progresses to respiratory distress. Caregivers and those who accompany patients to the hospital are not required to undergo RT-PCR testing if they are asymptomatic, unless with history of exposure to COVID-19. Everyone should wear a mask before they enter the hospital and masking is mandatory throughout their hospital stay. Minimum health standards should be practiced at all times. COVID-19 positive pediatric cancer patients classified as mild and asymptomatic may have chemotherapy as scheduled as long as the management team waits until 5 to 7 days after symptom onset, provided no new symptoms appear. There was no need to modify chemotherapeutic dosing or use different treatment strategies based on intensity of chemotherapy since it was seen that some COVID-19 positive pediatric cancer patients shed the virus longer and remain RT-PCR positive for 4 to 6 weeks. Full dose chemotherapy was given with no problems but is not recommended if patient is symptomatic with respiratory symptoms.

Globally, due to problems and delays in cancer diagnosis and treatment, the medical team has been seeing more cancer patients with advanced disease. Because of travel restrictions, many people are reaching the hospital in advanced stages. Management guidelines and practical experience should be shared constantly among experts in the country.

In the tertiary hospital where these cases were reported, the scheduled chemotherapy continues provided that the following are present:

1) CT value is >25 if with mild symptoms related to COVID-19
2) CT value is >20 if with no symptoms related to COVID-19
3) ANC count is ≥1000 pre-chemotherapy

Overall, the general rule followed is that the benefits of cancer treatment should still outweigh the risks of chemotherapy.

CONCLUSION

Demographics, comorbidities, and type of malignancy played an essential role in the pre- and post-chemotherapy outcomes of patients with cancer and COVID-19. Factors such as CT values, comorbidities, co-infections, COVID-19 classification on admission, and overall blood count picture are all instrumental in these cases' overall outcome. These variables helped predict COVID-19 risk and disease severity and became the basis for carrying on with their treatment. Altogether, it is noteworthy to maintain pediatric cancer treatment as a priority to avoid the harrowing effects and prevent children from becoming indirect victims of the COVID-19 pandemic due to disrupted therapies.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

None declared.

INFORMED CONSENT STATEMENT

Informed consent was obtained from parents for the publication of the cases.

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