

Covid-19 Pandemic and Childhood Cancer: Lessons Learnt from a Pediatric Oncology Unit in a Developing Country

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Background: COVID-19 pandemic has caused unprecedented challenges to healthcare delivery globally. Children with cancer are a vulnerable group given their immunosuppressed state. There is paucity of data regarding the organisation of pediatric cancer care and outcomes of children with cancer who developed COVID-19 infection. We describe the organisation of care in a Pediatric Oncology unit in a tertiary care hospital in South India and describe the clinical profile and outcomes of children with cancer who were diagnosed with COVID-19 infection.

Methods: This was a retrospective chart review of all children admitted to the pediatric oncology unit and diagnosed with COVID-19 infection between March 2020 and October 2020. Descriptive statistics were calculated.

Results: A total of 144 children were on active chemotherapy during the study period. Of these, Nine (6.2 %) were diagnosed with COVID-19. Fever and cough were the predominant symptoms. Majority (88%) had mild symptoms. COVID-19 was positive at cancer diagnosis in 22%. PICU care was required for 33%, but for non-covid related concerns. Recovery from Covid-19 was seen in 88%. Chemotherapy administered during or after Covid-19 infection was well tolerated. Co-existent sepsis or CMV infection resulted in severe symptoms leading to mortality and this was not related to severe covid related symptomatology.

Conclusions: In our study, majority of children with cancer who developed covid-19 had mild symptoms and recovered uneventfully. Chemotherapy should not be delayed in children with active cancer. The overall outcomes of pediatric oncology care during the pandemic are reassuring.

Introduction

The Covid 19 pandemic has caused unprecedented challenges in every aspect of life around the world, especially the delivery of health care [1, 2]. The severity of infection is variable as are the clinical manifestations. [3, 4] Guidelines developed by various international and national bodies provide suggestions to the care of individual patients and also the delivery of health care [5-7]. It has been suggested that immunosuppressed patients including those with cancer are a high risk

group with potential to develop severe disease. Children have been reported to have less severe manifestations of COVID 19.

Children with cancer are a potentially vulnerable group given the degree of immune suppression caused both by the cancer and the intensive chemotherapy regimens used. There are a few guidelines by national and international bodies on the day to day functioning of a Pediatric Oncology unit and administration of chemotherapy during the pandemic [5-7]. These guidelines are based largely on expert opinion and outcomes of following these guidelines are not widely reported. The outcome of children with cancer who have Covid 19 infection is also not widely reported [8]. There are also no standard guidelines for the management of children with covid 19 infection during cancer treatment.

We present our experience from a Pediatric Oncology Unit of a large tertiary care teaching hospital during the covid 19 pandemic. We present the protocols followed in the unit and the outcomes of children affected by covid-19.

Materials and Methods

This was an observational study of all children aged 1 month to 18 years registered and on follow-up in the Pediatric Oncology unit between March 1st 2020 and October 31st 2020. The charts of nine patients who were diagnosed with COVID 19 infection admitted to during the study period were reviewed. We abstracted demographic details, symptomatology, severity of symptoms, interventions required and outcomes of children with cancer who tested positive for COVID 19 infection. Children with cancer referred from other centers for management of Covid 19 infection were not included in the study. Institutional Ethics committee clearance was obtained to perform this data collection.

The Pediatric Oncology Unit at our institution is a 30 bedded unit and a 15 bed day care facility within a 1200 bed general tertiary care teaching hospital. Our institution was a COVID hospital as per the government requirements during the pandemic, with 700 beds earmarked during the pandemic for covid positive patients. These beds were segregated from the non-covid patient beds and housed in a separate block of the hospital. Early in the pandemic as per our institution guidelines, protocols were developed for screening and care of children in the Pediatric Oncology Unit. This included the following precautions for routine functioning of the unit. All personnel, patients and caregivers had to compulsorily use a face mask, sanitize their hands frequently and also practice social distancing. The number of attendants permitted in the out-patient, in-patient and day care wards was restricted to one per patient. Outpatient visits were pared down to essential visits during intensive chemotherapy. Maintenance chemotherapy visits were performed by teleconsultation or emails to help limit patient visits to the hospital and overcrowding. All patients and attendants were screened for symptoms and any covid contact prior to entry to the OPD and ward areas of the Oncology unit.

All admitted patients were screened with a rapid antigen test (RAT) for COVID 19. If RAT was negative and the patient asymptomatic no further testing was performed and patients were admitted to the Oncology unit. If RAT was negative but patient developed symptoms suggestive of COVID 19 infection (fever, cough, and diarrhea) RT PCR was performed. Oncology patients who were COVID 19 negative by RT PCR were cared for in the Oncology wards. Those who were positive by RT PCR were admitted to single rooms in the COVID designated area which was physically in a different building in the hospital. Doctors from the Pediatric Oncology unit assessed and cared for these patients in full PPE in the COVID designated wards. Out patients and Day care patients did not undergo either RAT or RT PCR testing. No tests were performed on the caregivers accompanying the child.

Protocols were developed by the Pediatric Oncology unit during the pandemic for care of children

who were COVID 19 positive while on chemotherapy. This was in accordance with institutional guidelines. Briefly, children with new diagnosis of cancer or those with life threatening cancers were treated emergently with appropriate chemotherapy. If unstable from a COVID 19 perspective, the child was stabilized before administration of chemotherapy. Chemotherapy ports were placed by the Pediatric Surgery department after confirming negative RT PCR reports. Radiotherapy continued to be delivered after confirming negative RT PCR especially for those who needed intravenous sedation during radiotherapy. Children with cancer diagnosed with COVID 19 infection were treated for COVID 19 as per national guidelines during that period [4].

Results

During the study period we had 144 children on active chemotherapy and 40 new diagnosis of cancer. The unit managed 2342 out patients, 989 day care visits and 324 inpatient admissions (including benign hematology patients). Of these, 9 (6.2%) children with cancer had COVID 19 infection. Diagnosis in 7 patients was by RT PCR and in two children by RAT testing. There were 7 boys and 2 girls with covid 19 infection. The mean age of patients was 5.7 years (range 6 months – 15 years). Eight of these children were on active chemotherapy while one was on follow up. Of the 8 children on treatment, two were diagnosed with COVID-19 at the time of presentation with cancer (AML – 1, Neuroblastoma -1). Six children were on intensive chemotherapy for ALL, Burkitt lymphoma and Atypical Teratoid Rhabdoid Tumour (ATRT). None of the children on maintenance chemotherapy were diagnosed with COVID-19.

The details of children who were COVID positive are presented in Table 1.

| Patient No | Age/ Sex | Diagnosis | Phase of treatment | Test /Reason for test | Symptoms | ANC | ALC | Treatment | Outcome |
|------------|----------|-----------------------------------|----------------------------------|---------------------------|---------------------------------------|------|------|--|---|
| 1 | 3/M | B cell ALL | Post consolidation | RTPCR/ symptomatic | Fever, cough | 1 | 11 | IV antibiotics/azithromycin | Recovered/ on chemotherapy |
| 2 | 1.5/M | ATRT | Post 1 st cycle chemo | RTPCR/symptomatic | Fever, cough | 7765 | 3282 | IV antibiotics/azithromycin | Recovered/ died of disease progression |
| 3 | 0.5/M | Neuroblastoma - Intermediate risk | At diagnosis | RTPCR/symptomatic | Fever, loose stools | 1550 | 4009 | Azithromycin | Recovered/ on chemotherapy |
| 4 | 3/M | Neuroblastoma - high risk | Post completion of treatment | RTPCR/ symptoms in father | Fever | ND | ND | Paracetamol | Recovered/ on follow up |
| 5 | 15/F | AML | At diagnosis | RAT/ pre admission | Fever, throat pain, hyperleucocytosis | 0 | 75 | IV antibiotic | Recovered and remission/ DAMA after CMV pneumonitis |
| 6 | 12/M | B cell ALL | During induction | RAT/pre admission | Fever, loose stools, shock | 159 | 283 | IV antibiotics | Recovered/ on chemotherapy |
| 7 | 2.5/F | AML | During relapse | RTPCR / symptomatic | Fever, cough, hypoxia, sepsis | 3444 | 7347 | Gancyclovir (CMV), Dexamethasone, IV antibiotics | Died from Sepsis and relapsed AML |
| | | | | | | | | | |

| | | | | | | | | | |
|---|------|------------------|---------------|--------------------|---------------------|------|------|--------------|----------------------------|
| 8 | 4/M | B cell ALL | Consolidation | RTPCR/ symptomatic | Fever, cough | 3379 | 1620 | Azithromycin | Recovered/ on chemotherapy |
| 9 | 10/M | Burkitt lymphoma | Consolidation | RTPCR/ symptomatic | Fever, loose stools | 2142 | 478 | Azithromycin | Recovered/ on follow up |

Table 1. Demographic Details and Outcome of COVID-19 Positive Cancer.

The predominant symptoms at presentation were fever (77%), cough (66%) and loose stools (30%). Three children required PICU admission for treatment. The details of these patients are presented in Table 2.

| Age/ Sex | Diagnosis | Reason for PICU admission | Duration of PICU admit | O2support | Inotropes | Covid specific treatment | Outcome |
|----------|-------------|---------------------------------------|------------------------|-----------|-----------|--------------------------|--|
| 15/F | AML | Hyperleucocytosis with RAT positive | 7 | No | No | No | Remission from AML Had severe CMV pneumonitis in remission |
| 12/M | B cell ALL | Shock during induction chemotherapy | 4 | Yes | Yes | No | Remission and continues on chemotherapy |
| 2.5/ F | AML relapse | Respiratory distress and septic shock | 14 | Yes | Yes | Dexamethasone | Died of Multiorgan dysfunction |

Table 2. Details of Patients Requiring PICU Care.

None of these patients cared for in the PICU were admitted in PICU due to COVID related concerns. Majority of children were managed with symptomatic treatment and azithromycin (as per pediatric covid guidelines of the institution). None of the children received hydroxychloroquine, remdesivir, or tocilizumab. As four children also presented with neutropenia (related to disease or chemotherapy) they also received IV antibiotics for febrile neutropenia as per unit protocol. Only one child was hypoxic and required oxygen. Two children developed shock at acute presentation. However this was due to concomitant Febrile neutropenia with sepsis. None of the children died due to covid related complications. All children except one recovered from the covid infection. The only child who died at the time of COVID infection had relapse AML with sepsis and CMV infection at the time of covid infection and progressed to multiorgan dysfunction.

Chemotherapy was given as per protocol for two children (AML with hyperleukocytosis and B cell ALL) who presented with COVID at time of diagnosis and during induction chemotherapy respectively. Both children tolerated chemotherapy well and went into remission with no worsening of COVID infection related to the administration of chemotherapy. The absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) at the time of infection are described in Table 1. We did not note any relation between the degree of leucopenia and severity of symptoms. In seven children who were in remission at the time of COVID 19 infection, chemotherapy was deferred for 1-2 weeks till children recovered and were asymptomatic for COVID. Chemotherapy was restarted and well tolerated in these children. Minor changes were made in the chemotherapy protocols and our management to ensure uninterrupted treatment for primary disease during the period of COVID 19 positivity which has been listed in Table 3.

| Sl No. | Age/ Sex | Diagnosis | Phase of treatment | Change from the usual protocol to ensure continuation of primary treatment |
|--------|----------|------------|--------------------|--|
| 1 | 3/M | B cell ALL | Post consolidation | Inj G - CSF to decrease |

| | | | | |
|---|-------|-----------------------------------|------------------|--|
| | | | | the duration of neutropenia |
| 2 | 15/F | AML | At diagnosis | Inj G - CSF to decrease the duration of neutropenia |
| | | | | Metronomic therapy post remission induction till RTPCR negativity for second induction |
| 3 | 0.5/M | Neuroblastoma - Intermediate risk | At diagnosis | Biopsy from metastatic skin nodule under sedation and local anaesthesia to avoid more intensive biopsy from primary site requiring aerosol generating procedure like intubation during General anaesthesia |
| | | | | Femoral line instead of more invasive chemoport insertion to avoid intubation during General anaesthesia |
| 4 | 12/M | B cell ALL | During induction | Oral chemotherapy with 6 MP and Methotrexate at doses as per ICiCle maintenance |

Table 3. Details of Patients who Needed Additional Therapy / change from the Usual Protocol to Ensure Continuation of Primary Treatment.

Of the above cohort of nine patients, six children are on follow up and doing well. Four continue to be on chemotherapy and two have completed treatment. One child had progressive brain tumor (ATRT) and died. Two children with AML died of CMV pneumonitis. One was in remission and the other had relapsed disease.

All caregivers of children with COVID 19 were screened for active infection at the time of diagnosis of COVID in their child. Only one caregiver was noted to be positive for COVID 19, and he recovered uneventfully.

Discussion

The pandemic of COVID 19 and the challenges with management of cancer chemotherapy in children in our unit has provided some important insights into the epidemiology, clinical course and natural history of the disease in this setting. It was noted that with adequate screening protocols, strict precautions in the ward and testing prior to inpatient admission, only a small number of patients (9/144 i.e. 6.25%) developed covid 19. It was reassuring that the majority of children had mild manifestations of the disease. Most did not require oxygen support or intensive care. A small proportion needed intensive care but for reasons unrelated to COVID.

It is our observation that though these children had significant immunosuppression they did not have any severe manifestations of the COVID 19 infection. These results correlate well with the results of studies from New York and Chennai. Boulard et al reported 19/20 children with mild symptoms from Memorial Slone Kettering Cancer Center [9]. Radhakrishnan et al from Cancer Institute Chennai report 15 patients all of whom had mild presentation and are doing well with full recovery from COVID [10]. Reports from China, Italy and France document children with cancer developing severe respiratory symptoms [11-14] but this was not seen in our cohort.

Delays in chemotherapy can adversely affect outcomes of cancer treatment. Optimal timing of chemotherapy and avoiding delays due to hospital logistics of isolation and covid 19 infection is important in this cohort of patients. It was reassuring to note that the children with active covid infection tolerated chemotherapy well. Delays in chemotherapy especially in newly diagnosed cancers in children should be avoided especially if they are not unwell from a covid perspective. Though the patient numbers in this series is small, neither the children who got chemotherapy with active covid infection nor those who resumed chemotherapy after covid infection had any adverse events noted due to the administration of chemotherapy. Our series, though small in number clearly demonstrates that there is no rationale in delaying chemotherapy in children with covid infection especially where prompt institution of chemotherapy will be life saving. It is imperative to individualize the relative risks versus the benefits of instituting chemotherapy during the pandemic. Comparing the COVID 19 related risks versus the cancer related risks is a helpful strategy to guide treatment planning to optimize outcomes.

The reactivation of CMV infection as a concomitant or subsequent infection is an important finding in our series that needs further study. There are few reports that describe this in literature [15, 16]. Both patients in our series had significant CMV disease with concomitant or previous COVID infection. The possibility of worsening CMV pneumonitis due to COVID related lung injury cannot be ruled out.

Overall, the severity of COVID 19 infection in children is low. There has been a correlation drawn with the ALC and the severity of covid infection in both adults as well as children [17]. Though the majority of our children on cancer chemotherapy had low ALC, this did not correlate with the frequency or severity of COVID infection. Neutropenic children with or without covid 19 in the oncology wards did not have any increased morbidity or mortality. One hypothesis for severe covid infection is related to severe inflammation with cytokine storm. It is possible that children on cancer chemotherapy with a weakened immune system do not have the potential to develop a severe immune activation and a resultant cytokine storm. This needs to be studied prospectively and may potentially have important implications to the management of covid infection. The successful use of dexamethasone, a lymphocytotoxic immune suppressant in covid 19 correlates well with this observation of less severe manifestations in children on cancer chemotherapy. There are some important limitations to this study.

As per hospital policy we performed RAT (to decrease cost to the patients) and not RTPCR as a screening test. This potentially would have resulted in higher false negative results as RAT is not a very sensitive test [18]. However in spite of this screening strategy and potentially missing positive cases in the in-patient unit, we did not face any specific challenges of outbreaks in the wards. During the pandemic we remained vigilant to episodes of febrile neutropenia and had a low threshold to perform COVID-19 RT PCR for children in the oncology ward with fever. As per our hospital guidelines we did not screen asymptomatic patients, care givers or medical personnel as has been the protocol in some units around the world. We may potentially have found a higher number of positives had we adopted this strategy of screening but this would undoubtedly add to costs. Despite this, there was no outbreak of COVID 19 in the outpatient or day care areas. In conclusions, the covid pandemic has placed significant challenges to patients, caregivers and medical personnel due to the many unknowns related to the infection. Our case series has shown that Pediatric Oncology units can continue to deliver cancer care and chemotherapy without compromising on the safety of patients or caregivers. Importantly we have shown that covid infection even in those severely immunocompromised children with cancer is usually mild. We have also shown that chemotherapy schedules can be adhered to even with recent covid infections. Larger patient numbers from various oncology units from across the country are required to confirm these preliminary observations. The challenge of concomitant CMV and sepsis that leads to severe manifestations requires further study.

Conflict of Interest

None

Contributors

MK, NB, KSA acquisition of data, MK involved in clinical care, VB analysis of data and revising the draft, AP concept, analysis, initial draft and revising draft. All authors approved the final version of manuscript.

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