



Management of Hemato-oncology children during covid-19 crisis

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Article History:

Received on: 26 May 2020

Revised on: 27 Jun 2020

Accepted on: 29 Jun 2020

Keywords:

COVID-19,
Haemato-oncology,
Children,
Chemotherapy,
Radiation,
Bone marrow
transplantation

ABSTRACT

The Coronavirus (COVID-19) caused by severe acute respiratory syndrome, coronavirus 2(SARS-CoV-2). The COVID-19 pandemic has had a catastrophic effect on global health. About 2% of confirmed cases of COVID-19 were among children aged <18yrs old. Children, teens and young adults are at higher risk for severe complication and presentation with multisystem inflammatory disease. Management of children with COVID infection is not yet standardized. However, cancer children are at potential risk due to immunocompromised status and their management is unknown. The immunocompromised children are at risk of severe infection, and they have a high mortality rate. Here in this article, we are describing when to suspect COVID infection, how to manage newly diagnosed cancer children and existing patient including bone marrow transplantation and immunosuppression therapy and also blood transfusion policy during COVID pandemic time.



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ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v11iSPL1.2728>

Production and Hosted by

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INTRODUCTION

As of May 02, 2020, the 2019 coronavirus (SARS-CoV-2) has been responsible for more than 3300000 infections and more than 200000 deaths worldwide, but data regarding the epidemiologic characteristics and clinical features of infected children are limited ([Guan et al., 2020](#)). A recent review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that less than 1% of the cases

were in children younger than ten years of age ([Wu and McGoogan, 2020](#)).

Pediatric cancer management is different since most of the childhood cancers are highly curable; treatment regimes are intense and often need good quality supportive care. Cancer and bone marrow transplantation make the children more immunocompromised we don't have many available data how to proceed on daycare chemotherapy, admitting new children for aggressive chemotherapy in haemato-oncology wards, managing neutropenic sepsis and indication for taking bone marrow transplantation. There is also anticipatory financial burden will fall slowly on the families and cancer services in low and middle-income countries. Therefore this paper aims to summarize the general principles for continuing multidisciplinary care during COVID-19 pandemic period in paediatric cancer children.

Clinical symptomatology in pediatric COVID infections

Preliminary evidence suggests children are just as likely as adults to become infected with SARS-CoV-

2 but are less likely to be symptomatic or develop severe symptoms (Zimmermann and Curtis, 2020). The children transmitting the infection remains uncertain. Children with the disease often have gastrointestinal symptoms than compared with adults. Children often have household contact in contrast to adults who have nosocomial exposure (Zimmermann and Curtis, 2020).

Cancer children do not have any specific presenting symptoms, but since immunocompromised, they have more severe disease. However, they have prolonged viral shedding >21days, in particular, those with hematopoietic stem cell transplant (HSCT) recipients, in the setting of steroid use, and myeloablative conditioning (Ogimi et al., 2017).

Common presenting symptoms in children

Fever, cough, nasal congestion/rhinorrhoea, diarrhoea, dyspnea

Uncommon presentation

1. Myocarditis –Kawasaki disease
2. Meningo-encephalitis
3. HLH / Macrophage activation syndrome
4. Thromboembolic phenomena.

Oncology Services General Guidelines

Where possible, all elements of cancer treatment should continue without modification unless resources become overwhelmed.

The crucial factors for managing the overwhelming service demand included: [THE LOMBARDY EXPERIENCE]

1. Clear clinical leadership
2. A dynamic standard operating procedure for the service
3. SARS-CoV-2 viral testing of all staff and all patients before any elective procedures or admission
4. Professional monitoring of handwashing and the use of appropriate personal protective equipment (PPE) by staff and families on entering and leaving clinical areas
5. Restricting accompanying persons to one per patient
6. "Cohorting" of a team for work and rest periods
7. Physical separation of oncology staff from staff working in COVID-19 areas and
8. Elective reduction of high-risk procedures (CAR-T and stem cell therapies) to reduce the demand for intensive care services.

New Diagnosis of Childhood Cancer

Global pandemic response team by SIOP and COG proposed guidelines for new diagnosis protocol for children with cancer, all children suspected of having cancer should be investigated thoroughly as per protocol without delay. They recommend following existing institutional protocols and standard operating protocols to confirm diagnosis, staging and risk stratification.

Children who present with cancer and concurrent COVID-19 (either symptomatic or detected on screen), the essential investigations should be carried out to establish accurate cancer diagnosis and interim therapy to control the disease may be safe approach and permit recovery from COVID-19 before attempting disease directed therapy.

In non-emergency presentations with concurrent COVID-19, such as abdominal mass, intra-ocular retinoblastoma or early-stage Hodgkin lymphoma, it is safe to defer diagnostic investigations until child recovered and then proceed with adapted studies as best can be achieved.

Multidisciplinary tumour board meetings should be continued for decision making, if necessary by phone/telemedicine to ensure social distancing.

There are concerns about children with early signs of cancer may remain in the community. They are not referred for further investigations due to travel restrictions, fear of presenting to hospitals or financial issues, however, there is already evidence of delayed presentation, advanced disease and even death of children due to the late presentation (Lazzerini et al., 2020).

Acute Lymphoblastic Leukaemia (ALL)

Existing children

The intensive phase of therapy: continued as scheduled, if far away find a local place where it can be delivered. Maintenance phase: no modification recommended, but clinic visit may be minimized by extended dispensing of maintenance chemotherapy support by telemedicine services, doing in this way may ensure ongoing treatment compliance and avoid abandonment.

New cases

Ideally should undergo a full investigation to establish the diagnosis and risk stratification and commence treatment according to institutional protocol. Children with concurrent covid-19 and hyperleukocytosis: immediate treatment with supportive care and steroid prephase and disease directed therapy after recovery from COVID-19 (Vaitkeviciene et al., 2013).

If flow cytometry and molecular diagnostics not available – initiate treatment based on bone marrow / peripheral smear, however, store multiple extra unstained aspirate smears for a later diagnostic purpose (Smith *et al.*, 1996).

Acute myeloid leukaemia

Treatment may be started based on morphological and flowcytometry confirmation. Cytogenetics and Molecular testing may have to be done later on stored samples. DNA extraction if available, can be used to preserve the sample for later use. Initial induction therapy is the same across the risk groups. Most patients would need to be initiated on intensive chemotherapy. In case of constraints on inpatient beds bridging chemotherapy using low dose Ara C, Capizzi like regimens using L-Asparaginase may be tried to defer induction or space the intensive chemotherapy cycles.

Burkitt Lymphoma

Existing cases

Since Burkitt's lymphoma is aggressive cancer and highly curable, it is advisable to continue without modifications.

New cases

In fully equipped settings: no pandemic modification recommended for the initial assessment and diagnosis, even if the child has concurrent covid-19.

In limited-resource settings

Simplified assessment based on clinical signs, minimally invasive biopsy and diagnostic imaging with Ultrasound and chest X-ray is sufficient and to start supportive care and therapy. If the disease is advanced with concurrent comorbidity, prophase treatment with a reduced dose of steroids alone along with supportive care before disease specific chemotherapy safe approach to mitigate the severity of life-threatening tumour lysis syndrome.

Using a short pre-phase of steroids or using cytoreductive chemotherapy (e.g., COP) for two cycles, using non-methotrexate regimens like Rituximab+DA-EPOCH are some of the options to deliver similar outcomes without severe toxicities like neutropenic enterocolitis and sepsis. Conventional FAB-LMB based approach may be challenging to achieve in the current scenario due to the intense supportive care it mandates.

Hodgkin Lymphoma

All children and adolescents presenting with progressive lymphadenopathy undergo an immediate clinical evaluation and the best available diagnostic imaging and biopsy. If functional image/PETCT if

not available staging or response assessment can be done with contrast CT scan, consider an outpatient-based therapy approach rather In-patient kind chemotherapy.

Chemotherapy only approaches without radiation is a safe and reasonable approach for a low and intermediate-risk group (Parambil *et al.*, 2020). Hodgkin lymphoma is broadly managed using regimes like ABVD and intense chemo regimes like OEPA+COPDAC or BEACOPP. Strategies may be deferred to avoid admission for complications, and ABVD approach may be more suitable, especially for the limited-stage disease. IFRT [Involved Field radiation therapy] may be delivered in the involved field of bulky disease or to sites with an inadequate radiological response.

Retinoblastoma

Examination under general anaesthesia can be with-held if the child is having fever and cough. Assessment of Rb1 germline mutation testing can be deferred until after COVID-19 pandemic completed. Minimum required investigations to diagnose MRI/CT orbit and brain.

Group A-C Unilateral or Bilateral (IRSS 0)

Local therapy is standard care. If worried about the non-availability of chemotherapy drugs CEV/ CV for young infants, only single-agent carboplatin alone can be considered as adjuvant therapy. Delay in routine surveillance.

Group D-E Unilateral, no Buphthalmos (IRSS I)

Enucleation without delay, if no pathological risk factors delay the surveillance. Interim chemotherapy with either CEV/single-agent carboplatin.

Locally advanced disease

Can be considered for neoadjuvant chemotherapy. After 2-3 cycles of chemotherapy surgery can be planned.

Metastatic disease

Palliative chemotherapy depending on the availability of drugs. If supportive care facilities are minimal or not available, don't consider aggressive chemotherapy, only single-agent carboplatin can be considered.

Neuroblastoma

After histological confirmation, staging may be done with a CT scan of abdomen, thorax and Bone marrow biopsy if MIBG scan/PET scan is unavailable. Chemotherapy can generally be delivered through daycare. Patients requiring HDCT may require deferral and can be given additional cycles of chemotherapy before HDCT can be arranged.

Wilms Tumour (Nephroblastoma)

In high recourse settings, all staging workup and treatment should be done without much modification of protocol since high curability. In resource-limited –low to middle-income settings if CT scan not available consideration may be given to staging with US and Chest X-ray (CXR). Whenever possible thoracic CT should be done, as it may recognize COVID-19 infection in asymptomatic children and avoid the spread of the infection by adopting adequate isolation of infected children.

Therapy

Due to operating room limitation, primary surgery or biopsy may not be possible therefore better to follow SIOP protocol with pre-operative chemotherapy protocol. If the SIOP protocol initiated, the full SIOP approach should be applied. If SIOP protocol used, Nephrectomy should be planned for week five but could be delayed up to a further four weeks in non-metastatic settings responded was seen during the first 4weeks. In both COG and SIOP settings, avoid delaying tumour nephrectomy beyond 12weeks. In the case of tumour progression despite pre-operative chemotherapy, immediate surgery should be attempted despite the pandemic situation.

In general, surgeons should not perform laparoscopic tumour nephrectomies due to the prolongation of the surgical time. Tumour nephrectomy should be done in a well-equipped centre where both ICU and blood products support available. Avoidance of sharing a critical care unit with ventilated COVID-19 patients is highly recommended. The need for metastatectomy [lung metastatectomy] need to be balanced on an individual basis if further intensification of therapy may avoid surgery ([Verschuur et al., 2012](#)).

Metastatectomy should be performed in the context of SIOP protocol, in case of high risk or unfavourable histology, if no CR can be achieved by chemotherapy alone ([Pasqualini et al., 2020](#)).

Postoperative chemotherapy/adjuvant chemotherapy in low and intermediate-risk tumours should be given as a current treatment plan. If molecular biomarkers are not available for risk stratification, then consider starting chemotherapy based on histological morphology and stage. Adjuvant radiotherapy can be delayed, but no longer than 10-12 weeks if the local situation does not allow a faster start, in high-risk tumours such delay should be avoided.

Dosing, fractionation and radiation field should not be changed. In the case of Lung irradiation planned,

it should always be considered if the intensification of chemotherapy can prevent it. Follow up visits should be reduced to minimal, telemedicine services can be used for follow up, and parents should be thought to examine the abdomen for masses.

Sarcomas

Most sarcomas can proceed with treatment once the morphological diagnosis is confirmed by histology. FISH, molecular testing may be done on PPFE samples later if these cannot be done immediately. Supply of radioactive tracers for PET scan has been affected at many centres. CT scan of thorax and bone marrow biopsy will help to stage most sarcomas. A bone scan is required in most sarcomas but may have to be skipped due to non-availability of dyes. Whole-body MRI scan in centres which have standardized the procedure can help with staging in selected cases.

Interval compression strategy in Ewing sarcoma may be challenging to achieve and can be changed to 21-day cycles. Surgeries and radiation therapy should be done as per protocol. However, delays have to be anticipated, and chemotherapy is to be continued to cover the delays. For osteosarcoma, High dose methotrexate based treatment may not be feasible due to shortage of in-patient beds. Hence non-HDMtx based regimes like IAP regimen may be used as it can be delivered on a daycare basis. Use of G-CSF is to be considered after all intensive chemotherapy cycles since it may shorten hospital stay.

Low-grade gliomas

Diagnosis based on imaging can only be suspected, based on further imaging therapy based on resources availability about OT,surgeon, Pediatric ICU and histopathology and molecular diagnostic services. If resources are limiting immediate shunt or third ventriculostomy only approach if raised ICT features present, this allows prompt discharge within 24hrs and for planned resection child can be presented to centres. If the child is receiving chemotherapy, the recommendation is to continue the planned treatment without modification. During the pandemic crisis, monthly carboplatin and TPCV are most suitable protocols.

Brain tumours: [medulloblastoma/PNET]

Aggressive tumours like medulloblastoma and PNETs require urgent surgical excision whenever feasible. Adjuvant radiation therapy is ideal in most cases of embryonal brain tumours in children. Some centres face the difficulty of getting radiation therapy on time or transferring children to centres with radiation facilities on time. In such cases,

adjuvant chemotherapy may be initiated and RT to be delivered at the earliest possible time.

Radiotherapy

Radiotherapy plays an essential role in the cure of many pediatric cancers. The COVID-19 crisis may have a significant impact on the accessibility of radiation therapy when managed appropriately more likely to be curable than adults cancers. Therefore curative treatment in children should be given high priority. Radiation oncologists treating children should take responsibility to triage and coordinate cases with a respective pediatric oncologist.

Impact of COVID-19 on Radiotherapy Resources

The pandemic may have a direct impact on radiotherapy resources, primarily due to a shortage of staff at the workplace because of a lockdown or due to staff infected with the virus. There may be disruption in equipment supplies and machine maintenance. Because of a limited number of pediatric dealt with radiation oncologists, should protect them for exposure risk by avoiding cross-coverage of adult services (ESTRO, 2020).

General guidelines for radiation therapy during COVID-19 crisis

Radiotherapy is one of the components of treatment protocol both in solid cancer and also for Total body irradiation(TBI) in bone marrow transplantation. Radiotherapy units also should be involved in the radiation of blood products which is an integral part of any cancer treatment. During COVID pandemic time to reduce the exposure both health care workers and children, we need to follow certain principles.

Decrease patient numbers by prioritization and triaging of cases based on acuity, curability, etc. Investigate options of delaying treatment, alternative modalities and condensed regimens, when feasible. Screening of patients before their appointments (some recommend testing of patients, especially if anaesthesia and intubation required, before the commencement of treatment, if testing is readily available, with a policy to delay patients with active COVID-19 infection where it will not influence prognosis). Strict adherence to social distancing standards in patient waiting rooms. Limit foot traffic into the department by allowing a single patient escort.

Restrict entry to children (siblings or multiple family members) who may be vectors of the virus without being symptomatic. Strict adherence to enhanced cleaning and sanitation of surfaces between cases, with approved disinfectants (particular attention to high touch surfaces like treatment equipment, immobilization devices, keyboards, doors, etc.)

Identification of high-risk areas within the radiotherapy department and use of PPE in areas where aerosolization procedures may be done, including ear nose and throat examinations, making of thermoplastic masks, and during the fitting of masks and positioning for radiotherapy treatment (Janssens *et al.*, 2020).

We need to safeguard the staffing personnel, especially in a large community transmission environment, by implementing a shift system for therapists, nurses and other clinic personnel where possible. Allocation of a specific machine for treatment of patients with known positive COVID-19, who cannot be delayed, treating those patients at the end of the day with strict zoning. During later stages of the pandemic, where rising numbers of community-acquired infections are seen, measures such as full PPE for staff is required. Use of telemedicine/telehealth tools for appropriately selected patient encounters—deferral of routine long-term follow-up, survivorship and screening visits (Liang *et al.*, 2020).

Blood product use and support during COVID -19

Blood transfusion support is the integral part of cancer treatment in particular for Leukemia's, hemoglobinopathies and bone marrow transplant patient, during this pandemic situation availability of donor is the biggest hurdle due to fear complex in the donors and restriction for travel to reach the hospital for donation. For a donor, surveillance can use social media support to trace donors like WhatsUp group messages, Facebook and television media. The extended life products available such as Red cells, FFP and Cryoprecipitate will not have any issues. The major problem would be with platelets and granulocytes having a shorter life span of the product and limited availability of Aphaeresis machines (Red Cross, 2020).

For COVID crisis the threshold for the transfusion can be reduced, In asymptomatic children, the safe limits for red cell transfusion is Hb<7.0g/dl, the threshold for prophylactic platelet transfusion in patients with no risk factors for bleeding is recommended as 10,000/cmm, For procedures, the platelet threshold for lumbar puncture (LP) in a new diagnosis of ALL is recommended at 50,000/cmm and 20000/cmm for subsequent LPs; for bone marrow aspirate 10,000/cmm and bone marrow biopsy it is 20,000/cmm.

For Single Donor Platelet if group-specific donor not available, can use alternate group donor. Platelet requirements for surgical procedures vary according to the intervention but should be reviewed with the surgical teams. Irradiation of blood products to

prevent the TA GVHD is essential, During the pandemic situation, if irradiator availability is a limitation due to staff scarcity conventional radiotherapy machine can be used for irradiation of blood products and protocol should be well in place in the units (WHO, 2020).

CONCLUSION

In summary, delivering cancer care during the pandemic is challenging, given the risks of death from cancer versus death from infection. The likelihood of severe illness from COVID-19 is higher among patients with cancer. This document would give more insight regarding cancer children management during COVID pandemic based on an evidence base. A balance is required keeping the risk associated with COVID-19 and management of childhood cancers.

ACKNOWLEDGEMENT

Nil.

Funding support

No financial support.

Conflict of Interest

The author declares that there is no conflict of interest.

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