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CARE IN CRISIS: MANAGEMENT OF HEMATOLOGY PATIENTS DURING COVID 19 PANDEMIC

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ABSTRACT

COVID-19 pandemic is probably the biggest crisis mankind has ever seen. It changed everything; how we live and how we die. Our healthcare is over- burdened and frontline warriors are getting down more than any other illness has ever caused. We need fresh guard and make our priorities regarding individual patient. Our 'hit hard and hit fast' has changed to 'go soft and go slow'. In the disease entities other than potentially curable acute leukemias and aggressive lymphomas, we should consider low intensity and preferably oral therapy. Allogenic stem cell transplantation (SCT) for aplastic anemia should not be deferred unlike autologous SCT for myeloma. We should promote more collaboration, reporting to various registries and make use of digital medicine to minimize in-person visits and categorizing cancer patients into tiers and thus reducing risk of covid 19 infection. Hopefully, with real time data and new information, we will win the war and can answer the big unknowns.

KEYWORDS: Covid 19 crisis, hematology care, minimize in-person visits, digital medicine.

INTRODUCTION

The first half of 2020 so far has been the worst till date humanity has witnessed because of Covid 19 pandemic. It has changed everything in the pretext of 'how we live and how we die'. It has affected healthcare, education, jobs, economy and almost everything including diplomatic relations between the countries. For hematologists it is very challenging as our patients require a lot of resources in terms of manpower, blood products, chemotherapy drugs, ICU facility etc. Cancer patients are more vulnerable to Covid 19 and its effects.[1] Thus, suddenly our approach of saving life by treating as early as possible has taken a back seat and more often we are trying to save life by delaying treatment with a careful watch and wait approach. Initial studies from china has shown cancer patients to be at higher risk of having severe Covid19 infections and meta analysis showed 2% pooled prevalence of covid 19 in cancer patients.[2,3] A recent analysis from the UK showed that patients with hematological malignancies were at a more than threefold higher risk of hospital mortality due to COVID-19 up to five years from the hematologic diagnosis and nearly double the risk thereafter.[4] Thus, extra caution is warranted while dealing with patients suffering from hematological disorders who are going to be more vulnerable to the direct and indirect perils of the COVID-19 pandemic. A Chinese study including 1590 Covid 19 cases have shown more adverse events in cancer patients compared to non-cancer patients (39% vs. 8%; p=0·0003).[5]

Why we need to change?

With the emergence of Covid 19, here in India a national lockdown was put in place from 24thMarch 2020 with almost everything on standstill except the rise of cases. Even after the unlock process started, covid 19 cases are growing exponentially and we are on the verge of a major epidemic; India is already a third worst hit country. This pandemic has stretched the already overburdened healthcare which has one of the lowest doctor and nurse ratio to the patient.[6]

In respect to hematology care especially hematological malignancies, we need to change our 'hit hard and hit fast' approach because of various reasons like intensive and resource consuming setup in terms of trained manpower, beds, ICU setup, blood bank support.[7] A big chunk of healthcare personnel is getting affected and quarantined thus limiting the manpower worsening the situation. Problems are further compounded due to travel restrictions. Hospitals are a hotspot and thus a danger zone for immune-compromised patients which means we need to minimize hospital visits and need to embrace digital therapy.[8] Till date, Covid 19 doesn't have any curative treatment but it causes a lot of fear, anxiety, worry, and despair. Many patients understandably fear the future risk of cancer recurrence more than the

immediate risk posed by the virus. These are not easy decisions, and we do not have a crystal ball.[9] There are big unknowns like when and how long to delay? In view of daily new information and recommendations we want to learn in real time what kind of approaches might be right for our patients.

Role of The Hematologists

Alike pre Covid era, therapy related decisions are still individualised but we, the haematologists now are opting for delay or low intensity treatment and our risk-taking behaviour has gone down. We want to free our burdened healthcare by minimising in patient days, avoiding intensive chemotherapies for most malignancies except curable acute leukemia and lowering threshold for requirement of blood products. National cancer grid utilisation is most relevant in this era where we can send the patient to nearest centre or ask an accustomed physician nearby to deliver treatment based on our telemedicine advises.[10] It would be nice to have covid experts in the team. Some of the challenges faced during covid 19 pandemic are outlined and discussed in table 1.

Table 1: Effects of covid 19 pandemic on the patients, caregivers and stakeholders.

Cancer Patients: Avoidance of myelosuppressive and immunosuppressive therapy, liberal use of growth factors, Minimized clinic visits, Injectable drugs changed to oral where possible, adoption of tele-consultation and online mode of answering their queries, increased interaction with palliative care team.
Non COVID, Non-cancer patients: transport restrictions, restricted clinic visits, care compromised
Caregivers: transport restrictions, more frequent telephonic counseling to alleviate fear and anxiety, afraid to visit hospital/clinic in fear of getting infected by SARS-CoV-2.
Society: transport restrictions and restricted social mobility,
Hospital: setting up fever clinic, segregation of symptomatic cases at the entry point, using Infrared thermo detectors for screening, increased and diverted workload in the already loaded health care facility.

Prioritization: The Need Of The Time

In the following sections we have discussed a prioritized approach to guide disease specific decision making for the care of hematology patients.To have a uniformity across guidelines we have chosen ESMO guidelines[11] of prioritizing cancer categories into different Tiers like:-

High priority/Tier 1: Patient's condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (e.g. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL]).

Medium priority/Tier 2: Patient's situation is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority.

Low priority/Tier 3: Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (e.g. no survival gain nor reduced QoL).

To mete out the challenges we need to follow expert guidelines along with advisories by central and state governments from time to time. We can manage the situation by minimizing hospital visits, tele consult, pre hospital screening for symptoms, appointments for in-person visit only for high/medium priority cases, maintaining social distancing and 6 ft distance amongst others. Wearing masks and avoiding crowded places was usual for our patients in pre COVID era also.

Limitations Of Health Facilities

With the uncertainties regarding future and a goal to not compromise care of non covid patients, the governments have decided to divide hospital campuses into covid and non covid area. Separate fever clinic have been created so that less number of people are exposed to covid patients. We need to test early, especially in immune-compromised patients as they are already prone to certain respiratory infections mimicking Covid. Still, it is anticipated that most tertiary hospitals would have to continue to provide both covid and non covid services. Therefore, healthcare facilities may have to continue to deliver cancer care through some strategic re-organization of resources. The available source status of health care facility in terms of beds, manpower and transfusion support is a key consideration before choosing the intensity of various therapies being employed for care of hematology patients.

Travel Restrictions

Travel restrictions have imposed serious problem for patients in accessing tertiary health care facilities especially cancer care as most of these facilities are in cities and the drainage population lives in rural areas.[12] In view of uncertainties and evolving guidelines regarding chemotherapeutic modification we need to counsel in detail as there is increased risk of side effects and uncertain disease course.

Disease Specific Decision Making

In general, the approach for Covid 19 positive and negative patients is different. For Covid positive patients we wait for a period of 2-3 weeks and start therapy after the recovery. There are certain disease wise recommendations which can be implemented, however local policy and resource availability must be considered before starting any therapy in discussion with patients and relatives. All the treating physicians and nurses can use the handy covid ready communication and utilise the

vital talk which gives answers to some of the most common scenarios.[13]

Treatment of hematological malignancies

In case of acute leukemia the blanket policy will be to test all cases for Covid 19 before starting intensive induction therapy and if not feasible then at least a CT chest to rule out radiological finding of COVID-19.

Acute Myeloid Leukemia (AML)/ myelodysplastic syndrome (MDS): All patients should undergo Covid testing before starting chemotherapy. Standard 3+7 induction chemotherapy is most challenging and resource draining, thus option of intensive 3+7 chemotherapy should be chosen in young fit covid 19 negative AML/high risk MDS patients. Post induction chemotherapy should be followed by 3 cycles of intermediate dose cytarabine consolidation preferably over days 1-3. Alternatively hypomethylating agents can be considered for consolidation over high dose cytarabine.[14] In older adults, therapy with hypomethylating agents along with standard antimicrobial prophylaxis is preferred one. To reduce the incidence of febrile neutropenia routine use of G-CSF (filgrastim) is advised after chemotherapy is over.[15-17] For relapsed/refractory patients palliation may be offered. For low risk MDS patients, growth factors and erythropoiesis stimulating agents (ESA) may be employed.[16]

*Acute promyelocytic leukemia (APL)***:** APL should be managed with ATRA+ATO combination, and chemo based protocols are avoided as ATO based protocols have a good outcome and less risk of infection and decreased blood product requirements.[18,19]

*Acute Lymphoblastic Leukemia (ALL)***:** Pediatric ALL, being one of the most curable malignancies, should not be deprived of standard chemotherapies. They should undergo baseline COVID testing. Post induction G-CSF should be given to facilitate count recovery. Post induction remission chemotherapy should be as per protocol. One can choose to jump to maintenance therapy by minimizing consolidation if MRD negative.[19] While in adults, the dose of anthracycline and L-asparaginase may be reduced. During the maintenance phase, avoid dexamethasone, and goal is to keep a higher ANC. For Ph-positive ALLs, tyrosine kinase inhibitor (TKI) + chemotherapy are advised in the pediatric group while in adults TKI with minimal steroid is the 'go go'. For relapse refractory ALL treat intensively including inotuzumab if there is an option of allo SCT; otherwise, palliation should be advised.[20-22]

Chronic Myelogenous Leukemia(CML): Regarding TKIs and COVID, we should keep in mind the cardiopulmonary side effects of 2nd generation TKIs like nilotinib and dasatinib. Wherever possible, it is advisable to choose time tested Imatinib in this COVID era. Newly diagnosed CML-CP should be started with Imatinib, and those who are symptomatic (infected) with COVID one may consider hydroxyurea temporarily to tide over the acute phase. For patients with advanced CML (AP, accelerated phase and BC, blast crisis), 2nd gen TKIs can be considered. If the patient is COVID infected, then 1st gen TKI should be chosen and switched to 2nd line TKI can be considered later because of possible side effects.[20,23] Second generation TKI or reduced-intensity protocols (like, steroid +vincristine +TKI for lymphoid BC and HMA/LDAC + TKI for myeloid BC) for blast crises are a safe bet.[24] Sticking to 3 monthly BCR-ABL (IS) ratio monitoring is preferable, while 6 monthly monitoring is an acceptable option for those in deep molecular response (DMR). Considering uncertainties and frequent hospital visits for laboratory monitoring it is advisable to avoid treatment free-remission (TFR).

*Ph(-) Myeloproliferative Neoplasm***:** Patients with chronic myelomonocytic leukemia (CMML) and other overlap MDS/MPN develop leukemoid reactions and cytokine storm in the presence of severe Covid-19 infection leading to fatal hypoxemia and hemodynamic instability. In all these patients, cytoreduction should be strongly considered, and the risk of severe cytopenia should outweigh the potential benefits in an individual case-to-case basis.[16]—To minimize hospital visits, polycythemia vera (PV) patients should undergo phlebotomy if hematocrit is > 48-50%, and hydroxyurea may be considered to avoid phlebotomy in low-risk categories. Cytoreduction is advised if active/prior thrombo-hemorrhagic episodes are there.[18, 20]

Chronic Lymphocytic Leukemia (CLL): The threshold for starting therapy in CLL should be high, like symptomatic cytopenias. Therapy in lymphadenopathy and bulky splenomegaly can be deferred. However, while choosing therapy, oral ibrutinib should be preferred. Treatments like FCR or BR should be avoided as they pose an increased risk of infection.

Hodgkin lymphoma(HL): Being highly curative patients of HL should not be deprived of therapy. For less aggressive disease, 2-4 cycles of ABVD and involved field radiation therapy (IFRT) can be done during the Covid-19 pandemic. Bleomycin can be omitted in the elderly, young with pulmonary co-morbidity and those having remission in the interim PET scan. Intensive therapies like escalated BEACOPP are best avoided during the pandemic.[25] Young fit cases of relapsed HL should not be deprived of salvage therapy followed by Autologous SCT as they fall in priority 2 as per ESMO.[11,26]

non-Hodgkin lymphomas (NHL): In low-grade NHL, generally watch and wait policy is followed for low grade lymphomas. For relapsed patients, we advise oral metronomic therapy (chronic, equally spaced administration of generally low doses of various chemotherapeutic drugs without extended rest periods) along with telemedicine. Aggressive high-grade

NHL has the standard CHOP (± R) as a reasonable option, including IT MTx in each cycle if CNS IPI is high.[20]

*Multiple Myeloma***:** For most cases of myeloma without COVID symptoms, 6-8 cycles of bortezomib based protocols (VRd/VCD/VTD) can be considered. Following initial induction, they can be considered for lenalidomide maintenance. Autologous transplant may be deferred given newer drugs and recent data that it does not affect OS.[27-29] Zoledronic Infusion is advised monthly for the first 6-9 months, followed by every 3monthly. Low-intensity lenalidomide can be considered in older frail patients. Whenever possible, it is recommended to use weekly and oral regimens. Delay SCT (including stem cell collection and storage) till the pandemic abates. In such cases, bortezomib may be continued alone for cycles beyond 6 (unless collection and storage can be done earlier). If the facility for stem cell cryopreservation is available, it can be done while autologous stem cell transplantation can be postponed.[28]

Treatment of benign hematology disorders

Aplastic Anemia(AA): AA can be cured with AlloSCT, which should not be deferred if available as delay meaning an increased risk of infections and allo immunizations. In Acquired AA, immunosuppressant therapy like ATG can be considered. Eltrombopag and cyclosporine, along with androgen, can be considered if oral therapy is planned. Because of scarcity blood products during the pandemic, may have to maintain a lowered transfusions threshold. Supportive care and antimicrobial prophylaxis is critical and should not be neglected.[30, 31] Anti-fibrinolytic agents like tranexamic acid should be liberally used as prophylaxis.

Immune thrombocytopenic purpura(ITP): For newly diagnosed non-bleeding ITP with platelet count <30,000/ul American Society Of Hematology (ASH) advise to start prednisolone 20mg/day (irrespective of weight) and increase the dose after 3-5 days in no response and then taper after two weeks. If mucosal bleeding/bleeding symptoms are present, then Prednisolone (1mg/kg/day) or IVIG 1g/kg/day should be considered. Oral thrombopoietic (TPO) agents (eltrombopag or avatrombopag) can be considered in case of no response.[32-34]

Venous thrombosis: Covid-19 is known to cause lethal DIC like presentation, known as COVID Associated Coagulopathy (CAC). So, for thrombosis, VTE prophylaxis is essential in a hospitalized patient. LMWH prophylaxis is suggested if platelet count > 30000/µl and if platelet count < 30000/ µl then intermittent pneumatic compression is an alternative option.[35-37]

*Hemophilia and Bleeding Disorders***:** Only interim guidance is provided by WFH for the management of bleeding disorders during COVID-19 pandemic.[38] With the widespread increase in number of cases, patients with bleeding disorders are at higher risk of acquiring this infection. Haemophiliacs should continue their usual prophylaxis if adequate stocks are available as stock availability was affected by lockdown and travel restrictions; suggested maintaining higher plasma factor levels to prevent bleeding into the vital organs e.g.-lungs and brain. Therefore, the rapid identification of their bleeding status, regular co-ordination with the haemophilia treatment centres (HTCs) and adequate therapy with clotting factor concentrates are essential in preventing complications. They should clearly follow the same protocols for admission criteria and preventive measures as the rest of the population. In cases where CFC not available, they can continue receiving FFP/Cryoprecipitate as there is till now no evidence of COVID transmission through blood and blood products.[39]

*Thalassemias***:** Thalassemics (both TDT and NTDT) have chronic organ damage, mainly because of iron overload and are at increased risk of severe COVID-19 disease in some cases. However, a small Italian cohort has reported mild to moderate COVID-19 disease in most cases.[40,41] They should continue their regular blood transfusion. Splenectomy should be deferred in view of increased risk of infections. Oral deferasirox should be continued for iron chelation.[42]

*Sickle cell disease***:** Cases of sickle cell disease present a unique challenge as Acute chest syndrome (ACS) can be confused with Covid-19. High dose steroids should be given early in ACS. If safe transfusion practices are limited during the COVID pandemic, then patients should be put on hydroxyurea. Pain management needs special consideration, and they should be advised to have good analgesic so that emergency visit for pain can be minimized.[43,45]

Stem cell transplantation

Although SCT itself is a very demanding process, it is severely affected by the COVID pandemic due to travel restriction, lockdown guidelines, and limitations of resources. ASCT for HL should not be withheld. Allo SCT for aplastic anemia and curative ALL/AML can go ahead with reduced intensity conditioning (RIC) and PBSC as it has faster engraftment. Allo SCT for benign disorders like thalassemia, sickle cell disease should be deferred.[26,46]

Future Directions

Currently most national and international recommendations are based on "expert opinions" due to the lack of data regarding the clinical impact of COVID-19 in hematologic disorders. There are several online registries for the COVID data collection. Hematologists worldwide can submit data regarding their cancer patients to the ASH RC COVID-19 Registry, data Hub platform, captures data on individuals who test positive for COVID-19 and have a hematologic condition (past or present) and/or have experienced a post-COVID-19

hematologic complication.[47] Similarly, the Center for International Blood and Marrow Transplantation Research (CIBMTR) reports real-time data on COVID-19 in patients of hematopoietic cell transplantation on their website.[48] Hematologists are encouraged to report COVID-19 cases in their patients suffering from hematological disorders (both benign and malignant) to national or international registries so that in future, we can have robust data backed by evidence and the big unknowns can be solved.

CONCLUSION

With limited and rapidly evolving data and new real-time information flying in, we need to choose and act wisely, so that the hematology patients in the large community are not affected much. Hematologists need to be in the loop and keep themselves updated as our patients, by nature of their disease, consume the bulk of the hospital resources. According to our strata and as per government directives from time to time, we need to modify the available guidelines so that services in large are minimally affected.

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