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Covid-19 and Hematological Malignancies: What we have to know?

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Abstract

Cancers of blood and bone marrow often directly compromise the immune system. Patients with blood cancers are particularly vulnerable to serious illness if they become infected with severe acute respiratory syndrome corona virus 2. Furthermore, the death rate was high among patients with hematological cancers. COVID-19 testing may be a reasonable advice even in asymptomatic patients who will receive immunosuppressive anticancer therapy to guide treatment decision making. Modifying or withholding therapy should be individualized. Factors such as chemotherapy indication, the goals of cancer care as well as where the patient is in the treatment course and the number of chemotherapy cycles given to the patients should be considered.

Abbreviations: MPNS: Myeloproliferative Neoplasms; NHL: Non-Hodgkin Lymphoma; WHO: World Health Organization; CML: Chronic Myeloid Leukemia; TKI: Tyrosine Kinase Inhibitor; HSCT: Hematopoietic Stem Cell Transplantation

Introduction

The estimate prevalence of cancer was 2% in patients treated for covid-19 [1]. Cancer patients especially those with bone marrow disorders, febrile neutropenia, patients on chemotherapy, transplant recipients, etc. should be considered as special population due to their higher risk of acquiring secondary infections and faster decline rate [2]. Symptoms of COVID-19, neutropenic sepsis and pneumonitis may be difficult to differentiate at initial presentation [3]. Patients having systemic anticancer treatments may have atypical presentation of COVID-19 [3]. Cancer patients are more likely to have higher rate of severe/ critical symptoms defined as the percentage of patients admitted to an intensive care unit and requiring invasive ventilation, or death. The death rate was highest in those with hematological cancer mostly acute myeloid or acute lymphatic leukemia (33.33%), and lung cancer (18.18%) [1].

Cancer patients at increased risk of complications from COVID-19 include:

Hematological Cancers

The case rate of COVID-19 amongst hospitalized persons was 10% for hematological cancers and <1% for other cancers in Wuhan [4]. Patients with blood and bone marrow cancers are more likely to be immunosuppressed than other cancers [5] and are particularly vulnerable to serious illness if they become infected with severe acute respiratory syndrome corona virus 2 [6]. These cancers are probably most at risk to acquire more infections since they often directly compromise the immune system [6]. Chronic leukemia, lymphoma or myeloma affects the immune system even if no treatment is being given [5]. All patients with MPNS except CML (less than 70 years) are extremely vulnerable to COVID-19 infection [7]. CML patients do not appear to be at a higher risk of getting COVID-19. Data on CML is limited. Very few CML patients on TKI were infected in the Hubei province in China and their outcome was similar to the general population [8].

Chemotherapy

Patients having chemotherapy or who have chemotherapy in the last 3 months are more susceptible [5]. An association between anticancer therapy in the past 14 days and severe effects of covid-19 infection was reported [1]. A recent study suggested that withholding effective cancer treatments from cancer patients during the pandemic runs the very real risk of increasing cancer morbidity and mortality perhaps much more than COVID-19 itself [9].

Other susceptible cancer patients are:

- Patients having immunotherapy or other antibody treatments for cancer [5].
- Patients having targeted cancer treatment that can affect the immune system such as protein kinase inhibitors [5].
- Bone marrow or stem cell transplant people in the last 6 months or those who are still taking immunosuppressive drugs [5].
- Those taking prednisolone ≥ 20 mg (0.5 mg/kg) or equivalent per day for more than 4 weeks. Also, those taking prednisolone ≥ 5 mg or equivalent per day for more than 4 weeks plus at least one other immunosuppressive medication (e.g. azathioprine, mycophenolate, or cyclosporine) or rituximab within the last 12 months [10].
- People who are on a combination of 2 immunosuppressive medications including rituximab within the last 12 months plus an additional comorbidity (age >70, diabetes mellitus, any preexisting lung disease, renal impairment, any history of ischemic heart disease or hypertension) [10].

Modification of the usual service to cancer patients during COVID 19 pandemic

Recent data are strongly indicative that cancer plus COVID-19 mortality is principally driven by advancing age and other non-cancer comorbidities [9]. The increased case fatality rate of hospitalized subjects with hematological cancers and COVID-19 seems to be predominantly related to bacterial co-infections resulting with higher probability from decreased granulocyte concentrations because of their disease or therapy thereof [4]. Cancer centers should develop strategies for symptomatic cancer patients including development of infection prevention guidance to ensure appropriate management of such patients should they require an in-person visit [11].

Follow up

i. -Rescheduling of non-essential visits [11]. Change outpatient clinics to telemedicine using video conferencing or messaging platforms [12].

ii. -Test all patients with fever for SARS-CoV-2 if positive transfer to other area of hospital [12]. Multiple myeloma patients should have PCR test of nasopharyngeal swab for SARS-CoV-2 before hospital admission, starting a new treatment line, cell apheresis, or ASCT [13].

- Test all patients who arrive via the emergency unit for SARS-CoV-2 prior to admission [12].

iii. -Prohibit visitors during the peak of the pandemic [12].

Systemic Chemotherapy

When COVID-19 positive cancer patient can resume systemic anticancer therapy?.

Decisions on modifying or withholding chemotherapy should include consideration for chemotherapy indication, the goals of cancer care as well as where the patient is in the treatment course and their tolerance of treatment [14]. Stop chemotherapy if the patients are in deep remission and are receiving maintenance therapy [1]. Interrupting anticancer treatment in patients with active COVID-19 should be strongly considered as treatment continuation will lead to further immunosuppression and risk of serious complications [1].

Defer systemic anticancer treatment if possible until the patient has 2 consecutive negative nasopharyngeal swab collected ≥ 24 hours apart and there is resolution of fever and respiratory symptoms for immunocompromised patients [11]. Patients who were previously treated with Rituximab have a possibility of a negative serological test if they were exposed to the virus [15]. In centers with no access to testing defer treatment for at least 3 days since resolution of symptoms and at least 7 days since first appearance of symptoms (CDC recommendation) [11]. Continue systemic anticancer treatment in a patient having COVID-19 if urgent control of the cancer is needed [3].

How can we minimize patients' visits to hospital?

- Surgical masks are recommended to those who are more likely to contract or already have the infection to avoid spreading it further [13].

- Use shorter treatment regimen especially if there is evidence of good response [3].

-Switch intravenous treatments to subcutaneous or oral alternatives if possible [3].

-Provide repeat prescriptions of oral medicines at home for e.g. hypomethylating agents [3] provided that oral regimen is not inferior to the alternative intravenous scheme [13]. Home delivery of oral medicines is recommended if possible [3].

-Switch to once weekly administration of drugs (instead of twice weekly) with dose adjustment [12].

-Use treatment breaks for long treatment (possibly for longer than 6 weeks) while the risk of COVID-19 is particularly high [3].

-Decrease the frequency of immunotherapy regimens for e.g. every 4 weekly or 6 weekly [3].

-Avoid T cell suppressive agents [14].

Consider the following when giving these chemotherapies for specific hematological diseases

- All TKI can prolong the QTc interval and strongly interact with chloroquine and azithromycin currently evaluated against

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COVID-19. Combining these medications with TKI in the absence of medical prescription and supervision may lead to fatal torsade de pointe [16].

- Try to avoid or skip treatment with monoclonal antibodies (rituximab, obinutuzumab) in CLL patients especially when given in combination with targeted agents. Avoid venetoclax because it requires multiple and extended clinic visits and lab testing unless it is the most appropriate for a particular patient [17].

- Myelofibrosis patients taking ruxolitinib have a weakened immune system and are at increased risk of COVID-19 infection and severe infections from other viruses [6,7]. A dose reduction of ruxolitinib can be considered in patients on corona virus directed medications in particular lopinavir/ ritonavir (kaletra). Avoid abrupt cessation of ruxolitinib otherwise there is a risk of sudden worsening of the cytokine reaction from myelofibrosis as well as from the COVID-19 infection [18].

-Hydroxyurea, anagrelide and interferon does not need to be empirically adjusted in someone with COVID-19 infection [18].

-Caution with polypharmacy in myeloma patients. Close monitoring of organ function is important. Anti SARS-CoV-2 agents including (hydroxyl)chloroquine, azithromycin and remdesivir may result in significant interactions with other drugs and may result in significant hepatic, cardiac or renal toxicity [13]. A case report of a patient with severe COVID-19 and underlying myeloma showed a clinical benefit with use of monoclonal antibody against intereukin-6 (tocilizumab) possibly by reducing the cytokine storm responsible for several symptoms of severe COVID-19 [13].

Care of central venous catheters / ports:

-Flushing can occur at frequencies as long as every 12 weeks with no notable increase in adverse events or harms [1].

Supportive Measure:

-No evidence on the use of prophylactic antiviral therapy for COVID-19 in immunosuppressed patients [1].

-Prophylactic antiviral therapy directed at other viral infections should be continued according to standard clinical guidelines [1].

- Mitigate the risk of neutropenia to avoid the risk of simultaneous COVID-19 and bacteria septicemia [9]. There is no evidence supporting a routine use of hematopoietic colony stimulating factors to prevent neutropenia during pandemic [19]. Use prophylactic growth factors and prophylactic antibiotics in high-risk chemotherapy regimens to maintain the overall health of the patient and make them less vulnerable to potential COVID-19 complications [1].

-Vaccinate against seasonal influenza and pneumococci [12].

-Continue receiving intravenous immunoglobulin at the prescribed dose and schedule [1].

-Use erythropoietin-stimulating agents, if serious and/or symptomatic cancer/treatment-related anemia is anticipated [1].

-Transfusion should be given in serious and/or symptomatic cancer/treatment related anemia. Do not give more than the minimum number of RBC units necessary to relieve symptoms or achieve a safe hemoglobin range [1]. Prophylactic transfusion in asymptomatic patients based on laboratory values should be avoided [1].

-Defer and/or reduce frequency of antiresorptive therapy (zolendronic acid, denosumab) [3]. Switch monthly zolendronic acid to once every 3 months especially for those with at least one year of prior therapy and those at first line therapy who achieved VGPR or better (and clinically stable bone disease). Avoid long term discontinuation of denosumab as it may result in a rebound effect [4].

Concerns surrounding concomitant medications for cancer patients?.

-Ibuprofen and similar drugs may make COVID-19 worse. Acetaminophen is the preferred antipyretic [10].

- Aspirin, warfarin, apixaban, or rivaroxaban or venesection alone does not increase the risk of COVID-19 infection [7].

-Avoid steroids if there are alternative treatment options (WHO, 2020) [10].

-Continue treatment with RAAS antagonists (e.g. ACE inhibitors) [1].

Should immune checkpoint inhibitors treatment be delayed or interrupted?

Relapsed NHL and CD19 positive lymphoma are the prime indications [12]. COVID-19 testing prior to therapy with these agents is reasonable. Adjust to the less frequent dosing intervals when different schedules are considered reasonable options for the patient's indication [1]. However, immunosuppression may not be advisable for some novel immunotherapy and T-cell therapy agents. These agents may cause immune-related serious adverse events. There is preclinical evidence of cytokine storm and/or potentially increase inflammatory reactions and complications such as pneumonitis [1] and neurotoxicity [12]. Coordinate with the ICU to determine if an ICU bed is available (mainly within 2-3 weeks post-infusion) if the patient requires it [14].

Radiotherapy

Balance the risk of not being treated optimally with the risk of the patient becoming seriously ill from COVID-19 [20].

Options include:

i. Avoid radiotherapy if evidence suggests that there will be little to no benefit or if an alternative treatment is available [20].

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ii. Defer radiotherapy if clinically appropriate [20].

iii. Radical radiotherapy or chemoradiotherapy with curative intent if the patient has a rapidly proliferating tumor and treatment has already started and there is little or no possibility of compensating for treatment gaps. Urgent palliative radiotherapy for patients with malignant spinal cord compression who have salvageable neurological function [20].

Bone Marrow Transplantation

For autologous transplantation

Patients with myeloma and indolent NHL are recommended to receive additional cycles of induction and postpone transplantation. Diffuse large B cell lymphoma and high-grade lymphoma like mantle cell lymphoma should be evaluated for the risk /benefit ratio in each case scenario [12]. Nonmalignant indications should be deferred until the peak of COVID0-19 passes. Use GCS-F alone and minimizes the use of chemotherapy for priming [12].

For allogeneic Transplantation

Defer HSCT by at least 3 months for COVID-19 positive patients except patients who have a high risk of disease progression, morbidity, or mortality. HSCT for these last patients should be deferred until patients show no longer symptoms and have 3 repeated negative PCR tests at least 1 week apart [21]. There is unlikely an impact on patients' outcome if allo SCT is delayed in patients with myeloproliferative neoplasms, second transplant or patients with refractory disease [12]. The national marrow donor program requires all transplant centers to receive and cryopreserve unrelated donor products before starting recipient-conditioning chemotherapy [9]. Donors with known or suspected COVID-19 should not provide other blood products (including lymphocytes) for at least 3 months from when their symptoms resolve [21].

Pre-SCT

Ideally all transplant patients should be screened at least twice, 1 week apart, before starting conditioning if they have a history of recent contact with symptomatic individuals (travel to high risk countries). Advise the patients to avoid crowded places, public transport, use good hand hygiene measures and ideally remain in self-isolation for 14 days prior to the start of conditioning [22].

Post-transplant

Manage the patients in a strict protective isolation. Advice the patients who had HSCT to follow the UK government guidance on shielding and protection if they had autologous HSCT within the last year and if they had an allogeneic HSCT within the last 2 years, had continuous immunosuppressive therapy, had chronic graft versus host disease or evidence of ongoing immunodeficiency until the COVID-19 pandemic risk has passed [21]. Isolate COVID-19 positive patients in negative pressure cubicles or neutral pressure cubicles if this not possible [21].

Conclusion

In general, any clinic visits that can be postponed without risk to the patient should be postponed. Initiating or restarting anticancer treatment should be based on risk benefit assessment. Anticancer treatment should be resumed only when symptoms of COVID-19 have resolved, and SARS-Cov-2 test is negative unless the cancer is rapidly progressive.

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