aGvHD, GvHD Prophylaxis

Caring for patients with hematological malignancies during the COVID-19 pandemic. Recommendations from IACH, EHA, and EBMT

Emily Smith | Apr 14, 2020

This article is based on two webinars organized by European hematology institutions. The first was arranged by the International Academy of Clinical Hematology (IACH) and was entitled 'COVID-19 in hematological malignancies: a few practical issues'. This webinar, held in a question and answer format, was chaired by Mohamad Mohty, who was joined by Christian Chabannon — both of whom are from France.[1] The second was organized by the European Hematology Association (EHA) and European Society for Blood and Marrow Transplantation (EBMT) and was entitled 'COVID-19 and hematology patient care'.[2] The key messages from both webinars have been summarized in this article; we hope you will find the recommendations useful to your clinical practice.

The COVID-19 pandemic is an evolving situation, and the GvHD Hub would like to remind readers to check current guidelines in their own country, as recommendations provided in this article may have been superseded by other guidelines as more data are released.

What are the objectives of a treating hematologist during the coronavirus disease (COVID-19) pandemic?[1]

- Protecting highly immunocompromised patients from contracting SARS-CoV-2 and developing COVID-19
- Maintaining effective management of the hematological malignancy
- Protecting healthcare professionals (HCPs) from infection

How important is the risk of COVID-19 in patients with hematological malignancies?[1]

The risk is significant because patients with hematological malignancies may have a higher likelihood of contracting SARS-CoV-2 and of developing more severe disease. This is because

- some hematological malignancies, by nature, are associated with immune deficiency
- immunosuppressive therapy, such as steroids, is widely given to patients with hematological malignancies

The United Kingdom has classified patients with hematological malignancies as 'vulnerable'; this population are being told to stay inside for a period of 12 weeks.

How to manage patients with hematological malignancies during this novel coronavirus pandemic?

- Avoid bringing patients to hospital, where the risk of infection is higher, with the aim of lowering circulation of the virus[1]
- Switch to oral drug regimens[1]
    - It was acknowledged that there may not be randomized trials or evidence basis for this, but these extraordinary times call for extraordinary measures
- Administer drugs at home where possible, depending on the capacity of the nurses and doctors. For example, hypomethylating agents can be administered at home[1]
- Switch to once-weekly administration of drugs (instead of twice weekly) and make dose adjustments where possible[1]
- Consider switching from intravenous infusions to subcutaneous administration, to minimize the duration of time spent in hospital[1]
- Avoid contact in hospitals, for example using specific circulation pathways[1]
- Identify symptomatic patients before they get to the ward/day hospital[1]
- Change outpatient clinics to telemedicine, using video conferencing or messaging platforms[1]

Table 1. Recommendations of the EHA and EBMT for hematologic diseases[2]

Hematologic disease	**Recommendation**
Aggressive lymphomas	**Initial therapy**: no change, outpatient visits as much as possible **Visits**: replaced with telemedicine **Rescue therapy**: delivered in the outpatient setting if possible **Auto-SCT**: defer
Indolent lymphomas	**Asymptomatic:** watch-and-wait approach (instead of rituximab, for example) **Chemotherapy**: defer as much as possible; use R-COP/R-CHOP regimens in place of bendamustine **Maintenance**: defer onset of rituximab, e.g. in patients with FL, and increase the intervals between rituximab cycles. Use ibrutinib for MCL and CLL

Hodgkin lymphoma	**Localized stages**: avoid radiotherapy (multiple sessions) **Advanced stages**: Use ABVD regimens or similar, telemedicine, and outpatient regimens with bendamustine for relapse. Defer auto-SCT and allo-SCT
AML	**Before therapy**: conduct a PCR test (mandatory) **Induction**: use standard regimens and extreme prophylactic measures **Consolidation**: aim to use home protocols **Allo-SCT**: do not excessively delay **Relapsed patients**: enroll in clinical trials if possible
Multiple myeloma	**MM without CRAB symptoms:** delay onset of treatment **Initial and maintenance therapy**: do not change for patients both eligible and ineligible for transplant **COVID-19 infection**: interrupt maintenance until infection resolved **Clinic visits**: decrease as much as possible using remote labs, telemedicine, and prescription delivery via mail **SCT**: delay until the pandemic abates

ABVD, doxorubicin + bleomycin + vinblastine + dacarbazine; allo-SCT, allogeneic stem cell transplant; AML, acute myeloid leukemia; auto-SCT, autologous stem cell transplant; CLL, chronic lymphocytic leukemia; COVID-19, Coronavirus Disease 2019; CRAB, symptoms experienced by most patients with multiple myeloma: calcium (elevated), renal failure, anemia, bone lesions; FL, follicular lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; PCR, polymerase chain reaction; R-CHOP, rituximab + cyclophosphamide + hydroxydaunorubicin + Oncovin + prednisone; R-COP, rituximab + cyclophosphamide + vincristine + prednisone; SCT, stem cell transplant

Prophylactic measures to protect patients from respiratory infections[2]

- Administering intravenous immunoglobulin (IVIg), as recommended by the European Medicines Agency (EMA)
- Avoiding additional antimicrobial prophylaxis, such as antibiotics and granulocyte colony stimulating factor (G-CSF)
- Vaccinating against seasonal influenza and pneumococci

What are the risks and challenges in the autologous (auto) and allogeneic (allo) stem cell transplant (SCT) settings?

General guidance of the EBMT[2]

- Patients who have received SCT should restrict their risk of exposure to infected individuals and avoid travel that is not absolutely necessary
- Minimize the risk of infection by isolating at home for 14 days prior to the start of SCT conditioning
- Test patients for SARS-CoV-2 infection prior to the start of conditioning
- If a patient has had close contact with a person infected with COVID-19, transplant procedures should not be performed within 14, preferably 21, days of contact

Patients with multiple myeloma (MM) may be particularly affected by disruption to SCTs, since auto-SCT is a key treatment for these patients. Additionally, numerous combination therapies used in the frontline and relapsed setting contain dexamethasone, which is associated with pneumonia — a severe complication of treatment in this population of patients.[1]

Auto-SCT requires multiple visits to the hospital, each of which increase the risk of infection. Hospitals are restricting access in order to reduce the spread of the virus, and so it is important to consider when and where to plan the auto-SCT[1]

- For patients with MM: it is recommended to postpone auto-SCT and reorganize the treatment plan to include additional cycles of induction, with all-oral regimens being preferable. This is the recommendation of the Intergroupe Francophone du Myéloma (IFM) and is endorsed by many other groups worldwide. Importantly, randomized trials have shown the outcomes of patients who proceeded to auto-SCT was similar to those who received additional cycles of induction
- For patients with lymphoma:
    - Some subgroups of lymphoma, such as diffuse large B-cell lymphoma (DLBCL), show benefit from consolidation therapy with high-dose chemotherapy and auto-SCT; in these cases it may be important to not delay high-dose chemotherapy. The risk:benefit ratio should be evaluated in each specific scenario
    - Other subtypes, such as first-line high-grade lymphomas, like mantle cell lymphoma, should be assessed on a case-by-case basis
    - For patients with indolent non-Hodgkin lymphoma (iNHL), it may be more beneficial to increase the number of induction chemotherapy cycles, as with MM, and delay auto-SCT

For allo-SCT, it is difficult in the current situation to obtain grafts from unrelated donors, especially when the donor is located in a different country. Therefore, it is recommended that each patient is carefully evaluated, as patients undergoing SCT are at risk of needing access to intensive care unit (ICU) beds. Physicians should aim to reduce the burden on ICU beds and their ICU colleagues during the pandemic, so the timing of transplant must be carefully considered.[1]

In many cases, as with myeloproliferative neoplasms, second transplant, or patients with refractory disease, there is unlikely to be an impact on patient outcome if allo-SCT is delayed. Therefore, it is recommended to convert to non-transplant modalities. Additionally, it is important to consider whether the SCT is consolidative or curative.[1]

With regards to chimeric antigen receptor (CAR) T-cell therapy, where relapsed NHL and CD19-positive lymphomas are prime indications, the speakers noted the following[1]:

- Treatment with the two currently approved CAR T-cell therapies, tisagenlecleucel and axicabtagene ciloleucel, is still possible, as the manufacturing and supply chain is currently still able to operate
- It is important to consider that CAR T-cell therapy is associated with severe toxicity, such as cytokine release syndrome and neurotoxicity
    - This puts patients at high risk of needing an ICU bed. Therefore, prior to treatment with CAR T cells, hematology departments should coordinate with the ICU to determine if an ICU bed is available (mainly within 2–3 weeks post-infusion), if the patient requires it

All decisions should account for the probability of needing to send the patient to ICU and the ICU bed availability.[1]

Read more about the EBMT recommendations for transplant centers and advice for donors and recipients of SCT here.

What are the practical measures to be taken? E.g. multidisciplinary meeting, ambulatory care, clinical research, transfusions, and so on

- In inpatient units[2]
    - Avoid patients with SARS-CoV-2 infection entering/being in the hematology unit
    - Test all patients with a fever for SARS-CoV-2 infection — if positive, transfer to another area of the hospital
    - Test all patients who arrive via the emergency unit for SARS-CoV-2 prior to admitting them to the hematology unit
    - Prohibit visitors during the peak of the pandemic
    - Transplantation restricted to patients where it is clearly indicated and urgent
    - Have a back-up team working at home to be able to substitute with infected physicians/nurses if the need arises
- It was noted that one positive to come from the current situation is that telemedicine solutions are being adopted more frequently, and it is hoped this will remain in place once the pandemic resolved[1]
- Conducting clinical research is currently difficult due to the strain on resources (samples, people, data, etc.) that involves long-distance travel. Therefore, many sponsors have stopped enrolling new patients onto clinical trials. For those already involved in a trial, the decisions are made on a case-by-case basis. In some instances, it is possible to monitor these included patients. It is important to note that the safety of the patient is a priority, and that they can return to standard-of-care treatment if necessary. The exception to the clinical trial hold is for those involving COVID-19, as these trials are necessary to better inform treatment decisions[1]
- The supply chain for blood products must be maintained for patients with hematological malignancies, as these patients often need transfusions. While there may be less of an issue with red blood cells, since planned surgery is being postponed, there is a supply issue with platelets. Both speakers urged people to continue donating blood and platelets if they could[1]

Current treatment options for patients with COVID-19[2]

- Hydrochloroquine for 7–14 days: 400 mg twice per day (BID; some centers are using 200 mg BID)
- Antibiotic coverage: ceftaroline if admitted; amoxicillin/clavulanate or ceftriaxone in the emergency room or at home

- Evaluation of anti-inflammatory therapy:
  - Methylprednisolone: 1 mg/kg for 5 days (unless already severely immunocompromised)
  - Tocilizumab if not receiving other immunosuppressants and there is systemic inflammation
- Supportive care:
  - Early non-invasive ventilation (continuous positive airway pressure [CPAP])
  - Anti-coagulants due to the risk of pulmonary embolism
- Other treatments under investigation include JAK-inhibition and cytokine blockage (interleukin (IL)-1 and IL-6)
- A patient with MM with COVID-19 was recently successfully treated with tocilizumab[3]

The speakers thanked all HCPs worldwide for their ongoing efforts and dedication in maintaining the excellent quality of care being given to patients. They encouraged everyone to stay safe and take good care of themself and their family.

Further resources

- Read more specifically about COVID-19 in patients with lymphoma here
- Read more about the European experience with COVID-19 in patients with MM here and the United States experience here

References

1. Mohty M & Chabannon C International Academy of Clinical Hematology (IACH) webinar: COVID-19 in hematological malignancies: a few practical issues. Mar 26, 2020.

2. Rambaldi A, Ribera JM, von Lilienfeld-Toal M, Mikulska M. EHA and EBMT webinar: COVID-19 and hematology patient care. Apr 1, 2020.

3. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv*. 2020;4(7):1307-1310. DOI: 1182/bloodadvances.2020001907