COVID-19 - Bone Marrow Failure and PNH

Recommendations On behalf of the Severe Aplastic Anemia Working Party, European Group for Blood and Marrow Transplantation (EBMT)

The SARS-CoV-2 infection has become a major medical emergency worldwide, due to the morbidity and mortality of the consequent Coronavirus Disease 2019 (COVID-19). Patients with acquired and inherited Bone Marrow Failure syndromes, including Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria (PNH), are exposed to a significant risk of infection with this novel coronavirus named SARS-CoV-2 and mostly to its possible complications. Treating physicians must consider the current SARS-CoV2 outbreak in the management of these patients, in the interest not only of individual patients, but also of public health. No widely recognized guidelines are available or can be offered, but we strongly recommend to adhere to the restrictions imposed by each European country as well as to EBMT guidelines (https://www.ebmt.org).

Overall, we should aim as much as possible to keep patients safely at home, limiting access to hospitals and to any other health care providers in the interest of reducing the spread of the disease. It also seems essential to recommend all the efforts to keep hematological wards, and even more BMT units, free from circulating SARS-CoV-2; it has to be remarked that due to the professional exposure, health care providers are the most obvious carriers of the infection. Life-saving treatments should not be deferred. On the contrary, whenever possible, treatments potentially increasing the susceptibility to SARS-CoV-2 infection and/or increasing the risk of becoming infected (e.g. deferrable in-patient hospitalization or accesses to out-patient clinics) or at risk of ICU requirement may be postponed. A risk-to-benefit assessment should be discussed for patient before taking any decision, which obviously has to be tailored on each specific situation. Policies and measures useful to reduce the spread out of SARS-CoV-2 in hospitals and health care structures are described in EBMT guidelines (https://www.ebmt.org).

For reasons so far unknown, children are reported to be far less affected than adults (less than 1 child affected every 100 affected adults according to some rough estimation from Italian population). Also severity of the COVID-19 appears to be largely inferior as compared to that in adults. Children have been reported to be a potential asymptomatic reservoir of the disease. In some pediatric hospitals a specific triage has been set up to separate patients in COVID-19 negative or COVID-19 positive areas that have been identified within the hospitals themselves. Whenever possible, this separation is highly recommended not only for the sake of the children but also for that of the adult operators who appear more susceptible to contagion and whose activity has to preserved to offer care to children. During ward and outpatient admissions accompanying persons have to be limited to one parent/relative. Homecare services, whenever available, have to be prioritized. Specific trucks have to de dedicated to those children who get in and out of adult hospitals to use services (e.g. radiotherapy, PET scan) therein located.

APLASTIC ANEMIA AND CONSTITUTIONAL MARROW FAILURES

Some specificity related to aplastic anemia and constitutional marrow failure diseases are described below:

1. Bone Marrow Transplantation (BMT).

a) It is recommended to postpone BMT whenever possible (according to disease severity, blood products immunization, infections risk) especially in case of unrelated transplantation, until the situation come back to normal, due to the risk of COVID-19 infection and also the possible lack of Intensive Care Unit availability, entirely occupied by severely COVID-19 injured patients.

b) BMT may be a saving treatment for severe aplastic anemia patients, and in several cases cannot be deferred. In case of urgent BMT, we recommend to carefully evaluate patients and donors for possible SARS-CoV-2 infection before admission in the hospital. A swab for SARS-CoV-2 should be performed before the start of the conditioning regimen and the patients should be admitted in BMT unit only once SARS-CoV-2 testing has proven negative (to avoid the risk of infecting the health care professionals). Transplant procedures (e.g., conditioning regimen, GVHD prophylaxis, post-transplant immunosuppression) do not need to be changed because of the SARS-CoV-2 outbreak.

2. Immunosuppressive therapy (applies only to acquired aplastic anemia):

a) There is no information about the risk of SARS-CoV-2 infection, nor about the clinical evolution of COVID-19, in patients who receive or have received immunosuppressive treatments. Nevertheless, it is commonly accepted that patients who have received intensive immunosuppression (i.e., using T-cell depleting agents such as horse-ATG, rabbit-ATG or Campath) have an increased morbidity and mortality from many viruses (including common coronaviruses). Thus, patients receiving T-cell depletion need to be considered at higher risk of SARS-CoV-2 infection.

b) An intensive immunosuppressive therapy (IST) using T-cell depleting agents should be carefully considered in patients newly diagnosed with aplastic anemia. Treatment should be limited to patients with severe cytopenias with immediate risk of death (e.g., severe, or even very severe neutropenia), and deferred for patients who may safely stay at home. Theoretically, intensive IST might be appropriate in patients already hospitalized, but even here we should avoid the use of treatment who needs long-term hospitalization (anti-thymocyte globulin notably), to limit the presence of patients in the hospital and to free hospital resources which can be dedicated to COVID-19 emergency. As for BMT, we recommend to carefully evaluate patients for possible SARS-CoV-2 infection before admission in the hospital; ideally, they should be admitted in the unit only once SARS-CoV-2 testing has proven negative.

b) The use of alternative treatments which do not require hospitalization and do not lead to long-lasting immunodeficiency should be considered. In particular, the use of the

thrombopoietin-mimetic agent eltrombopag may be considered even as bridge to a more definitive treatment with BMT or intensive IST. This seems an acceptable compromise considering that for many patients the standard treatment of their aplastic anemia (either BMT or IST) is precluded by the COVID-emergency, and that in these circumstances eltrombopag treatment (even if not immediately effective) may reduce the immediate risk of complications associated with severe cytopenias.

c) For patients already receiving maintenance IST with cyclosporine (or other immunosuppressive agents requiring plasma level monitoring), no dose decrease should be applied during the following months to prevent the risk of relapse, in a future time in which hospital resources might be reduced because fully absorbed by COVID-19 infection. Furthermore, we recommend to keep maintenance doses within a level which do not require frequent monitoring (for drug plasma level, or even possible complications such as kidney failure), to limit the access to hospital or other medical structures for blood testings.

d) For relapsed patients, the risk-to-benefit assessment is the same as that of newly diagnosed aplastic anemia. In brief, keep patients at home whenever possibly, trying to defer intensive etiologic treatment with BMT or intensive IST. The early use of eltrombopag seems very reasonable in this situation.

In general whenever available, home care services have to massively utilized (and potentiated) both for eligible treatment delivery and for test monitoring (e.g. blood count, serum drug levels).

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Some specificity related to paroxysmal nocturnal hemoglobinuria:

1. Transplantation: with the exception of PNH patients who have developed severe aplastic anemia, the indication to BMT in PNH is questionable, and for sure it does not represent a medical emergency. Thus, it is recommended to postpone BMT for the same reasons mentioned for aplastic anemia patients.

2. Anti-complement treatment:

a) There is no information about the risk of SARS-CoV-2 infection, nor about the clinical evolution of COVID-19, in patients receiving anti-complement treatment (standard anti-C5 agents, as well as novel experimental agents targeting either C5, C5, complement Factor D or complement Factor B). However, our knowledge of SARS-CoV-2 (and of previous coronaviruses) does not suggest that the complement system has a major role in the clearance of the virus. Thus, at the moment there is no evidence that patients receiving anti-complement treatment have higher risk of being infected, or higher risk of developing a more aggressive disease course.

b) Even if there is no increased risk of SARS-CoV-2 infection in PNH patients (either untreated or on anti-complement treatment), it has to be remarked that in case of SARS-CoV-2 infection very likely massive complement activation may occur, leading to severe

hemolysis possibly associated with severe anemia and life-threatening thrombosis complications, as well as with hospitalization. For untreated patients, these hemolytic crises may represent an obvious indication to start treatment with eculizumab immediately. For patients already on eculizumab treatment (or any other anti-complement treatment), they may lead to clinically meaningful breakthrough hemolysis; even if there is no standard recommendation for breakthrough hemolysis during eculizumab treatment, in these specific circumstances a transient modification of the treatment schedule may be recommended (i.e., early administration of the next dose, and/or dose increase).

c) All patients receiving anti-complement treatment must continue their treatment even during the SARS-CoV-2 outbreak, indefinitely. Whenever possible, strategies to minimize the risk SARS-CoV-2 infection should be adopted delivering the treatment, for instance aiming to limit all contacts between patients and health-care providers (e.g., strict policies regulating the access to out-patient clinics, use of personal protective equipment). Home care must be a priority.

d) Whenever the long-acting novel anti-C5 agent ravulizumab is available, the switch to ravulizumab is recommended to reduce by 4 folds the access to the hospital.

e) For patients in clinical trials with alternative complement inhibitors, treating physician should follow the recommendation from Sponsors. We strongly recommend to deliver experimental treatment at home when the disease situation is stable and to postpone unnecessary study procedures, to reduce the risk of infection associated with frequent hospitalization.

SUPPORTIVE CARE

Some specificity related to supportive care, for all patients with bone marrow failure syndromes or other cytopenias:

1. Our patients are chronically anemic and thrombocitopenic. In case of stable patient and absence of hemorrhage, level for transfusions might be hemoglobin 7 g/dL and platelets 10,000 G/μL, to reduce the number of hospitalizations.

2. Neutropenic patients are often used to live with neutrophil counts <1,000/μL (or even <500/μL), without developing meaningful infection. In these circumstances, in selected patients one may consider the transient use of G-CSF to reduce the risk of bacterial infections which may mimic COVID-19, eventually requiring hospitalizations (or even just medical assessment, with increased risk of SARS-CoV-2 infection). G-CSF needs to be continued for patients on chronic treatment like those with Severe Chronic Neutropenia. The best use of supportive care nowadays should be very conservative to limit all access to any health care provider (e.g., even to the laboratory to perform CBC), because resources are limited and fully dedicated to the COVID-19 emergency.

Those recommendations are supposed to guide physicians in this particular difficult pandemic situation. However, each Country (or even each small geographic area) might be in a different situation and some situation might require different approach. Keep your

patients at home as much as possible, use homecare services if available to avoid the risk of infection and to avoid virus spreading independently from the chances of the patient to be safely rescued from COVID-19. If helpful, the SAAWP is fully available to give an opinion in particular situation, even for individual patients, again to help as much as possible to take the best decision for each of our aplastic anemia, PNH and constitutional marrow failure patients in this difficult context.

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