January 11, 2024

EBMT Infectious Diseases Working Party Recommendations regarding pre-therapy positivity for SARS-CoV-2

During the first two years of the Covid-19 pandemic, the EBMT produced recommendations regarding management of SARS-CoV-2 infections in stem cell transplant and CAR T cell treated patients. Since 2022, the EBMT has contributed to the European Conference of Infections in Leukemia (ECIL) recommendations for Covid-19 management (1, 2). The majority of these recommendations are current and should be regarded also as the EBMT's recommendation. The current recommendations are:

1. *In HM patients with asymptomatic SARS-CoV-2 infection (and no previous COVID-19), defer chemotherapy, HCT, CAR-T therapy, therapy with monoclonal antibodies or other targeted therapies after assessment of clinical risk/benefit ratio (BIIu).*
2. *In HM patients with COVID-19, defer cellular therapy (HCT, CAR-T). AIIt)*
3. *In case of patients persistently shedding the virus after complete recovery from COVID-19, defer chemotherapy, HCT, CAR-T therapy, therapy with monoclonal antibodies, and other targeted therapies after assessment of the clinical risk/benefit ratio (BIIu)*

The increased immunity to SARS-CoV-2 (though vaccination and past infections) in the population, the development of different Omicron variants, probably resulting in a milder course, as well as the progress of preventative and new therapeutic interventions such as antivirals, and immunotherapy have resulted in the need for reassessment of previous recommendations~~,~~ One remaining area of controversy is what to do with patients requiring either transplantation or cellular therapies while being SARS-CoV-2 positive frequently continuing for several weeks to months. The above-mentioned recommendations were based on very limited published data including an EBMT survey that reported the practice of the centers, while there are case reports, small patient series and unpublished experiences by the authors suggesting that the risk of progression to severe-critical COVID-19 is lower in asymptomatic patients with prolonged positivity for SARS-CoV-2 (3, 4). It has also been observed that prolonged shedding frequently occurs in clinically recovered cases after severe-

critical COVID-19 (ref spaniard 2023). However, prolonged RNA shedding is not synonymous with persistent replicating virus. Thus, both the patient's individual risk as well as the risk to spread SARS-CoV-2 within transplant or cellular therapy units have to be taken into account since the highest risk for mortality exists for patients during the first months after either allogeneic HCT or CAR T cell therapy (5)(Spaanjard et al manuscript 2023).

During the fall of 2023, new variants of concern (VOC) of SARS-CoV-2 are circulating with limited information about their pathogenicity. The new EBMT registry allows the reporting of patients coming to transplant or CAR T cell therapy while being SARS-CoV-2 positive. We encourage reporting including in the added extended dataset/study form to get enough experience of this situation to better being able to update the recommendations.

Currently, we see the situation as follows:

1) To take a patient to HCT or CAR T cell therapy in the situation of detectable SARS-CoV-2 can result in progression of the infection including development of lower respiratory tract disease. The risk most likely will depend on how long ago the patient got infected, presence of pulmonary co-morbidity, whether the patient had signs of lower respiratory tract involvement, the "viral load" as assessed by the CT-value as it is expected to correlate with virus viral load and possibly its replication (although no specific cut-off can be determined), previous antiviral therapy against Covid-19, previous vaccination and SARS-CoV-2 infection history, and the treatment planned to be given.
2) Patients being symptomatic either with upper respiratory symptoms or signs of lower respiratory tract involvement should be deferred until clearance of all symptoms (presumably for 2-4 weeks) regardless of given therapy and preferably until confirmed SARS-CoV-2 negativity.
3) Patients having cleared symptoms of infection with positive SARS-CoV-2 testing result:
    a. If the deferral of therapy can be done safely (patients with non-malignant disorders or patients with stable malignancies not requiring therapy), deferral is still the main strategy also to reduce the risk for transmission or clinical relapse.
    b. In patients with persistent PCR positivity, regardless of previous treatment, and if the cell therapy deferral is regarded as risky, consider antiviral therapy,

preferably with nirmatrelvir/ritonavir or remdesivir in case of renal failure or unmanageable risk of drug-to-drug interactions.

c. The duration of therapy has to be decided on an individual basis depending on the urgency of the planned treatment but preferably until PCR-negativity has been documented.
    i. If the patient has received one course of antiviral therapy and the duration of viral shedding persists or have recurred, or the patient harbor risk factors for prolonged SARS-CoV2 detection while on one antiviral therapy (i.e. severe COVID-19, pneumonia, need for oxygen support, timing from SARS-CoV-2 detection to antiviral onset >5 days, prior anti-CD20 treatment in the last year, B-cell NHL, chronic lymphocytic leukemia, PCR Ct value of <20 and/or use of corticosteroids during COVID-19), consider prolonged treatment with an antiviral or possibly with a combination of antivirals or combination of antiviral(s) and high titer convalescent plasma (CVP) in order to increase the probability of obtaining clinical improvement and prevent disease progression (2, 6-9).
d. The following antiviral therapies can be considered and in selected cases be used in combination:
    i. Nirmatrelvir/ritonavir orally, if ClCr > 30 ml/min; refer to an expert for the management of DDIs since most of them can be successfully managed with drug interruption or substitution. FDA authorized its use also in pediatric patients 12 years of age and older weighing at least 40 kg.
    ii. Remdesivir IV, can be used also in case of renal failure and in children at least 4 weeks of age and weighing at least 3 kg.
    iii. High titre CVP active against circulating variants (if available).
    iv. Molnupiravir has been refused the marketing authorization by the European Medicines Agency in February 2023, so its availability in Europe is limited, although it remains authorized by FDA for adult high risk patients for whom alternative COVID-19 treatment options are not accessible or clinically appropriate.
    v. Combination of antivirals and monoclonal antibodies (MoAbs) has been associated with better results than monotherapy/dual therapy and

prolonged treatment courses might be required (currently reported up to 20 days). However, there is currently no MoAb with activity against the circulating variants.

4) If patients, who are PCR-positive for SARS CoV-2 are being treated with either HCT or CAR T cell therapy, they should be carefully monitored to assess activation of SARS-CoV-2 infection (decreasing CT value, becoming virus isolation positive, or developing symptoms). In such cases, an extended course of antiviral treatment or combination antiviral therapy unless contraindicated should be considered. Other options could be MoAbs if such has effect against the documented variant or CVP (if available)
5) In such patients, the risk of SARS-CoV-2 transmission should be evaluated based on clinical and virological characteristics, and logistics of the center and weighted against the quality of care provided outside the unit performing the treatment, and the risk of transmission within the unit. If feasible, HSCT or CAR-T procedures should be performed outside a unit where other severely immunocompromised patients are treated.
6) Infection control precautions (FFP2 mask, isolation) should be strictly followed. Positive room pressure should be avoided if possible.

These recommendations apply both for adults and children (with age-dependent restrictions depending on drug approvals).

Per Ljungman, Dina Averbuch, Simone Cesaro, Lidia Gil, Malgorzata Mikulska, José Luis Piñana, Jan Styczynski, Rafael de la Camara

References

1. Cesaro S, Ljungman P, Mikulska M, Hirsch HH, von Lilienfeld-Toal M, Cordonnier C, et al. Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9). Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2022;36(6):1467-80.
2. Cesaro S, Mikulska M, Hirsch HH, Styczynski J, Meylan S, Cordonnier C, et al. Update of recommendations for the management of COVID-19 in patients with haematological malignancies, haematopoietic cell transplantation and CAR T therapy, from the 2022 European Conference on Infections in Leukaemia (ECIL 9). Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2023;37(9):1933-8.

3. Styczynski J, Cesaro S, von Lilienfeld-Toal M, Marchesi F, Gil L, Mikulska M, et al. Current attitude to deferral of cellular therapy or nontransplant chemotherapy due to SARS-CoV-2 asymptomatic infection: Survey of Infectious Diseases Working Party EBMT. Transplant infectious disease : an official journal of the Transplantation Society. 2022;24(2):e13773.
4. Krajewski J, Chen J, Motiani J, Baer A, Appel B, Zakrzewski J, et al. Hematopoietic stem cell transplant in two pediatric patients testing positive for SARS-CoV-2: A case report. Pediatr Transplant. 2022;26(2):e14179.
5. Ljungman P, Tridello G, Pinana JL, Ciceri F, Sengeloev H, Kulagin A, et al. Improved outcomes over time and higher mortality in CMV seropositive allogeneic stem cell transplantation patients with COVID-19; An infectious disease working party study from the European Society for Blood and Marrow Transplantation registry. Front Immunol. 2023;14:1125824.
6. Pinana JL, Heras I, Aiello TF, Garcia-Cadenas I, Vazquez L, Lopez-Jimenez J, et al. Remdesivir or Nirmatrelvir/Ritonavir Therapy for Omicron SARS-CoV-2 Infection in Hematological Patients and Cell Therapy Recipients. Viruses. 2023;15(10).
7. Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, et al. Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients. Clin Infect Dis. 2023;77(2):280-6.
8. Da Silva L, Klopfenstein T, Gendrin V, Clouet J, Toko L, Richier Q, et al. Prolonged SARS-CoV-2 Infection in Patients Receiving Anti-CD20 Monoclonal Antibodies: A Diagnostic Challenged by Negative Nasopharyngeal RT-PCR and Successful Treatment with COVID-19 High-Titer Convalescent Plasma. Viruses. 2023;15(11).
9. Orth HM, Flasshove C, Berger M, Hattenhauer ST, Biederbick KD, Mispelbaum R, et al. Early combination therapy of COVID-19 in high-risk patients. Infection. 2023.