Management of patients with multiple myeloma during the COVID-19 pandemic

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A novel coronavirus of zoonotic origin emerged in China at the end of December 2019. The infection, named coronavirus disease 2019 (COVID-19), is now spreading worldwide. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA beta-coronavirus, which has a phylogenetic similarity to another known coronavirus, SARS-CoV-1, the causative agent of SARS responsible for a major epidemic in 2003. The contagious potential of this virus is proving to be very rapid and unpredictable. As of April 20, 2020, more than 2·4 million cases of COVID-19 have been confirmed resulting in more than 150 000 deaths worldwide. Mortality can be as high as 15% in older patients and those with comorbidities.[1] The severity of COVID-19 is classified into four types: mild, ordinary, severe, and critical. In addition, approximately 18% of patients are estimated to have asymptomatic SARS-CoV-2 infection.[2] At present, no treatment options have been approved in Europe, and no vaccine is available. Avoiding exposure by adhering to recommended hygiene procedures, isolation of infected people, and social distancing are the only prevention strategies recommended by the WHO.

Risk factors for COVID-19 severity and death include increased age and the presence of comorbidities such as diabetes, hypertension, or cardiac diseases.[1] In addition, data from China suggest that patients with cancer have a significantly higher incidence of severe events (including intensive care unit admission, need of assisted ventilation, and death) after contracting SARS-CoV-2 than patients without cancer (seven [39%] of 18 patients with cancer *vs* 124 [8%] of 1572 patients without cancer; p=0·0003).[3] Another study[4] reported that patients with cancer were twice as likely to be infected with SARS-CoV-2 than patients without cancer. Importantly, this study suggests that hospital admission and recurrent hospital visits, inherent to the management of patients with cancer, are potential risk factors for SARS-CoV-2 infection. Data regarding patients with haematological malignancies are scarce. Nevertheless, we can expect that the SARS-CoV-2

	Recommendations
Autologous haematopoietic cell transplantation	Pursue induction regimens of up to six cycles in all patients to postpone the transplant procedure In standard-risk multiple myeloma, consider doing additional cycles of induction, and delaying transplant until first relapse Patients with high-risk cytogenetics (especially those with deletion of chromosome 17p) should still receive high-dose melphalan and AHCT as first-line treatments whenever possible Test patients for SARS-CoV-2 infection before transplant
Use of steroids	Consider reducing steroid doses, as done in older patients, and to possibly interrupt steroids in patients already in complete remission while receiving continuous treatment
Management of outpatient visits	To reduce unnecessary visits to the hospital, consider doing the following: Use teleconsultation Pharmacists should be able to provide prescription doses for 2–3 months of treatment at a time Favour home hospitalisation or home care Change the treatment administration schedule to one with a lower frequency Change the administration of daratumumab to every 4 weeks instead of every 2 weeks after the initial 8-week weekly administration, in patients with very good partial response Switch from an intravenous or subcutaneous treatment to a fully oral treatment combination For bisphosphonate intravenous home administration, switch from an intravenous to an oral bisphosphonate or transient interruption
Clinical trials and clinical research activities	For patients already enrolled in clinical trials, their participation should, in principle, continue with the following recommendations: Outpatient visits should be replaced by teleconsultation Clinical research organisations should allow home delivery of the medication under investigation to avoid hospital visits Hospital pharmacies should be authorised to deliver 2–3 months' worth of medication For patients who are likely to benefit substantially from inclusion in a clinical trial, test them for SARS-CoV-2 infection before enrolment For inclusion of new patients in a clinical trial, each team must carefully weigh the advantages and disadvantages of each inclusion

AHCT=autologous haematopoietic cell transplantation. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table: **Recommendations for management of patients with multiple myeloma during the COVID-19 pandemic**

For more on the **French High Council for Public Health guidelines** see **Comment** *Lancet Oncol* 2020; published online March 25. https://doi.org/10.1016/S1470-2045(20)30204-7

infection pattern will be similar to that of patients with solid cancers. Recommendations for the management of patients with solid cancer and haematological malignancies have been published (eg, from the French High Council for Public Health). However, these guidelines are general and more specific ones could be required for individual types of malignancies, including multiple myeloma, as patients with this disease have severe humoral and cellular immune deficiency.[5] This deficiency is associated with impaired responses to tumour, microbial, and vaccine antigens. Therefore, attention should be paid to this high-risk population during the ongoing COVID-19 outbreak. Here, we summarise some recommendations to help with the management of patients with multiple myeloma during the COVID-19 pandemic (table).

High-dose melphalan and autologous haematopoietic cell transplantation (AHCT) remain the standard of care for fit patients with newly diagnosed multiple myeloma. Although haematopoietic recovery after AHCT occurs within 3 weeks, full recovery of T-cell and B-cell function can take months to years, and vaccine responses during this period are typically poor. Furthermore, the COVID-19 outbreak is expected to be associated with a shortage of ventilators and intensive care beds, putting patients receiving treatment for multiple myeloma at increased risk, as they might also require these interventions. Other vital services for patients that have had high-dose melphalan and AHCT that could be negatively affected by COVID-19 include the availability of blood products, as the number of blood donors might decrease with the recommendation to self-isolate, leading to a shortage of blood and platelet products.[6,7] Therefore, deciding whether high-dose melphalan and AHCT are the right treatments for patients with multiple myeloma should be carefully considered in the current setting of the COVID-19 pandemic. Although the general practice is to use three to four cycles of induction chemotherapy before AHCT, the use of six cycles has been reported and was associated with deeper responses than standard practice.[8] Therefore, we recommend pursuing an induction regimen of up to six cycles in all patients to postpone treatment with high-dose melphalan and AHCT. Furthermore, as the evolution of the COVID-19 outbreak is unpredictable, doing additional cycles of induction, and delaying transplant until first relapse, should be considered in standard-risk multiple myeloma. Data supporting the potential lack of negative outcome of delaying AHCT comes from the IFM 2009 trial,[9] during which patients were treated with three cycles of bortezomib, lenalidomide, and dexamethasone (RVD) and then consolidation therapy with either five additional cycles of RVD or high-dose melphalan plus AHCT followed by two additional cycles of RVD. Although patients in the upfront transplant group had better outcomes in terms of complete remission, progression-free survival, and measurable residual disease negativity than patients in the RVD group, no difference in overall survival was observed, probably because most patients received high-dose melphalan and AHCT as second-line treatment in the RVD group. Of note, collection of stem cells for cryopreservation during the first line of treatment is not mandatory in every patient, because the use of plerixafor can prevent collection failure when cryopreservation is done during the second-line of treatment. For patients with high-risk cytogenetics (especially those with deletion of chromosome 17p), the situation is more complex. These patients might need to have high-dose melphalan and AHCT as first-line treatments. Nevertheless, given that approximately 18% of patients have asymptomatic SARS-CoV-2 infection, we recommend testing patients for SARS-CoV-2 before transplant.

The detrimental effect of steroids on patient outcome has been established during previous coronavirus outbreaks (SARS-CoV-1 and Middle East respiratory syndrome coronavirus), and a similar effect is expected in patients infected with SARS-CoV-2.[10] Therefore, we recommend re-evaluating steroid use in every patient with multiple myeloma. On one hand, reassuring patients and reminding them that steroids are a major anti-multiple myeloma drug and that they should not interrupt their treatment themselves is important. On the other, the physician should consider reducing steroid doses, as done in older patients, and even to interrupt steroids in patients already in complete remission while receiving continuous treatment.

Apart from patients having high-dose melphalan or AHCT, most patients with multiple myeloma are treated as outpatients, with frequent visits to the hospital. As previously stated, hospital admission and recurrent visits required for the management of patients with cancer could put these patients at increased risk of becoming infected with SARS-CoV-2.[4] Therefore, physicians should be particularly vigilant to reduce unnecessary visits to

the hospital. Teleconsultation should always be favoured when possible, particularly for patients who are off treatment or receiving only oral treatment. Furthermore, pharmacists should be able to provide prescription doses for 2–3 months of treatment at a time, instead of the usual 1 month.

For patients requiring intravenous or subcutaneous drugs, efforts should be made to minimise hospital visits, according to each patient's situation. This minimisation could be achieved by doing the following: using home hospitalisation or home care whenever possible, keeping in mind that home hospitalisation services might also be overwhelmed during the COVID-19 outbreak; changing the treatment administration schedule to one with a reduced frequency (eg, switching patients receiving twice-weekly carfilzomib to the once-weekly regimen); given the pharmacokinetics of daratumumab, after the 8-week weekly administration of 16 mg/kg needed to rapidly saturate target-mediated clearance, the subsequent schedule could be changed to a dose every 4 weeks instead of every 2 weeks (in patients with very good partial responses); and consider switching from an intravenous or subcutaneous treatment to a fully oral treatment combination (eg, bortezomib could be replaced with the oral proteasome inhibitor ixazomib). Regarding bisphosphonate specifially, intravenous home administration, switching from an intravenous to an oral bisphosphonate, or transient interruption are all valid options.

For patients enrolled in clinical trials, their participation should, in principle, continue. Nevertheless, patient safety should remain the priority and, as with patients treated outside clinical trials, outpatient visits should be replaced by teleconsultation whenever possible. Furthermore, for patients receiving oral treatment within a clinical trial, most clinical research organisations can arrange home delivery of the medication under investigation to avoid hospital visits. Alternatively, hospital pharmacies should be authorised to deliver 2–3-months' worth of medication, rather than the standard 1 month.

When considering enrolment of new patients in clinical trials, it should be noted that most clinical trials are on hold during the COVID-19 pandemic. Furthermore, each team should carefully weigh the advantages and disadvantages of each inclusion. For some patients (eg, those who are refractory to or have relapsed from treatment), clinical trials allow access to off-label drugs or combinations that can be highly beneficial but are otherwise unavailable. Therefore, suspending all clinical trial inclusions would lead to missed opportunities for a substantial number of patients. Finally, we recommend testing patients for SARS-CoV-2 infection before any inclusion in a clinical trial.

Overall, the management of patients with multiple myeloma is likely to be challenging during the current COVID-19 pandemic. Although haematology departments should use similar guidelines consistently for patient management, some decisions will need to be taken on an individual basis, according to disease characteristics and the patient's history. Decision making should not lead to missed opportunities for patients with multiple myeloma to receive the most efficacious treatment, as disease relapse or progression puts these patients at risk of death.

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