



## Special article

# Managing patients with multiple myeloma during the COVID-19 pandemic: recommendations from an expert panel – ABHH monoclonal gammopathies committee



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## ABSTRACT

Since the World has been facing the COVID-19 pandemic, special attention has been taken concerning cancer patients; related to their immunosuppression status, adding risk for more aggressive COVID-19 and mortality, but also concerns about the access and the quality of care in cancer therapy. The COVID-19 pandemic impacts the number of infected, its related mortality, as well as the care of cancer patients. Multiple myeloma patients are a particular group with several important aspects to be considered during pandemic times. In essence, they are immunosuppressed in different intensities during their treatment. Most of them are elderly and all of them require long-term therapy, with prolonged contact with the health care system, possibly including a stem cell transplant during the treatment. A panel of

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experts in multiple myeloma and infectious diseases discusses pieces of evidence and the lack of the same in the scenario of COVID-19 in myeloma patients, while also exposing what is expected for the next phases of the COVID-19 pandemic.

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## Introduction

The world is facing a challenge. A global pandemic related to a new Coronavirus infection (SARS-CoV 2) initiated in China in December 2019 and reaching all continents but Antarctica, with millions of infected by April 2020.<sup>1</sup> Asia, followed by Europe and now the Americas, are reorganizing and managing their health care systems, financial resources and research to face the COVID-19. Several measures have been taken: global lockdown, access to a diagnostic test, improvements in the health care assistance for the infected, in addition to measures to reduce the tragic economic impact of COVID-19.

Cancer care in this scenario is particularly challenging. New cases demanding urgent intervention, patients that are already under cancer treatment, intense therapies, such as stem cell transplant, and several other issues have to be discussed and planned to ensure that the quality of patient care is maintained, with minimal impact on their prognosis.<sup>2</sup>

In this manuscript, a panel of Experts discusses multiple myeloma and the challenges of diagnosis and therapy during the COVID-19 pandemic.

### *Special considerations about multiple myeloma patients*

Multiple myeloma and other plasma cell disorders have a close association with immune system disorders. Dysfunction in humoral response against virus and bacterial agents, concerning immune senescence, can be noted in newly diagnosed patients and during all treatment phases of the disease.<sup>3</sup>

Anti-myeloma therapies, mostly resulting from a combination of different classes of agents, also contribute to intensifying the immune damage. Corticosteroid, a backbone agent in several protocols, proteasome inhibitors and monoclonal antibodies decrease T-cell response. Immunomodulatory agents impact the immune response and, in some settings, can also induce myelotoxicity and neutropenia. In addition, myeloma patients are frequently elderly, or present comorbidities. All these characteristics negatively impact infection events, not only increasing the risk of infection acquisition, but also worsening the outcomes. Cohort data from 9,000 Swedish patients demonstrated that myeloma was associated with a 10-fold increased risk of viral infections, and mortality related to infection increases from 2% to 12%, compared to healthy controls.<sup>4</sup>

Vaccine response is another important issue in myeloma patients. Low rates of seroconversion have already been documented in Influenza and pneumococcal vaccination.<sup>5</sup>

Although international oncohematological societies are considering multiple myeloma alone a risk factor for COVID-19, few data were published addressing incidence and

outcomes of COVID-19 in myeloma patients. There are some data from the International Myeloma Foundation<sup>6</sup> showing that until April 30, 2020, few myeloma patients have tested positive for COVID-19 and are almost all doing well in the Asia-Pacific region. In the US, few multiple myeloma patients were diagnosed with COVID-19 and, with rare exceptions, they are performing very well. On the other hand, there were more COVID-19 cases in Italy, Spain and France, and some of them died from the infection. Deaths have been reported mostly in fragile elderly patients in end-stage myeloma. Full data have not been published to date.

### *Special considerations about SARS-CoV-2*

The SARS-CoV 2 is a novel coronavirus that was first documented in China. It is a betacoronavirus, closely resembling the SARS-CoV, the coronavirus related to SARS, in the years of 2002 and 2003. The SARS-CoV 2 has a very efficient mechanism of entry in host cells by angiotensin-converting-enzyme 2 (ACE 2) receptors, and it has RNA-dependent RNA polymerase and proteases. In the majority of cases, it causes asymptomatic or oligosymptomatic respiratory diseases. These characteristics have been essential to the great and fast spread of the virus, as it spreads person to person through respiratory droplets. After a median incubation period of 4 to 5 days, symptomatic patients can experience one or more symptoms, such as fever, cough, sore throat, gastrointestinal symptoms, anosmia and ageusia.<sup>7,8</sup> Patients can develop worsening of the respiratory disease, with shortness of breath, hypoxemia, or other signs of multiorgan involvement. The COVID-19 has been described as a disease with two different phases.<sup>9</sup> The first phase presents symptoms and signs related to viral infection and the late phase is related to severe inflammatory disease with a high rate of necessity for intensive supportive care, such as mechanical ventilation, with a high mortality rate.<sup>10</sup>

Fortunately, most of the cases do not experience the inflammatory phase, but special groups of patients, so-called high-risk groups, have shown worse outcomes. The elderly individuals suffering from comorbidities and obesity and other subgroups have been described as having a worse prognosis.<sup>11</sup> Patients under specific drugs, such as corticoids, are also considered at high risk for COVID-19 complications.<sup>12</sup>

Few studies have reported the incidence and outcomes of COVID-19 in cancer patients suggesting a worse prognosis, but they have had a limited design regarding control groups.

The diagnosis of COVID-19 is based on clinical-epidemiological data confirmed by laboratory tests. There are tests to detect the virus, using polymerase chain reaction (PCR) or rapid antigen identification, and tests to detect

immunoglobulin against the virus, expressing a late exposition to the agent.<sup>13</sup> All tests have limitations and different interpretations following the indication. The PCR for SARS-CoV2 is regarded as the best procedure to detect acute diseases, but the sensitivity depends on the specimen, time from the onset of the symptoms and technical issues. Rapid antigen detection does not perform well and serological tests are restricted to the confirmation of the infection, retrospectively.<sup>14</sup>

Until now, there are no antiviral or anti-inflammatory agents that demonstrate a clear benefit in the treatment of COVID-19. There are many ongoing trials, including agents with different targets, namely the blocking of the SARS-CoV 2 from the entry host cell (arbidol, chloroquine, hydroxychloroquine), the production of ribonucleic acid (RNA) and virus replication (lopinavir, ribavirin, remdesivir, favipiravir), as well as the targeting of the immunological response, such as anti-IL 1 and anti-IL 6 (anakinra, tocilizumab).<sup>15</sup> In very recent days, preliminary results from a randomized controlled trial demonstrated that COVID-19 patients who received remdesivir had a shorter hospital stay, compared to placebo controls. On May 1, the FDA (United States Food and Drug Administration Agency) authorized the prescription of this drug in severe cases of COVID-19 in the US. Other drugs, such as heparin and defibrotide have been tested, targeting prothrombotic status and endotheliitis.<sup>16,17</sup> Regarding a vaccine, research is ongoing, and no preliminary data have been published to date.<sup>18</sup>

Few reliable measures to control the COVID-19 pandemic are available, but one is categorical. Social distancing is necessary to reduce the spread of transmission and to prevent a health care system collapse.<sup>19</sup>

There is another significant issue in regard to the health care staff. High rates of infection have been reported all over the world, including in-hospital transmission and dissemination. This has been causing a reduction in the staff taking care of patients, as well as the loss of health care staff lives. Health care workers must be protected from SARS-CoV 2 when they are providing clinical care.<sup>20</sup>

### **Considerations about the health care system: how can the hematological service be prepared nowadays?**

Important issues regarding the health care system should be addressed. The system has to be adjusted to receive an increasing number of patients in emergency rooms, some needing intensive care and mechanical ventilation. Measures to control the risk of in-hospital dissemination should be implemented, such as the reduction of patient visitation by medical and nursing staff, increased personal protective equipment (PPE) supply and implementation of part-time home office, when applicable.<sup>21</sup> At the same level of importance, the maintenance of the quality of care provided to cancer patients must be the goal.

Cancer centers have a very challenging situation in keeping going. Delaying new diagnoses or postponing urgent therapies can negatively impact the prognosis. For multiple myeloma patients, postponing diagnosis or induction therapy can increase the burden of disease, affect the staging category and enable renal involvement and bone destruction. As

a result, the patient outcome can be compromised. Therefore, health care institutions should maintain their full activity.

Hematologists should participate in the elaboration of infection control protocols aimed at adequate areas and patient flow. All the staff should be trained to follow these protocols. Surmising that the crossing of health care professionals from one area to another constitutes an important vector for virus dissemination, distinct staff should be designated to attend to COVID-19 and "COVID-19 free" sectors. Patients and staff should always be screened before entering the facility or the hospital for the symptoms of, and exposition to, SARS-CoV 2. Symptomatic patients or staff must not be admitted to a "COVID-19 free area", even for testing. Patients should undergo SARS-CoV 2 testing (PCR) before starting myeloma treatment. Health care professionals should undergo serological testing to better organize patient care. Information about COVID-19 and how patients and families can protect themselves should be provided systematically. Medical and nursing visits, routine laboratory testing, catheter maintenance and other regular visits should be scheduled as infrequently as possible. Implementation of telemedicine is also a good way to safely reduce patient exposure to the hospital environment.

Regarding therapy, options and strategies are separately discussed for each phase of myeloma treatment.

Regarding the PPE, the most recent recommendation supports the universal use of droplet-contact precautions throughout the whole patient clinical assistance, as SARS-CoV 2 can be transmitted before the onset of symptoms by asymptomatic carriers.<sup>22,23</sup>

### **Newly diagnosed multiple myeloma and first-line treatment**

During the COVID-19 pandemic, new diagnoses of multiple myeloma continue to be made. Risk stratification is important, as well as the decision on how urgent or not the need for treatment is. Patients with more aggressive diseases, with significant anemia, renal dysfunction, hypercalcemia and plasma cell leukemia, or high-risk cytogenetic patients, need to start treatment as soon as possible. Some experts recommend COVID-19 screening for all, and we suggest performing PCR and serological tests, if available. A positive PCR or a positive IgM or IgA for SARS-CoV 2 should be considered as "active COVID-19" and myeloma treatment may be postponed for 2 or more weeks, depending on the clinical decision. On the other hand, if an IgG positive serology test is documented, myeloma treatment can be initiated as usual. Several points should be addressed regarding the treatment regimen selection: oral versus parenteral drugs, corticosteroids dosing, schedule of medical visits and labs and the risk of adverse events.

For frail patients (elderly and/or with comorbidities), induction treatment with regimens including only oral drugs is an interesting option, if feasible. These regimes require fewer visits to the cancer unit, reducing patient exposure and the risk of SARS-CoV 2 infection.<sup>24,25</sup>

In our view, fit patients can be treated with approved standard therapy strategies. We do not favor any specific regimen in detriment of others, because of a lack of available data regarding COVID-19 and myeloma, or COVID-19 in the partic-

ular setting of chemotherapy or immunomodulatory drugs. In the case of the occurrence of adverse events, dosing reductions and/or interval prolongations between cycles should be considered. Our panel suggests reducing the weekly dose of dexamethasone to 20 mg to decrease the risk of infectious complications.

### **Stem cell transplant**

Autologous stem cell transplant (ASCT) improves the outcomes of myeloma patients, but on the other hand, this intense treatment requires adequate hospital facilities and experienced staff to ensure the best results. Although the necessity for intensive care occurs in a minority of cases, unpredictable events can take place. Furthermore, it is mandatory to ensure an adequate supply of blood components during the pre-engraftment phase. These issues can specially be modified during pandemic times. The decision to postpone stem cell transplants should be individualized, considering the patients and the characteristics of the Unit during the pandemic. The ASCT can be safely postponed for patients with controlled disease (very good partial response, at least). Extending the induction therapy for up to 6 cycles is recommended for all patients before ASCT during the pandemic. Patients who achieved a complete response and a negative minimal residual disease can extend initial therapy for up to 8 or 9 cycles and start maintenance thereafter, reserving ASCT for the first relapse.<sup>26,27</sup> On the other hand, uncontrolled disease, or ultra-high-risk patients, such as those with plasma cell leukemia, the ASCT can be a salvage therapy. In these situations, the ASCT may be performed if the patient, staff and center coordination take the necessary safety precautions. All patients should be screened for the SARS-CoV 2 before stem cell harvest and conditioning. If the screening is positive (a positive SARS-Cov-2 PCR or a positive IgA or IgM), the ASCT must be postponed for at least 3 weeks and stem cell harvesting and transplant conditioning should be performed only after a documented virologic cure (two negative SARS-CoV 2 PCRs).<sup>28</sup>

For ASCT candidates who experienced the COVID-19 (symptoms of the disease and Lab confirmation), transplant should be delayed for 3 months, or for a minimum of 21 days if the ASCT is considered a priority. The virologic cure is also mandatory before ASCT in these cases. For ultra-high-risk cases, some authors suggest that a minimum of 14 days can be a safety period to reduce Covid-19 complications risks. It is important to note that all these recommendations were based on viral kinetic data and they have not been validated by clinical studies. Patients with respiratory symptoms without COVID-19 lab confirmation and those who report contact with COVID-19 patients should be asymptomatic and wait at least 14 days to start ASCT procedures.<sup>28</sup>

### **Maintenance phase**

Patients who benefit from maintenance should continue treatment if adverse side effects are not a problem. If steroids are part of the regimen, a progressive reduction in the dose should be considered.

### **Relapsed or progressed myeloma patients**

The main issue is the time to consider the initiation of subsequent-line treatment. For clinical and more aggressive relapses, subsequent treatment cannot be postponed. Nevertheless, for standard-risk patients, experiencing biochemical relapses without symptoms, we recommend postponing the initiation of active treatment, if possible.

As mentioned for first-line therapy, we also do not favor any specific regimen for the relapse setting because until the present there is no available specific data on myeloma drugs.

For those with an indication for subsequent-line treatment, daratumumab-based regimens can be optimized to reduce infusion time to 90 min after the third dose, if the patient has had no prior infusion-related reaction.<sup>23</sup> For carfilzomib-based regimens, we recommend considering a one-day-per-week infusion (instead of two days per week) as an alternative to reduce patient exposure to health care units, depending on the combination regimen and dosing.<sup>29</sup>

### **Supportive measures**

We do not recommend modifications in supportive care during different phases of myeloma treatment, except for the use of bisphosphonates. For patients with no signs of active bone disease and no hypercalcemia, bisphosphonates can be deferred. For other cases, we recommend using zoledronate every 3 months, considering the interruption if the patient achieved complete response and has had at least 2 years of bisphosphonates. The indication of the antithrombotic agents acyclovir and sulfa as prophylaxis remains the same as before the COVID-19 pandemic and should be amenable to the treatment-phase and combination drugs in use. Any additional antimicrobial prophylaxis, considering the COVID-19 pandemic, is not recommended at the present time. Vaccination, especially against Influenza and pneumococcal species is crucial, as well as vaccination of family and contacts. The universal use of masks and intense hand hygiene are mandatory.

### **Considerations about community and family**

In addition to vaccination against other viruses, such as Influenzae, family members must improve measures to decrease the risk of the myeloma patient being exposed to SARS-CoV2. Family members and all communities should follow the WHO and National Health Ministry recommendations. Restricting the contact of the myeloma patient solely to close relatives is prudent, as asymptomatic or pre-symptomatic individuals are an essential key in the transmission of COVID-19. All families should be informed of the importance of reporting respiratory symptoms or exposure to a symptomatic person before having any contact with the myeloma patient or close relatives.

### **Multiple myeloma patients with a diagnosis of COVID-19**

Few data on the clinical course of COVID-19 in myeloma patients are available at the present.<sup>30</sup> All cancer patients have been considered high-risk groups and we confirm the impor-



tance of testing symptomatic myeloma patients, regardless of the status or treatment phase of the disease. Testing for other etiologies, such as influenza and other respiratory pathogens, is essential to adequate treatment. Algorithms for screening high-risk patients include physical examination (including oximetry), radiologic images and blood exams.<sup>31</sup>

The COVID-19 must be classified as a mild, moderate, or severe disease to decide between hospitalization or home monitoring. Close monitoring and ensured access to the health care system are crucial to the safety of home-monitoring cases, as clinical deterioration may occur at the end of the first week. Regarding myeloma patients, some considerations should be addressed: antineoplastic therapy should be discontinued during the infection and reintroduced only after convalescence, ensuring safety. The rationale for this recommendation is the same as for other types of severe infections. New data supports that there is an increasing risk of thrombosis and endotheliitis during the COVID-19 infection.<sup>17</sup>

Multiple myeloma patients are already at increased risk for thrombosis, especially in the initial months of treatment or during thalidomide treatment.<sup>32</sup>

Clinicians must be aware of this to decide on the prophylactic or therapeutic use of antithrombotic drugs. Until now, no clinical trials of therapy against the SARS-CoV2 or COVID-19 inflammatory phase have been published, let alone shown an advance. Although most data regarding COVID therapy are from cohorts and small or uncontrolled trials, there are several ongoing trials and we hope new and good options will soon be available. Great attention should be paid regarding safety issues and drug interactions, especially if the therapy is provided out of a clinical trial.

## Conclusions

The COVID-19 is challenging for all and the treatment of chronic diseases, such as multiple myeloma, requires attention, organization and compromises on the part of patients, clinical staff, health care institutions and families. In this manuscript, a panel of experts in multiple myeloma and infectious diseases provided recommendations to help manage myeloma patients from the diagnosis to the relapse, striving to ensure that the myeloma prognosis would not be affected by the current pandemic.

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