

MANAGEMENT OF MULTIPLE MYELOMA DURING COVID-19 PANDEMIC

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COVID-19 pandemic has changed healthcare dramatically. In case of multiple myeloma (MM), management strategies have to be changed due to both healthcare- and disease-related factors. It should be emphasized that currently there is no high-quality evidence based data to shape our methods of MM treatment during pandemic. Some guidelines depending on expert opinions have been published (1, 2). The first reference also summarizes currently available recommendations from various national and international societies. Our recommendations rely on these guidelines and personal experience. Undoubtedly, burdens of the pandemic are not similar in every country and they are prone to change. Therefore the management strategies are also apt to change under different circumstances.

1) Why to modify MM management during COVID-19 pandemic?

Many hospitals have modified their working strategies to admit COVID-19 patients. Therefore resources are now relatively limited for MM patients. High-volume hospitals, especially those caring for COVID-19 are risky places for SARS-CoV-2 exposure. This fact constitutes another factor for modification of cancer management. Finally, MM is a disease of elderly with frequent comorbidities. Both the disease and its treatment are associated with immune dysfunction. Advanced age, comorbidities and immune dysfunction are known to increase mortality risk during COVID-19 infection (1–3). These disease- and patient-related conditions also necessitate modifications in MM management.

Why to Modify Multiple Myeloma Management During COVID-19 Pandemic?
1) Limited healthcare resources

2) Increased risk of SARS-CoV-2 exposure in hospital environment

3) Patient-, disease-, and treatment-related factors rendering MM as high-risk for severe COVID-19 infection

2) How to modify MM management during COVID-19 pandemic?

This heading can be discussed under 3 main subheadings:

2.1. Responsibilities of state and local healthcare policy makers:

The modern healthcare systems and their hospitals are not planned to fight against a pandemic. Consequently it is difficult to re-organize the systems for maximum public benefit during the pandemic. It does not seem reasonable to convert a reference cancer hospital into a pandemic facility. But unfortunately this happened due to desperation. But healthcare policy makers are not desperate in taking some precautions aiming to limit unnecessary healthcare facilities visits and SARS-CoV-2 exposure of cancer patients. In that respect, regulations for shipping drugs to home, removing reimbursement limits (at least during the pandemic) for oral MM drugs, suspending bureaucratic barriers before reaching cancer medicines, promoting telemedicine, and in-hospital infection control measures are some useful measures.

2.2. Strategies for the treating physician:

MM is a very heterogeneous disease. Some cases are very aggressive. Fortunately, we have tools to recognize these patients. The Revised International Staging System (4) can help to determine high risk disease when deferral of treatment might harm patient. The patients with significant end organ damage (such as renal dysfunction, hypercalcemia, extensive and symptomatic bone disease, and spinal cord compression) should also be treated without delay. Treatment may be postponed in other cases (also including those with only SLiM criteria, smoldering MM cases and patients with isolated biochemical relapse from complete remission –CR–) if better healthcare conditions are expected after a bearable period. Rapidly acting treatments must be selected during MM emergencies. Combinations including parenteral proteasome inhibitors (PIs) may be more advantageous in these conditions. But otherwise oral medications such as immunomodulatory drugs and oral PIs should be

preferred as they can be used in home. SARS-CoV-2 testing is preferable before chemotherapy at least in communities where the disease frequency is high.

Some treatment approaches frequently used in MM do not depend on unquestionable benefits observed in adequately performed clinical studies. When it comes to use these approaches during the pandemic, physicians have better apply management strategies which involve least contact with hospital environment instead of most popular ones:

- 2.2.1. Treatment intensity: Selecting duotherapy in standard risk patients and in fragile patients should be considered. The treatment can be tuned up depending on response. To decrease drug dosages and prolonging dosing intervals should also be considered from the beginning of treatment or after adequate disease control. Once per week bortezomib and 20 instead of 40 mg doses of dexamethasone may be safer for some patients.
- 2.2.2 Stem cell transplantation: Autologous stem cell transplant (ASCT) is a significant treatment modality. It provides longer off-treatment disease control (5, 6). However it is not an urgent treatment in standard risk patients with satisfactory disease control (CR or very good partial response) after induction. Stem cell mobilization and ASCT can be deferred in such cases during the pandemic. ASCT postponing may not be suitable in patients with limited treatment options due to refractory disease or unavailable novel antimyeloma agents.
- 2.2.3 Maintenance: Unfortunately, many clinical studies investigating maintenance strategy in MM also included patients without satisfactory responses to induction chemotherapy. This type of treatment is more akin to continuous treatment instead of maintenance. Continuous treatment and maintenance are probably most necessary in high-risk patients. Maintenance with lenalidomid is a very frequent practice in many countries. This treatment undoubtedly prolongs duration of disease control. But its effect on overall survival (OS) is a conflicting issue. MM patients who attained CR after induction (i.e. real maintenance cases) probably do not take OS benefit (7, 8). Increased secondary primary tumour risk and other toxicities also require careful

consideration. We believe that continuous treatment or maintenance should be continued in high risk patients. Other maintenance patients should also continue their treatment if it is possible to reach their drugs without hospital visits.

2.2.4 Antiresorptive treatment: Bisphosphonates are important adjuvant treatments in MM patients with bone disease. They are not absolutely required by the patients without bone disease. Oral agents may not be equally effective to parenteral agents (9). Except for acute treatment of bone pain and/or hypercalcemia, bisphosphonate dosing intervals may be prolonged. It is also possible to temporarily switch to oral clodronate.

2.3 Responsibilities of the patient and companions/relatives:

Patients with MM and their relatives should be informed about the potential impact of COVID-19 on their health. They should obey the rules of outbreak control, i.e. staying home, social distancing, hand hygiene, covering coughs and sneezes with tissue or by using the elbow. They should stay in close contact with their physician.

How to Modify Multiple Myeloma Management During COVID-19 Pandemic?
1. Responsibilities of healthcare policy makers:
Regulations for shipping drugs to home, removing reimbursement limits (at least during the pandemic) for oral MM drugs, suspending bureaucratic barriers before reaching cancer medicines, promoting telemedicine, and in-hospital infection control measures
2) Strategies for the treating physician:
Determine high-risk patients in acute need for treatment and those in whom treatment can be postponed, adequately inform patients and their relatives about the potential impact of COVID-19, decrease treatment intensity (dose lowering, prolonging dosing interval, duotherapy) in suitable cases, hold/postpone non-essential treatments (stem cell transplant, maintenance, parenteral antiresorptive agents) in suitable patients, determine strategies of testing for SARS-CoV-2 in MM patients, stay in close contact with patients

3) Responsibilities of the patient and companions/relatives:

To obey the rules of outbreak control, i.e. staying home, social distancing, hand hygiene, covering coughs and sneezes with tissue or by using the elbow. Staying in close contact with their physician

3) When COVID-19 occurs in a MM patient

In this case chemotherapy should be held or postponed until recovery unless there is a MM emergency which cannot be managed without systemic chemotherapy. SARS-CoV-2 positive MM patients should be quarantined and possibly hospitalized according to local practices. Drug interactions should be considered during COVID-19 treatment planning. It may be preferable to correct hypogammaglobulinemia if present.

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