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## REVIEW ARTICLE

# Impact of the COVID-19 pandemic on treatment approaches of multiple myeloma

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### Abstract

Cancer has been recognized as one of the major comorbidities associated with severe outcomes in the novel coronavirus disease 19 (COVID-19) patients. Compared to those with solid tumors and those without cancer, patients with hematologic malignancies appear to have more severe clinical outcomes and higher rate of mortality from COVID-19. This was particularly demonstrated during the early pandemic period. The COVID-19 pandemic has posed additional challenges in the management of hematologic malignancies, including establishing prompt diagnoses, providing optimal treatment while minimizing the risk and sequela of COVID-19 infection. Given these challenges, clinical practice guidelines and recommendations on management of hematologic malignancies during the COVID-19 pandemic were developed and proposed based on expert panels and individual expert opinions. Multiple myeloma is the second most common hematologic malignancy. The management of patients with multiple myeloma during the COVID-19 pandemic is extremely challenging as patients with multiple myeloma are particularly vulnerable to infections due to underlying humoral and cellular immune dysfunction, cytotoxic chemotherapy, immunotherapy, cellular therapy and steroid regimens, advanced age, and the presence of other comorbidities. In this paper, we attempt to provide a general review of clinical practice management patterns during and after the COVID-19 pandemic in patients with multiple myeloma and demonstrate how changes evolved as more knowledge was gained over time. Specifically, we review the impact of the pandemic on treatment approaches, supportive care, and vaccinations for patients with newly diagnosed multiple myeloma, relapsed/refractory multiple myeloma, patients with stable disease, and those with precursor states like monoclonal gammopathy and smoldering multiple myeloma. During early pandemic several changes were noted in myeloma care including minor delay in time to treatment initiation and tendency to defer autologous stem cell transplant. However, after 2022, with the advent of effective vaccines and treatment strategies the severity of COVID-19 infection decreased and care of myeloma returned to usual management, incorporating transplant, CART and multiple novel immune therapy approaches. Finally, we highlight the importance of meticulous vaccination schedule for patients with myeloma for all common viral, bacterial pathogens and vaccination against COVID-19.

## Introduction

The novel coronavirus disease 19 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed significant challenges in cancer care. As of February 28, 2023, over 758 million confirmed cases of COVID-19 have been reported to the World Health Organization (WHO), including over 6.8 million deaths.<sup>1</sup> During the COVID-19 pandemic, cancer care has frequently been delayed due to a decrease or suspension of diagnostic services or patients' reluctance to present to healthcare services.<sup>2</sup> Additionally, management of cancer has been altered to optimize the treatment and minimize potential exposure of patients with cancer to SARS-CoV-2 as well as the sequela of COVID-19 infection as cancer patients with COVID-19 have a higher mortality rate compared with those without cancer.<sup>2-7</sup>

Patients with hematologic malignancies appear to have more severe clinical outcomes and higher rate of mortality from COVID-19 infection compared to those with solid tumors and those without cancer.<sup>3,8,9</sup> Some of the major adverse predictors of COVID-19 outcome include age, comorbidities, active hematologic malignancy, type of hematologic malignancy, intensive care stay, mechanical ventilation, and severe COVID-19 infection.<sup>9</sup>

Multiple myeloma (MM) is a neoplastic plasma cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction including skeletal destruction, renal failure, anemia, and

hypercalcemia.<sup>10,11</sup> Multiple myeloma is the second most common hematologic malignancy in high-income countries.<sup>12</sup> It accounts for 1% of all cancers and approximately 10% of hematologic malignancies, with an incidence of 4.5-6 per 100,000 per year and a median age at diagnosis of about 65 years.<sup>12,13</sup> Each year over 34,000 new cases are diagnosed in the United States, with estimated deaths of close to 13,000 patients.<sup>14</sup>

The management of patients with MM during the COVID-19 pandemic is extremely challenging as patients with MM are at increased risk of infection due to compromised immune system due to both the disease and antimyeloma therapies.<sup>15</sup> Some of the risk factors for infections in patients with MM include lymphopenia at diagnosis from suppression of normal B-cell development and function by the myeloma clone, decreased cluster of differentiation 4 (CD4) T-cell count at diagnosis, a loss of functional immunoglobulins, a combination of immunosuppressive therapies that worsen lymphopenia, neutropenia, and CD4 count.<sup>16,17</sup> In a study conducted in Spain, Martínez-López *et al.* found that inpatient mortality was 34% in MM patients with COVID-19 infection compared to 23% in age- and sex-matched noncancer patients with COVID-19 infection.<sup>17</sup> Additionally, among MM patients suffering from COVID-19 infection, male sex, age, high-risk MM, active/progressive MM, and comorbid renal disease were independent predictors of adverse outcome on adjusted multivariate analysis.<sup>17,18</sup> Given these challenges, clinical

practice guidelines and recommendations on management of MM during the COVID-19 pandemic were developed and proposed based on expert panels and individual expert opinions.

In this paper, we attempt to provide a brief review of clinical practice management patterns during the COVID-19 pandemic in patients with multiple myeloma and demonstrate how changes evolved as more knowledge was gained over time. Specifically, we review the impact of the pandemic on treatment approaches, supportive care, and vaccinations for patients with newly diagnosed MM, relapsed/refractory (RR) multiple myeloma, patients with stable disease, and those with precursor states like monoclonal gammopathy and smoldering MM.

### Approach to patients with newly diagnosed multiple myeloma

The general approach to the management of patients with newly diagnosed MM is to administer initial induction therapy over a period of 4 to 6 cycles prior to possible high dose chemotherapy and autologous hematopoietic stem cell transplant (ASCT) in transplant-eligible patients, followed by maintenance therapy until disease progression. Patients who are not a transplant candidate ideally complete induction and receive continuous maintenance therapy until progression of disease. The combination of a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) plus dexamethasone has been widely used for newly diagnosed MM patients. Since 2020, the addition of cluster of differentiation 38

(CD38) monoclonal antibody to this backbone has become a standard of care.<sup>19,20</sup>

Risk stratification of MM patients is crucial as patients with high-risk MM tend to have poorer outcomes than those with standard-risk disease and require a different treatment strategy. High risk features include patient's frailty status, TP53 mutation, cytogenetic abnormalities including del(17p), t(4;14), t(14;16), t(14;20), amp1q, del(1p), extramedullary disease, elevated lactate dehydrogenase (LDH) level, elevated  $\beta$ -2 microglobulin level, the presence of  $\geq$  5% circulating plasma cells in the conventional peripheral blood smear, and the Revised International Staging System (R-ISS) stage III prognostic score.<sup>12,16,21</sup> Patients with trisomies, t(11;14), or t(6;14) are considered standard risk.<sup>16</sup>

*Early Pandemic:* During the early pandemic for patients with standard risk disease, the European Myeloma Network recommended postponing stem cell mobilization, harvest, conditioning, and ASCT and giving novel triplet or quadruplet upfront combinations initially (combination of bortezomib with lenalidomide or thalidomide and dexamethasone or combination of daratumumab, bortezomib, thalidomide and dexamethasone) due to the anticipated immunosuppression following ASCT.<sup>22</sup>

During early 2020, other considerations that were proposed included weekly bortezomib dosing regimen, switching to monthly daratumumab infusions sooner to limit the number of infusions and visits, weekly carfilzomib dosing regimen for young and fit

patients, oral regimen comprising ixazomib, lenalidomide and dexamethasone or cyclophosphamide, lenalidomide, and dexamethasone to decrease the risk of weekly hospital visits and COVID-19 exposures, and reducing the weekly dose of dexamethasone to 20 mg oral weekly to decrease the risk of infections.<sup>16,22-25</sup>

In patients with high-risk disease, the European Myeloma Network recommended ASCT after 6 to 8 induction cycles of novel triplet or quadruplet upfront combinations due to increased probability of progression of disease.<sup>22</sup> Additional considerations included regimen comprising carfilzomib, lenalidomide, and dexamethasone (KRd) and if KRd regimen is not available, lenalidomide, bortezomib and dexamethasone (RVd) can be used.<sup>16</sup> It is important to note that these clinical practice guidelines and recommendations reflected the knowledge at the time point of writing when the risks associated with COVID-19 infection were largely unknown and there were still no available COVID-19 vaccines or therapeutics.

While the long-term impact of COVID-19 on patients with MM has not been well-investigated, a few studies have reported outcomes of the impact of COVID-19 on the diagnosis and treatment patterns in MM during the early COVID-19 pandemic.<sup>26-29</sup> In a study conducted in a comprehensive treatment center for plasma cell disorders in Western Canada, Jimenez-Zepeda *et al.* found a decrease of 22.8% in the rate of active MM diagnosis in 2020 as compared to 2019 period.<sup>26</sup> No changes in patterns of treatment including medication route administration

and corticosteroid dose were observed in 2020 as compared to 2019 period.<sup>26</sup> The center was able to offer transplants to all eligible MM patients with no major delays and there was no increase in transplant-related mortality in 2020 compared to previous years.<sup>26</sup>

In another study conducted using the nationwide Flatiron Health electronic health record, Neparidze *et al.* found that new MM patients during the early COVID-19 pandemic, compared to those during the pre-COVID-19 pandemic, were less likely to initiate treatment ( $p < 0.01$ ) and had a longer time to treatment initiation after adjusting for patient characteristics.<sup>27</sup> The study also revealed that more patients received IMiD-based regimen during the early-COVID-19 pandemic.<sup>27</sup> Similar to the findings of the study conducted by Jimenez-Zepeda *et al.*, transplant-eligible patients continued to receive appropriate chemoimmunotherapy regimens and ASCT during the early-COVID-19 pandemic.<sup>26,27</sup>

Richter *et al.* found that treatment patterns were generally similar pre- and during-COVID-19 via a study using the Connect® MM Registry, which is a large prospective, observational, United States-based, multicenter disease registry of patients with newly diagnosed MM.<sup>28</sup> However, they observed an increase in the use of anti-CD38 agents, particularly daratumumab, during the COVID-19 pandemic.<sup>28</sup> During the COVID-19 pandemic, patients attended fewer in-person office visits, completed fewer disease assessments, had fewer office, clinic and lab visits, and had more non-in-person office visits ( $p < 0.0001$ ).<sup>28</sup>

Shah *et al.* found a 22% decrease in the number of newly diagnosed MM patients and an 11% decrease in the total number of initiations of new therapy using a retrospective study investigating the impact of COVID-19 on intravenous (IV) and oral medication prescribing patterns pre and during the early-COVID-19 pandemic among MM patients insured by a large commercial and Medicare health plan in the United States.<sup>29</sup> They also observed an increase in the rate of new initiation of both IV (11%;  $p = 0.03$ ) and oral therapies (51%;  $p = 0.03$ ) for patients diagnosed with MM which may be explained by a 22% decrease in the total number of newly diagnosed MM patients during the early-COVID-19 pandemic.<sup>29</sup>

*Later pandemic:* The landscape of care, morbidity and mortality evolved as new treatments for COVID-19 were developed. With the emergence of effective vaccines, the severity of infections has diminished across all populations including those with hematologic malignancies.<sup>9</sup> Per European Society for Medical Oncology expert consensus, treatment should not be delayed for newly diagnosed MM patients with active disease with a caveat that MM patients presenting with one lesion or SLiM-only criteria (sixty percent bone marrow clonal plasma cells; involved/uninvolved serum free light chain ratio  $\geq 100$ ;  $> 1$  focal lesions on MRI studies) may delay treatment only for a limited time period in cases of extreme COVID-19 dissemination in the community.<sup>30</sup> Additionally, patients with a solitary plasmacytoma as the sole indication for treatment may only receive local radiotherapy initially depending on the

local incidence of COVID-19 infection.<sup>30</sup> Triplet regimen (IMiD plus PI) or daratumumab-based quadruplet combinations were suggested for induction therapy.<sup>30</sup>

With the availability of several effective vaccines and treatments strategies for COVID-19, United States oncology and our institutional practice of myeloma treatment has proceeded without significant changes or impediment. Generally, the combination of RVd, as well as the combination of daratumumab with RVd (Dara-RVd) is the preferred induction therapy for transplant-eligible patients with standard risk cytogenetics. Ideal induction strategy for patients with high-risk disease features is not well-defined; however, these patients should preferably receive carfilzomib-based triplet or quadruplet regimen (KRd, or Dara-KRd), followed by ASCT without delay.<sup>19</sup> Autologous hematopoietic stem cell transplant could be postponed in patients with standard-risk disease, but not more than 3 months if possible, depending on the epidemiology of COVID-19 in the community. Transplant-ineligible patients may receive regimens including RVd or daratumumab-based therapies such as daratumumab, lenalidomide, dexamethasone or daratumumab, bortezomib, melphalan, prednisone, the latter of which not commonly used within the United States. An all-oral regimen such as lenalidomide and dexamethasone (Rd) or ixazomib, lenalidomide, and dexamethasone (IRd) could be implemented and the addition of bortezomib or daratumumab could be made later or upon insufficient response in frail patients.



### Approach to patients with relapsed/refractory multiple myeloma

Triplet regimens are the standard approach to managing RR MM. The choice of therapy for RR MM depends on several patient-related and disease-related factors, including age, performance status, comorbidities, the type, efficacy, and tolerance of the previous treatment, the number of prior lines of therapy, the available remaining treatment options, the interval since the last therapy, the type of relapse, and cytogenetics profile.<sup>31</sup> An addition of drug with a new mechanism of action can improve outcomes and overcome class resistance. These drugs include monoclonal antibodies to CD38 (daratumumab, isatuximab), monoclonal antibodies to signaling lymphocyte activation molecule F7, SLAMF-7 (elotuzumab), antibody drug conjugate (belantamab mafodotin) and chimeric antigen T cells (CART) targeting B-cell maturation antigen, BCMA (idecabtagene vicleucel, ciltacabtagene autoleucel).<sup>32-36</sup> Additionally, G protein coupled receptor class C group 5 (GPC5D) and Fc receptor homolog 5 (FcRH5) have emerged as additional targets toward which MM therapies are currently designed.<sup>37,38</sup> Recent United States Food and Drug Administration (FDA) approval of BCMA bispecific antibody (BSA) teclistamab is welcomed by the myeloma community, and many more are promising.<sup>39</sup> However, all of the above therapies result in limited progression-free survival benefit, and none of them are curative at a molecular level.

*Early pandemic:* Similar to the pre-COVID-19 pandemic, management of RR MM is

individualized. Patients with a confirmed relapse as defined by International Myeloma Working Group (IMWG), refractory disease, new onset of CRAB features (hypercalcemia, renal impairment, anemia, or lytic bone lesions) or aggressive relapse should be aggressively treated without delay with either salvage ASCT or other high dose chemotherapy regimens.<sup>22</sup> Time between infusions can be extended in patients who achieve very good partial response.<sup>24</sup>

With regards to the treatment patterns during the early-COVID-19 pandemic, a decrease in clinical trial participation of MM patients was observed.<sup>26,27</sup> Use of oral agents such as ixazomib, lenalidomide, and pomalidomide was encouraged; however, we did not observe a high use of all oral agents such as ixazomib regimens in our study.<sup>27</sup> Richter *et al.* found that top regimens in second- through fifth line of therapy generally included daratumumab and/or pomalidomide, in both pre-COVID-19 and during COVID-19 periods.<sup>28</sup> All oral regimens with equivalent efficacy were suggested over regimens necessitating frequent hospital visits where possible. Alternatively, less intensive dosing schedules of IV and subcutaneous drugs were implemented, such as weekly administration of PIs and rapid infusions of monoclonal antibodies. Postponing salvage ASCT was also considered during the early-COVID-19 pandemic.<sup>30</sup>

*Later pandemic:* During the later pandemic, treatments for RR MM proceeded without significant impediment or compromise in care. Treatment should not be delayed in patients with relapse. Our institutional

practice includes administration of all appropriate parenteral therapies such as sequential triplet regimens, immunotherapy combinations, novel therapies including CARTs and BSAs with reasonable safety during later pandemic. Prophylactic intravenous immunoglobulin (IVIg) supplementation has been advised by the myeloma community in patients with severe hypogammaglobulinemia especially among those with CART, BCMA and prolonged CD38 monoclonal antibody therapy.

#### **Approach to patients with stable disease**

In patients with newly diagnosed, transplant-eligible, standard-risk MM, maintenance therapy with lenalidomide until disease progression following induction therapy and ASCT is the current standard of care while in transplant-ineligible newly diagnosed, standard-risk MM patients, continuous treatment with lenalidomide and low-dose dexamethasone or daratumumab, lenalidomide and dexamethasone is recommended.<sup>40-48</sup> In patients with high-risk disease, a proteasome-based regimen is favored for maintenance.

During the early-COVID-19 pandemic, some experts recommended that maintenance and continuous therapy be continued as long as there were no major side effects, and that if steroids were part of the regimen, a progressive reduction in the dexamethasone dose with the goal of discontinuing it be considered.<sup>16,23,25</sup>

Similarly, in the later COVID-19 pandemic, patients with MM who are in the maintenance phase should continue with their oral or parenteral therapy and minimize visits to the

clinic. Bortezomib injections or carfilzomib infusions every other week as maintenance therapy should be considered for high-risk patients. Some experts have advocated for extended interval of maintenance PIs during the COVID-19 pandemic; however, our institutional practice has been to adhere to every other week PI maintenance.<sup>30</sup>

#### **Approach to patients with monoclonal gammopathy of undetermined significance and smoldering multiple myeloma**

Several risk stratification systems have been developed to identify patients with smoldering MM who are at a higher risk of progression and may benefit from aggressive monitoring and treatment. In 2018, the Mayo Clinic published a risk stratification model incorporating the IMWG 2014 diagnostic criteria.<sup>49</sup> This model, validated by the IMWG in 2020, is based on the 20/2/20 criteria: bone marrow plasma cells (BMPC) > 20%, monoclonal (M) protein > 2 g/dL and involved to uninvolved free light chain ratio (FLC) ratio > 20.<sup>50</sup> Patients are stratified as low-risk (absence of any of these factors), intermediate-risk (presence of one factor) or high-risk (presence of two or more factors).<sup>49</sup>

Compared to the pre-COVID-19 pandemic period, the approach to patients with precursor states like monoclonal gammopathy of undetermined significance or smoldering MM during the early-COVID-19 period appeared largely unchanged except for the efforts to reduce clinic visits. During the early-COVID-19 pandemic, delaying routine follow-up of monoclonal gammopathy of undetermined significance or smoldering MM patients was

recommended by some experts.<sup>22,24</sup> However, patients with high-risk smoldering MM should be carefully monitored for the development of symptomatic disease necessitating treatment.<sup>22</sup> Currently, no clear consensus has been reached regarding an optimal management of high-risk smoldering MM.<sup>51</sup> During the early COVID-19 pandemic, Al Saleh *et al.* recommended monitoring patients with standard-risk smoldering MM with no active intervention.<sup>16</sup> In patients with high-risk smoldering MM, they recommended enrolling patients in a clinical trial if possible or active surveillance if there are no available clinical trials.<sup>16</sup>

#### Approach to supportive care

While MM is incurable at the molecular level, the emergence of new therapies in the last decade has significantly improved survival outcome in patients with MM, thus achieving an operational or functional cure.<sup>52</sup> MM patients may experience disease-related and therapy-related side effects such as lytic bone disease, infections, thrombosis, fatigue, and peripheral neuropathy. Prophylactic interventions to avoid or alleviate the severity of side effects from the disease or treatment play an increasingly important role in improving the quality of life of patients with MM.<sup>53</sup>

In clinical practice, monthly treatment with an osteoclast inhibitor for at least 12 months is recommended in MM patients with evidence of lytic bone destruction on imaging, or osteopenia/osteoporosis on bone densitometry.<sup>54-57</sup> After 12 to 24 months of osteoclast inhibitor treatment, decreasing the frequency of or discontinuing the treatment

can be considered once patients have achieved a very good partial response or better.<sup>54-57</sup> Re-initiation of therapy is recommended at clinical relapse of MM.<sup>54-57</sup> In MM patients with no active bone disease and with normal bone density, expert opinions somewhat differ with regards to the use of an osteoclast inhibitor. Some expert committees recommend osteoclast inhibitors to all patients with active MM regardless of the presence or absence of MM-related bone disease on imaging.<sup>54,56,57</sup>

During the early COVID-19 pandemic, considerations were given to minimize patient travel and community exposure to COVID-19. In patients with no active bone disease and no hypercalcemia, some expert opinions recommended that bisphosphonates be deferred.<sup>16,23</sup> In patients with diffuse bone disease or hypercalcemia, zoledronate every 3 months was recommended and the interruption can be considered if the patient achieved complete response and has had at least 2 years of bisphosphonates therapy.<sup>16,22,23</sup>

The indication for antithrombotic agents, herpes virus and *Pneumocystis jirovecii* infection prophylaxis remains unchanged during both the pre-COVID-19 and early-COVID-19 periods.<sup>23</sup> Specifically, thromboprophylaxis is recommended in MM patients who receive an IMiD-based regimen comprising thalidomide, lenalidomide, or pomalidomide.<sup>58</sup> In general, the choice of thromboprophylactic agent (antiplatelet therapy or anticoagulant) depends on the baseline risk of thrombosis associated with a given regimen and the presence or absence of risk factors for thrombosis.<sup>58</sup>



Prophylactic antimicrobial for *Pneumocystis jirovecii* pneumonia (PJP) is recommended in patients receiving long-term high dose steroids.<sup>59</sup> Prophylactic antiviral for varicella zoster virus (VZV) and herpes simplex virus (HSV) is recommended in patients receiving a PI including bortezomib, carfilzomib, or ixazomib.<sup>60,61</sup> Most experts recommend HSV and VZV antiviral prophylaxis to MM patients receiving a monoclonal antibody including elotuzumab, isatuximab or daratumumab.<sup>62</sup> Our institutional practice reinforces this recommendation of using antivirals. Additionally, PJP prophylaxis and fluoroquinolone use are recommended in patients with lymphopenia and in patients with ongoing anti-BCMA directed BSA and CART therapy.

### Approach to vaccinations

Infection is one of the major complications and leading causes of death in patients with MM.<sup>63-66</sup> The recommendations for routine vaccinations in patients with MM remain unchanged throughout the COVID-19 pandemic compared to the pre-COVID-19 pandemic period. Specifically, vaccinations against influenza, pneumococci, and herpes zoster are recommended for all patients with MM and vaccinations against *Haemophilus influenzae*, meningococci, hepatitis A, hepatitis B, tetanus, diphtheria, pertussis, measles, mumps, and rubella are recommended for certain MM patients with special conditions.<sup>22,23,64,67,68</sup>

As patients with MM have an increased risk for severe COVID-19 infection and mortality, vaccination against SARS-CoV-2 is strongly

recommended in all MM patients at any phase of treatment.<sup>17,69-71</sup> In ASCT and CART cell recipients, primary COVID-19 vaccination series is recommended at 3 months after ASCT or CART cell therapy regardless of vaccination status prior to transplant or cellular therapy.<sup>72</sup>

At our institution we advocate for COVID-19 vaccine administration to patients with myeloma at any stage of their disease including during induction, consolidation, and maintenance phase. COVID-19 vaccination is administered to patients 3 months following ASCT and to patients post-CART cell therapy after 3 months if there has been adequate recovery of lymphocytes (e.g., with CD4 count > 250 cells/mm<sup>3</sup>).

### Conclusions

The COVID-19 pandemic initially posed significant challenges in the management of hematologic malignancies, including establishing prompt diagnoses, providing optimal treatment while minimizing the risk and the sequela of COVID-19 infection. Given these challenges, clinical practice guidelines and recommendations on management of hematologic malignancies during the early COVID-19 pandemic were developed and proposed based on expert panels and individual expert opinions that reflected the knowledge at the time point of writing. With the rapid increase in our understanding of COVID-19 biology and the emergence of effective COVID-19 vaccines and therapeutics, the severity of COVID-19 infections has diminished across all populations including those with hematologic

malignancies.<sup>9</sup> In this paper, we demonstrate that the expert consensus, clinical practice guidelines and practice patterns surrounding management of MM evolved throughout the

COVID-19 pandemic as clinicians strived to ensure delivery of the most optimal care to MM patients while incorporating knowledge gained over time.

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