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Managing multiple myeloma during COVID-19: an ongoing saga

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“The show must go on”

Proverbial—initially applied to the United States 1876 centennial celebrations and originally printed in *The Morning Republican* (Scranton, PA) on 13 December 1875.

No other time in recorded history has this proverbial saying been more relevantly true to its meaning. As taken from the Merriam-Webster dictionary, simply means, ‘Must continue even though there are problems’ [1].

Over the last ten months and counting, we have witnessed a global health crisis and global catastrophe as they have unfolded since the first reported death from a mysterious pneumonia in China back on 11 January 2020 [2]. Currently, worldwide, over 94 million people have been infected with the virus and over 2 million deaths have been reported [3]. Furthermore, an unprecedented number of outbreaks continue to erupt globally. As a result, it has become quite evident that COVID not only has created a health care nightmare but also has paralyzed the economy across the globe while disrupting every phase of our way of life despite many efforts trying to mitigate and contain this deadly virus.

The novel coronavirus (COVID-19) became a worldwide pandemic on 11 March 2020 [4]. We now recognize three distinct phases associated with COVID-19: (a) an initial infection phase; (b) a respiratory distress phase and (c) a severe hyper-inflammation phase [5].

Since COVID-19’s initial recognition as a global pandemic, it became evident that this virus clearly targeted elderly patients and those with cardiovascular comorbidities and rendered these patients particularly vulnerable with worse clinical outcomes [6,7]. Unfortunately, data on outcomes in patients with cancers have been somewhat scarce and more so on patients with hematologic malignancies, particularly those with Multiple Myeloma (MM).

Specifically, MM patients are inherently at greater risk given their compromised humoral and cellular immunity as a result of not only the malignant nature of plasma cells but also the associated hypogammaglobulinemia. A vulnerable immune substrate that is certainly further compromised by the concurrent use of antimyeloma therapies currently available [8,9].

Although MM accounts for 1–2% of all cancers, it is the second most common hematologic malignancy after

lymphoma [8]. In a recent systematic analysis performed by Cowan and associates on the global burden of MM, the incidence of this hematological malignancy, though highly variable has been increasing since 1990 [10].

Despite the recent introduction of new and aggressive treatment regimens targeted at plasma cells, this now chronic disease process remains incurable and ultimately most patients die from this disease [8–10].

As this pandemic continues, healthcare care professionals have become quite familiar with the notion on how COVID-19 continues to postpone diagnosis as well as delay treatments for many patients. In fact, COVID-19 has forced health care centers and care providers to rethink their strategies, resulting in new recommendations aiming to avoid unnecessary contacts in an attempt to minimize exposure and risk of infections, particularly among the most vulnerable. However, despite all these strategies, patients remain afraid as well as reluctant to resume usual care for fear of causal contacts and risk of infection. This fear is once again heightened by the recurrence of reinfection spikes and widespread spread of the virus with daily record-breaking counts of both infection and deaths. Not only has this been a concern for the management of cardiac patients [11] but also, of cancer patients [12].

In response to the COVID-19 pandemic, great efforts have been placed on minimizing the risk of infection without compromising standards of care. For MM patients, this has either implied switching intravenous or subcutaneous agents to oral drug combinations in an attempt to minimize outpatient clinic visits, as long as the substitution is not inferior or alternatively, re-schedule or de-intensify treatments according to the disease state.

With regard to these efforts, the European Society of Medical Oncology took the initiative in publishing specific guidelines for the management of MM during these troubling and uncertain times [13]. These recommendations are based on both the patient’s age and transplant eligibility [13]. For instance, treatments should not be postponed for any young and transplant-eligible patients with newly diagnosed MM active/high-risk features. In contrast, MM patients with medium priority, induction cycles can be delayed for a short time. Most importantly, treatments should not be postponed for

elderly MM patients who are transplant ineligible and have either an active or high-risk disease characteristics. For medium priority patients and those with stable disease, continuing current management with regular follow up is recommended.

Furthermore, the European Myeloma Network (EMN) has also made some recommendations regarding treatment initiation and explicitly stated that treatment should not be postponed for patients with end organ damage, myeloma emergencies and for those patients with aggressive relapses, as shown in [Table 1](#).

Specifically, autologous stem cell transplant (ASCT) continues to be a mandatory indication to be considered in all newly diagnosed young eligible MM patients given its proven disease-free survival and improved overall outcomes in newly diagnosed MM patients [15]. Ideally, all patients should be tested for COVID-19 before receiving chemotherapy in anticipation of undergoing ASCT. Finally, supportive measures such as dexamethasone, G-CSF support for neutropenia and delaying anti-resorptive therapy (Zoledronic acid) should be minimized.

Aside from these specific guidelines, otherwise routine management of COVID-19 positive MM patients has been certainly challenging. According to Centers for Disease Control (CDC) guidelines, infection control and supportive care including supplemental oxygen and mechanical ventilatory support, when indicated, are established options [12]. The once experimental antiviral drug Remdesivir that was initially eventually granted emergency authorization by the US Food and Drug Administration this past May 1, 2020 for the treatment of severe COVID-19 cases, later in the year (October 22, 2020) this recommendation was then changed to be used in all COVID-19 cases requiring hospital admissions [16]. Unfortunately, the potential effectiveness of using convalescent plasma and other anti-viral drugs remains to be determined [16].

For now, all COVID-19 MM patients need to have all chemotherapy medications held while continue prophylactic co-trimoxazole prophylaxis for *Pneumocystis jirovecii* and acyclovir for antiviral prophylaxis. Furthermore, use of the novel IL-6 receptors blocking agent such as Tocilizumab has shown promise in managing MM patients with cytokine storm [17].

Table 1. Summary of recommendations.

Patients with newly diagnosed multiple myeloma
(1) Standard risk disease – European Myeloma Network recommends postponing stem cell mobilization, harvest, and ASCT and give novel triplet (or quadruplet) upfront combinations initially. The combination of bortezomib with lenalidomide or thalidomide and dexamethasone with or without addition of daratumumab can be considered [14].
(2) High risk disease – EMN recommends ASCT after 6–8 induction cycles due to otherwise increased probability of progression of disease [14].
Patients with relapsed/refractory MM
New onset of CRAB features or aggressive relapse should be aggressively treated with either salvage ASCT or other high dose chemotherapy combinations [14].
Transplant ineligible patients
Oral regimen with lenalidomide and dexamethasone can be considered in low-risk disease patients and addition of bortezomib or daratumumab can be considered for patients with high-risk disease [14].

Implementation of telemedicine/virtual visit encounters have been greatly advocated to decrease outpatient visits [7]. However, in order for these interventions to be effective, physicians need to exercise clinical judgment and treat each case individually by considering each patient's age, disease stage, comorbidities, cytogenetics/FISH and associated risk [7].

One of the first reports addressing the effects of COVID-19 on MM came from Wang and associates on 58 confirmed COVID-19 MM patients [18]. Eleven of these patients were not on MM therapy and 36 of the patients were admitted to the hospital. A total of 17 patients were treated with both hydroxychloroquine and azithromycin and 19 were treated with broad spectrum antibiotics. Ten patients were treated with steroids and the mortality rate was 39%, which was around the same rate for patients in the region at the time. At this center, there were no deaths in patients with milder symptoms and were managed outpatient [18].

Even though data has been scarce, more recently, data from Hultcrantz and associates reporting data on 100 MM patients with MM and COVID-19, from New York City documented a case fatality rate of 29% among hospitalized MM patients and specifically note that the strongest risk factor for adverse events were race/ethnic background and the presence of cardiovascular comorbidities [19].

Data from a group of investigators that performed a multivariate analysis on 650 patients with plasma cell disorders, the International Myeloma Society, reveals critical information that might be useful to better understand the initial challenges we all face during the COVID-19 pandemic in MM patients [20]. This international study not only found a high but variable mortality rate for hospitalized MM patients ranging from 27 to 57% but also, identified that advancing age, presence of high-risk MM features, renal disease, and suboptimal MM control were all independent predictors of adverse outcomes among COVID-19 infected MM patients [20]. Obviously this wide range in mortality rate can be easily explained as data were collected from 10 different countries and multiple centers.

As we move forward with the recent arrival of COVID-19 vaccines, it is time for all of us as health-care providers to help our patients put aside all their fears, perceived risks and anxieties as well those of their caregivers and make sure that they comply in following recommendations in getting either a prompt diagnosis with the institution of much needed therapies or that appropriate follow-ups are kept on schedule. Reassurance from our part is critical in trying to rekindle our patients' confidence in returning to health care facilities and initiate or continue with their scheduled MM treatments. Surely, MM patients are a particularly vulnerable group of cancer patients but the options without treatment are otherwise grim. Consequently, it is critically important that we individualize our approach of our MM patients on this regard. Certainly, that would be our greatest contribution.

Furthermore, as primary care physician we need to make sure to recognize that fever and COVID-19 symptoms among MM patients might be a late manifestation with a greater mortality rate. It may be important to collaborate with the patient's oncologist in helping monitor these patients in the outpatient setting. In general, the guidelines for management of MM patients with

concerns for COVID-19 appear to be the same as management of patients without MM. It is critically important, particularly for elderly patients with a known higher death rate from COVID-19, that disease control is attained using regimens that will decrease office visits. Steroid and high-dose therapies are not contraindicated and in fact should be continued to achieve better MM control that in fact is associated with improved outcomes even in those affected by COVID-19.

It has also become clearly evident that additional prospective studies are clearly needed, particularly as COVID-19 vaccination is about to begin for the general population, including MM patients. We are in need to identify treatment options and patient characteristics and how vaccination might alter outcomes among COVID-19 MM patients. More importantly, more comprehensive guidelines are clearly needed that could be applicable to all MM patients across the globe.

For the time being, we need to remind our MM patients and their caregivers to be extremely vigilant in following social distancing, continue wearing masks and to frequently hand wash as they usually do but with more determination than ever before.

Even when most resources are currently focused in getting a vaccine that can conquer this SARS-CoV-2 virus, continued efforts should not be delayed or interrupted so that we may continue to develop new cancer treatment options. The ongoing pandemic seems to have gotten a firm grip and with the incoming flu season upon us, it is too early to forecast what implications this might have. In other words, 'the show must go on.'

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