

Canadian perspective on managing multiple myeloma during the COVID-19 pandemic: lessons learned and future considerations

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 has necessitated changes to the way patients with chronic diseases are managed. Given that patients with multiple myeloma are at increased risk of COVID-19 infection and related complications, national bodies and experts around the globe have made recommendations for risk mitigation strategies for those vulnerable patients. Understandably, because of the novelty of the virus, many of the proposed risk mitigation strategies have thus far been reactionary and cannot be supported by strong evidence. In this editorial, we highlight some of the risk mitigation strategies implemented at our institutions across Canada during the first wave of COVID-19, and we discuss the considerations that should be made when managing patients during the second wave and beyond.

Key Words Coronavirus, COVID-19, multiple myeloma

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INTRODUCTION

In March 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19), caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), to be a global pandemic¹. That announcement launched a cascade of government-mandated lockdown measures to reduce the spread of the virus, including the closure of all nonessential businesses across Canada and restrictions on social gatherings and travel. Health units also reacted quickly by pausing all nonessential procedures and limiting access to health care facilities. Implementation of additional risk mitigation strategies were particularly important for individuals with coexisting medical conditions, including patients with multiple myeloma (MM) who could be at higher risk of COVID-19 infection and related complications because of a compromised immune system, requirement for immunosuppressive anti-myeloma therapies, and older median age at diagnosis².

Since June 2020, with the number of new daily cases in Canada consistently falling below 500³, many provinces loosened lockdown restrictions, and accordingly, risk mitigation strategies for patients with MM have also eased. However, as provincial health experts predicted, September 2020 has seen another rise in COVID-19 cases.

With the experience gained in managing MM during the first wave of COVID-19, it is now important to consider best practices for risk mitigation during the second wave. Given that managing MM during a viral pandemic is uncharted territory and that evidence to support risk mitigation strategies are lacking, we here discuss our perspective about the common adjustments made to MM management at our institutions across Canada and the considerations that are needed as care for patients with MM continues during the second wave.

DISCUSSION

Managing MM During the First Wave of the COVID-19 Pandemic

The Canadian approach to managing patients with MM during the first wave of the COVID-19 pandemic has closely followed recommendations from national bodies and experts across the globe^{2,4–8}. In general, the goal has been to continue providing high-level care to treat the underlying disease, while considering modifications to care that reduce the potential for patient exposure to infection and that avoid immune suppression. As is the case outside of a pandemic, treatment must be individualized based on

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patient factors (age, frailty, comorbidities), disease factors (cytogenetic and other risk factors, staging), environmental factors (proximity to clinic, reliance on caregivers), treatment goals, and patient preference. In the face of the COVID-19 outbreak, the local prevalence and risk of COVID-19 infection must also be considered, and modifications to management of MM should be made as appropriate. However, we believe that the morbidity associated with high-risk myeloma outweighs that with COVID-19, which justifies pursuing usual care, with little modification, in this population.

Autologous Stem-Cell Transplantation

One of the risk mitigation strategies used in Canadian centres was to pause noncurative autologous stem-cell transplantation (ASCT) for patients with MM, because hospitals were required to minimize elective procedures. There was also concern about the immunosuppression associated with ASCT and the potential scarcity of hospital resources to manage treatment complications should they occur (for instance, bed occupancy, intensive care unit availability, ventilator requirement). Patients eligible for transplantation were thus given additional cycles of induction therapy to delay conditioning until the prevalence of COVID-19 declined. Some (but not all) centres continued stem-cell collection during the COVID-19 peak to allow for quick escalation to transplantation if needed. Mobilization of stem cells using growth factor with or without plerixafor was considered in preference to intravenous cyclophosphamide to lower the risks of toxicity and febrile neutropenia, and to conserve hospital resources.

Systemic Therapy

A second risk mitigation strategy was to prioritize oral agents and to prefer subcutaneous to intravenous formulations (if appropriate and accessible) to reduce the risk of exposure through interactions of patients with health care facilities and staff. For example, to reduce hospital visits, lenalidomide and dexamethasone were generally preferred for treating transplantation-ineligible patients. For transplantation-ineligible patients who would benefit from a proteasome inhibitor, oral ixazomib was considered in preference to subcutaneous bortezomib at centres with a high regional prevalence of COVID-19. Switching patients on maintenance bortezomib to ixazomib and using ixazomib with lenalidomide and dexamethasone (in place of bortezomib) for induction in transplantation-eligible patients was also considered at some centres.

Although daratumumab is currently available only as an intravenous therapy, and although it has been associated with an increased frequency of respiratory infections, daratumumab-based regimens are highly effective and well-tolerated in patients with relapsed or refractory MM and newly diagnosed MM (though not yet reimbursed in the latter group). In many centres, a rapid-infusion protocol (90 minutes) was adopted for patients tolerating the first 2 infusions of daratumumab. Generally, daratumumab was given using the standard dosing schedule; however, in some situations in which the local prevalence of COVID-19 was high and a good clinical response was achieved early, the dosing schedule was extended to every 4 weeks from

every 2 weeks during cycles 3–6 to lower the frequency of patient visits. Centres using intravenous daratumumab in clinical trials were given the option of switching their study patients to subcutaneous clinical-supply daratumumab. Anecdotally, the change was made seamlessly from a logistics perspective and was well tolerated by patients. Unfortunately, new patient enrolment into clinical trials was put on hold during the first wave of the pandemic, which limited treatment options, particularly for patients with relapsed or refractory disease. For patients who would benefit from a clinical trial, bridge therapy was given with the intent of enrolment once restrictions were lifted.

Supportive Care

In terms of supportive care, bisphosphonate administration was reduced from every month to every 3 months for patients with stable disease, manageable bone pain, and minimal skeletal events. Other supportive care agents to bolster the immune system were given: for example, immunoglobulin therapy for patients with hypogammaglobulinemia (self-administration, if possible) and a long-acting growth factor for patients with neutropenia where coverage was available.

Alternative Health Care Delivery

Alternative methods of health care delivery and monitoring were also quickly implemented to further mitigate exposure risk. Those methods included a significant increase in patient follow-up through telemedicine, particularly for patients with stable disease or those on maintenance therapy. Patients with long distances to travel for appointments also had the option of having in-person visits with community physicians while their care was maintained with their primary centre by telemedicine. In centres in which bloodwork is the standard of care before each treatment dose, reducing the frequency of bloodwork from weekly to monthly was considered for select patients, particularly those with stable disease. If preferred and deemed lower-risk, bloodwork was performed in local labs or by in-home services (subject to availability, given the high demand), who could fax results to the treating physicians.

Considerations for the Second Wave and Future COVID-19 Outbreaks

As the COVID-19 situation evolves, it will be important to continue to focus on the need to deliver exceptional care in treating a patient's myeloma, while balancing the risk of SARS-CoV-2 exposure and associated morbidity. Pausing ASCT for patients in the first-line setting was shown to be feasible in the first wave, with patients requiring transplantation at the time seeing delays of only up to 3 months. However, that delay has created a waitlist for all patients now requiring ASCT, and it will be important to work through the backlog. Now that the country has entered the second wave, and now that better protocols are in place to reduce viral spread at our institutions (mandatory masks, limited entry points, screening upon entry, visitor restrictions) and in the community, it will be important to continue to closely monitor hospital resource availability and to consider less-stringent criteria for initiating ASCT in patients

with transplantation-eligible MM, particularly those with high-risk disease, to avoid further lengthening waitlists.

Although the clinical impact of delaying ASCT during the pandemic is not yet known, previous clinical studies have shown that overall survival is not affected by delaying ASCT to second-line therapy or extending induction beyond 4 cycles^{9,10}. Data about the impact on progression-free survival of deferring ASCT in eligible patients until after first relapse are limited. Some studies, including a meta-analysis, have demonstrated significantly longer progression-free survival when ASCT is performed as part of first-line therapy, and that consideration should be discussed with patients while weighing the benefits and risks of undergoing ASCT during a resurgence of COVID-19^{11,12}.

In terms of bisphosphonate administration, a reduced schedule of every 3 months has not been shown, in clinical studies, to affect skeletal events¹³; the absence of conflicting data therefore provides some reassurance for implementing such a strategy during the second wave.

Having sustainable access to oral and subcutaneous drug formulations will be important during the second wave. Thus far, access to ixazomib has been possible only through private insurance or a compassionate access program. However, because private insurance coverage is not consistent across provinces, another wave of COVID-19 might put a strain on the compassionate access program and alternative means to access ixazomib might be required. Solidifying access to subcutaneous daratumumab is also a high priority, because access to that critical anti-myeloma agent in that formulation can help to reduce the risk of COVID-19 exposure for patients with MM. Fortunately, Health Canada approved subcutaneous daratumumab as of 4 August 2020, making it a potential option for patients with private insurance¹⁴.

Considerations with respect to how clinical trials can continue to run during the second pandemic wave (for example, protocol amendments for monitoring, and feasible solutions for remote data collection and sharing) are also warranted to ensure that patients, particularly those with relapsed or refractory disease, have more therapeutic options.

Telemedicine has been a necessity for maintaining patient care during the first COVID-19 wave, and anecdotally, it has had several positive effects, including increasing convenience and reducing stress for patients who are anxious about visiting health care facilities, relieving congestion in clinics to allow for easier physical distancing, and shortening wait times for patients who require an in-person consultation. However, a remaining challenge is to identify the patients who can safely be monitored by telemedicine services. In general, patients with stable disease who are receiving maintenance therapy or are under observation could be considered for some follow-up by telephone. That approach might include reducing hospital visits to every 3–6 months, with a telephone consultation every 2–3 months to assure safety and compliance. However, physicians have expressed discomfort, in that telemedicine might miss a symptom or side effect that would otherwise have been detected, potentially resulting in a preventable visit to the emergency department or other compromise of therapy. There is also concern that patients will experience

delayed resolution of symptoms or side effects brought up in a telephone consultation, with a subsequent in-person visit potentially being required to address their worries. Some situations—for example, evaluation of rash, pain, or fatigue—might be more difficult over the telephone, and therefore patients with such symptoms would have to visit a clinic, as would patients for whom telephone communication appears to be lacking or who have a language barrier. When traditional face-to-face examination is not possible, aiming to augment telemedicine with video-conferencing tools, where appropriate, could aid in identifying evolving adverse events for patients on active and continuous therapy. Institutions will have to ensure that an infrastructure is created to efficiently manage and book “virtual visits” and to ensure appropriate vetting of the video-conferencing platform. Moving forward, it will be important to carefully consider which patients are best suited to virtual monitoring based on patient, disease, and environmental factors, and to take advantage of any windows of opportunity to see patients in person when the prevalence of COVID-19 is lower.

A question that is particularly important as new cases of COVID-19 rise is “What is the threshold of local COVID-19 prevalence needed to modify care in patients with MM?” A further question is “What is the potential benefit to patients of therapeutic alterations in the face of COVID-19 risk, even if it means starting a potentially inferior therapy or regimens for which limited data exist?” Those questions remain difficult to answer without a clear understanding of the exact risk of COVID-19–related morbidity or mortality for patients with MM.

A recent retrospective analysis that collected data for 100 patients with MM who tested positive for SARS-CoV-2 in New York found that risk factors for adverse outcomes were similar to the risk factors identified in the general population (older age, cardiovascular disease) and that the mortality rate for those infected with COVID-19 was 24% (Hultcrantz M, Richter J, Rosenbaum C, *et al.* COVID-19 infections and outcomes in patients with multiple myeloma in New York City: a cohort study from five academic centers [pre-print, not peer-reviewed]. *medRxiv* 2020:2020.06.09.20126516). Another study of 75 patients with MM infected with SARS-CoV-2 in the United Kingdom reported a mortality rate of 55%¹⁵. Moving forward, it will be important to consider those and more relevant Canadian data to identify the patients who would benefit from stronger risk-mitigation strategies. The large patient registry maintained by the Canadian Myeloma Research Group will be an important resource in answering that question and others to potentially guide treatment decisions during the second COVID-19 wave and future viral outbreaks.

FUTURE DIRECTIONS

The experience of managing MM during the COVID-19 pandemic has provided an opportunity to consider how new strategies of care that are less disruptive to the lives of patients and caregivers, and that also concurrently bring more efficiency to the health care system, can be implemented into regular practice or in the presence of other viral threats. The COVID-19 crisis has highlighted the need

for equal access to a variety of drugs, allowing for more individualized treatment and improved care. For example, sustainable access to more oral and subcutaneous formulations can reduce some burden on health care resources and improve patient well-being.

Workflow efficiency and clinic capacity were frequent topics of discussion before the COVID-19 pandemic; however, implementation of strategies such as telemedicine that might improve efficiency has been slow. The experience gained through the use of telemedicine during the first COVID-19 wave has shown that the strategy is feasible and potentially beneficial for some patients. There is now an opportunity to take those learnings and to consider policy issues such as remuneration, billing, and best administrative practices that will help to implement those strategies into standard practice.

Finally, because some patients with MM received treatment modifications born of necessity during the early height of COVID-19, and because some of those changes were made in the absence of supporting data, there is a need to collect real-world evidence to assess any potential impact of the modifications on clinical outcomes. An opportunity is now open to review retrospective data and to look for signals that minimizing treatment or monitoring (or both) might maximize benefit for patients and health care systems. The strategies adopted might be relevant not only for future viral outbreaks, but also for standard practice. New approaches to reduce dosing or monitoring schedules would be especially welcome for patients with MM, who are receiving continuous therapy and could be living with their chronic disease for many years.

SUMMARY

During the first wave of the COVID-19 pandemic, we have adopted several non-evidence-based practices at our institutions to reduce the risk of COVID-19 exposure and immunosuppression for our patients with MM (Table 1). Because COVID-19 will likely remain problematic until an effective vaccine for SARS-CoV-2 is found, there is a need for fluidity in risk-adaptive strategies based on the local impact of the infection, while keeping a strong focus on adequately treating the patient's myeloma. Unfortunately, many remaining unknowns must be considered as the next COVID-19 wave begins, including these: How severe will the second COVID-19 wave be, and how long will it last? What should be the threshold for escalating risk-mitigation strategies? How will seasonal influenza further affect health care resources and patients with MM? If a vaccine becomes available, will it be effective in patients with MM and other immunodeficiencies, who are already at higher risk of infection and complications?

Although early risk-mitigation strategies have resulted in dramatic decreases in SARS-CoV-2 infection rates, further innovative strategies built on the Canadian experience and environment are required to blunt the impact of the second wave of COVID-19 and to prevent future spikes. In addition, building contingency plans for treatment and implementing the necessary administrative or regulatory changes are urgent needs so that patients with MM continue to receive the best possible care during these uncertain times.

TABLE 1 Common risk-mitigation strategies for the management of multiple myeloma implemented at our institutions during the COVID-19 pandemic

Topic	Strategies and considerations
<i>Autologous stem-cell transplantation (ASCT)</i>	Risk mitigation strategies from first wave: • Pause noncurative ASCT by administering additional induction cycles. • Conditioning initiated once local prevalence of COVID-19 declined and hospital resource availability increased. • Stem-cell collection often not delayed, with preference at some centres for mobilization using growth factor with or without plerixafor. Considerations for second wave: • Consider loosening restrictions for patients to undergo ASCT, particularly for high-risk patients, to avoid excess waitlist accumulation.
<i>Systemic therapy</i>	Risk mitigation strategies from first wave: • Oral and subcutaneous administration prioritized over intravenous formulations where appropriate and accessible. • Lenalidomide and dexamethasone generally preferred for transplantation-ineligible patients. • For transplantation-ineligible patients who would benefit from proteasome inhibitor, ixazomib considered in place of bortezomib. • For daratumumab treatment, rapid infusion and subcutaneous administration preferred where available, and reduced dosing frequency from every 2 weeks to every 4 weeks in cycles 3–6 could be considered. Considerations for second wave: • Consider how sustainable access to oral ixazomib and subcutaneous daratumumab can be achieved.
<i>Clinical trials</i>	Risk mitigation strategies from first wave: • New patient enrolment paused. Considerations for second wave: • To allow clinical trials to move forward, consider protocol amendments for monitoring and solutions for data collection and sharing.
<i>Supportive care</i>	Risk mitigation strategies from first wave: • Bisphosphonate administration generally reduced from every month to every 3 months. • Immunoglobulin therapy given for hypogammaglobulinemia, and long-acting growth factor given for neutropenia. Considerations for second wave: • Continue supportive care modifications established in first wave.
<i>Alternative health care delivery</i>	Risk mitigation strategies from first wave: • Where appropriate, telemedicine preferred to replace some in-person consultation for patients with stable disease on maintenance therapy or observation. • Laboratory tests can be reduced to monthly and performed locally. Considerations for second wave: • Consider augmenting telemedicine with video-conferencing to aid in communication with patients.

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