

COVID-19 and myeloma: what are the implications for now and in the future?

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Summary

The pandemic has affected every aspect of myeloma care. Immediate focus is minimising risk of contracting coronavirus disease 2019 (COVID-19) and the sequelae of infection. However, what does the future hold for our patients? What lessons will be taken forward to tackle myeloma in the fiscally constrained future? If we embrace the challenges that will emerge in the post-pandemic environment, the treatment delivered to patients could be more cost-effective and better tailored than before. Healthcare delivery post-COVID-19 will not return to how it was, and now is the time to invest in novel strategies to deliver the best possible outcomes for patients.

Keywords: myeloma therapy, cost benefit, health services research, COVID-19, telemedicine.

Introduction

At the time of writing, the outbreak of the highly infectious novel coronavirus disease 2019 (COVID-19) has swept across all five continents, with >4 million confirmed cases globally (9 May 2020).¹ This pandemic has led to significant changes in the way physicians interact with all our patients and how our patients interact with us. In the short term, the focus has been on liberating much-needed capacity in our facilities, as well as minimising risk to patients and other essential care providers by eliminating all non-critical in-person interactions. In addition, we are choosing alternative management wherever possible to reduce individual patient susceptibility. Elective procedures, anything deemed non-essential and even clinical trials are, for the most part, on hold. Patients with underlying plasma cell dyscrasias are understandably anxious, concerned about progression of their disease during this time of crisis, but equally not wishing to undergo immunosuppressive therapy while the pandemic continues unchecked. Our immediate response is critical to reassure and optimise each patient to the best of our ability.

We also need to consider that the way we deliver care to patients with myeloma may forever be changed as a result of the outbreak of COVID-19. This global crisis could force the myeloma community to scrutinise our practices and ask whether every test, every treatment and every patient interaction are truly delivering value to our vulnerable population, both in the immediate term and also in the future. This can, and should serve as an opportunity to do better, delivering more value for patients in the face of global economic recession.

Immediate changes to myeloma care in response to COVID-19

The basics – limit, isolate and protect

There are now many resources that document the key steps necessary to protect patients with cancer, and centres in affected countries have largely adopted these approaches.^{2,3} In brief, patient visits that can be postponed or conducted via telemedicine (see below) should be changed. Wherever possible, geographical separation of low- versus high-risk patients should be aggressively pursued as per the infectious control guidance found on the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) websites.^{4,5} All patients should be screened prior to attending (ideally by telephone the day before) the chemotherapy unit or outpatient settings, and again (in person) at designated, restricted entry points. Patients felt to be at risk can then be identified early and appropriate referral either to a dedicated area for further assessment or to an acute care/COVID-19 assessment centre can be facilitated. Clear communication is key. Patients and their caregivers should be reminded of the signs and symptoms of COVID-19, as well as the importance of hand hygiene and other infection control measures.

Telehealth

One of the first and easiest changes in practice for many was to switch in-person visits to telemedicine.⁶ For patients with

myeloma, who are frequently elderly, may have co-morbidities, variable frailty or mobility issues this is probably one of the most welcome strategies that has been employed, and perhaps will be one of the most positive changes to emerge from this pandemic.⁷⁻⁹ It goes without saying that some patients will continue to require a direct clinical assessment and examination. However, limiting interaction to this group of patients only will liberate clinical space, allow better distancing and reduce the number of patients attending outpatient centres. There is reassurance out there that telemedicine has been shown to be at least equivalent to in-person care and is associated with high levels of patient satisfaction.¹⁰ The urgency of the situation created by the pandemic has forced the regulatory bodies and those responsible for reimbursement to finally address existing barriers to the delivery of telemedicine that will likely benefit patients with myeloma for years to come.¹¹

Changes to anti-myeloma treatment delivery – reduce or reform

Patients with myeloma are already an at-risk group for infectious complications, in particular viral infections and pneumonia.¹² Minimising immunosuppressive therapy, wherever possible, has become a key strategy in the face of COVID-19. There will remain a number of critically unwell or high-risk patients for whom this strategy cannot be employed. Myeloma can be very aggressive and if patients have very active disease limiting their ideal care is not advisable.

However, for those that can, many are considering the early reduction or elimination of corticosteroids once a patient's disease appears to have stabilised.^{13,14} A shift in focus in favour of dose reductions (especially in the maintenance setting) to minimise neutropenia,¹⁵ more liberal use of granulocyte-colony stimulating factor support and drug 'holidays' may be carefully considered for some if deemed appropriate. Careful discussion with each patient is required to establish the risk *versus* benefit of treatment modifications in the light of the ongoing pandemic.

Potential adaptations in appropriately selected patients in the face of this crisis could include:

- Temporary substitution of ixazomib for bortezomib, especially in patients with good disease control on combination therapy or maintenance^{16,17}
- Moving more quickly to monthly administration of daratumumab once tumour burden has been reduced¹⁸
- For many, once-weekly dosing of bortezomib and carfilzomib has already become standard of care, and if not, we would advocate in favour of reducing the schedule to this at minimum.¹⁹⁻²¹ In select patients with responsive, controlled disease with low tumour burden, temporarily decreasing the frequency of administration to every second week could be a potential option²²

Delay or cancellation of autologous stem-cell transplantation (ASCT) has been recommended wherever possible, given its significant and prolonged immunosuppression in the current landscape.^{23,24} For those patients in whom proceeding with ASCT has been deemed absolutely necessary, increased vigilance will be required in the short- and longer-term, given the increased susceptibility to viral infection that will persist beyond the initial post-transplant period.²⁵⁻²⁷ Until herd immunity is established, the threat of COVID-19 infection for this at-risk population will very likely persist beyond the immediate crisis and may change our recommendations for surveillance and prevention in the post-transplant period indefinitely.²⁸⁻³⁰

Switching to subcutaneous rather than intravenous preparations (e.g. bortezomib, daratumumab, denosumab) can reduce time spent 'in chair' and associated exposure risk for those patients needing to remain on parenteral treatment.³¹⁻³³ Reports of patient self-administration of subcutaneous agents at home suggest this could be feasible in appropriately trained and educated patients.³⁴⁻³⁷ Courier services can be used to deliver medications or 'drive through' collection of treatment facilitated. In addition, reasonable modifications to supportive care such as reducing the frequency of zoledronic acid to every 3 months rather than every 4 weeks can further reduce the risk of in-person interactions without significantly impacting outcome.³⁸

Pre-emptive documentation of goals of care

The very real risk of hospitalisation posed by COVID-19 has increasingly motivated both patients and treating physicians to actively engage in conversations regarding advance directives, goals of care and end-of-life planning, and to document these clearly.^{39,40} This open communication is crucial to ensure the development of a treatment plan for each patient that is medically appropriate and concordant with the patient's wishes.⁴¹

What are the longer term consequences of COVID-19 on myeloma care delivery?

Myeloma patients' actual susceptibility to COVID-19

Despite the fact that at the time of writing there are >3000 published articles on COVID-19, the data on the true risk posed by this virus to patients with myeloma remain immature. Early reports suggest that patients with underlying malignancy are at increased risk of both serious morbidity and death.^{42,43} Given the existing pre-disposition of patients with myeloma to infection generally, in particular viral respiratory infections, it seems reasonable to conclude in the short term that their risk of serious complications is increased.

However, there are early suggestions that certain agents used in the treatment of myeloma could be useful against COVID-19, including selinexor and ixazomib.⁴⁴⁻⁴⁶

Angiotensin-converting enzyme 2 (ACE2) is a co-receptor for COVID-19, but it remains unclear whether angiotensin-converting enzyme inhibitors or receptor blockers, which are commonly co-prescribed for patients with myeloma, could either aggravate or ameliorate the disease.^{47–49} In addition, if a vaccine is ultimately developed, it will need to be ascertained if patients with myeloma can mount effective responses or if additional booster doses are needed to confer sufficient protection.^{50,51} Will anti-viral prophylaxis (once available) be required for certain at-risk groups? Only time, and the emergence of more data, will tell.

The telehealth revolution should continue

It is hard to conceive that things will return completely to how they were in the wake of the immediate crisis. One myeloma physician has suggested things will now be considered in terms of whether they were ‘BC’ (Before COVID-19) or ‘AC’ (After COVID-19).⁵² One major benefit for patients with myeloma arising from this pandemic will be the ongoing expansion of virtual healthcare. It has significant advantages for both patients and healthcare systems, it is convenient, liberates resources on-site (frees up in-person clinic space), but more importantly saves patients the cost and inconvenience of travel.¹⁰ Shared virtual care with comprehensive myeloma centres could become an option for patients regardless of their geographical location, with potential benefits including improved survival.⁵³ Virtual visits and treatment could also increase access to clinical trials for those living at a distance from investigative centres.¹⁰ Which patients can be considered best served by telemedicine will vary, but could include those under surveillance, stable on maintenance therapy or every other cycle for those on prolonged treatment regimens. Whether a patient can be followed-up ‘virtually’ will always be a judgement call, but for those well-served by this approach the technology (and reimbursement) can, and should, support its use.

The cost of anti-myeloma therapy will be more important than ever

A global recession in the wake of COVID-19 seems undeniable and will undoubtedly have a significant impact on healthcare spending regardless of the underlying revenue source and infrastructure.⁵⁴ In an analysis of European countries, fiscal pressure resulting from increased unemployment prompted significant reductions in public spending on health.⁵⁵ At the time of writing, estimates suggest that in the USA alone, unemployment resulting from the COVID-19 pandemic could reach levels of to 52.8 million, more than three-times worse than the peak of the Great Recession.⁵⁶ In the aftermath of that recession there was a significant decrease in the number of employer-sponsored and privately insured patients seen by physicians.⁵⁷

With fewer privately insured patients, governments will be increasingly facing the bill for anti-myeloma drug costs.

Commonly employed triplet regimens have a price tag that can range from \$60 000–\$590 000 (American dollars) per annum.⁵⁸ Given that myeloma accounts for only 1% of all malignancies, patients are treated for long periods of time and it remains an incurable entity, it would seem inevitable that the cost of treatment will become a fundamental issue, regardless of payer, patient or government. The cost of medicines has been highlighted by the WHO as a leading source of inefficiency in health systems. Savings could be substantial if how myeloma drugs are developed, regulated and priced can be better addressed.^{55,58–60}

Striving for value and efficiency

In this post-COVID, resource constrained, global health economy, we will increasingly need to focus our attention on optimising outcomes and providing the greatest value possible for each and every patient. How might this be achieved in myeloma? There are many potential strategies that could be employed. Some possibilities include:

- Conducting appropriately designed trials that identify those who can safely stop therapy (e.g. ClinicalTrials.gov Identifier: NCT04221178)
- Using genomic information *a priori* to predict treatment benefit^{61,62}
- Establishing drug sensitivity of plasma cells upfront with the aim of selecting more cost-effective regimens^{63–65}
- Integrating a team-based approach to care, with increased utilisation of allied health professionals, pharmacists and nurse-practitioners^{66–68}
- Minimising waste with ‘LEAN’ approaches to myeloma care – process simplification, streamlining drug treatment, standardised and uniform protocols for therapy and surveillance^{69,70}
- Reforming the way anti-myeloma medicines are valued and paid for – advocating for better access and fairness for our patients around the globe^{58,71–75}

The importance of these (or any) approaches to improve the value delivered to patients with myeloma cannot be emphasised enough. In the grim reality that could emerge from this pandemic, resources will be tighter than ever before for patient and payers’ alike and rationing care could become an even more commonplace reality.

The need to triumph over adversity

COVID-19 has challenged the global population in ways we could not possibly have imagined. In the short term, our focus as myeloma treaters is on minimising risk and keeping our patients, wherever possible, out of harm’s way. In the longer term, we will need to rise to the challenges posed by the post-pandemic environment. We will need to find leaner

and smarter ways to deliver the best care possible to our patients. We will need to advocate with a united voice for better value therapy and use innovative technology and science to the best of their advantage. What started with adversity can, with the right mindset, evolve into great opportunity.

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Conflict of interest

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