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LETTER TO THE EDITOR

Myeloma care adaptations in the UK during SARS-CoV-2 pandemic: Challenges and measurable outcomes

To the Editor,

Following the emergence of COVID-19 as a global pandemic, cancer clinicians have been faced with the challenge of continuing to manage patients, with limited data to inform practice.[1] Recently, a largeprospective cohort study of 800 cancer patients diagnosed with symptomatic COVID-19 demonstrated a mortality rate of 28%, which was largely driven by age, co-morbidities and being a male.[2]

Patients with plasma cell dyscrasias (PCD), in particular, are known to be at a high risk of infections, in part due to immunoparesis and immunosuppressive therapy. Old age, frailty and co-morbidities add to the complexity of patient management. COVID-19 poses a significant new threat to their health and wellbeing. There is currently little evidence to suggest how myeloma patients will respond to this infection. The UK government recommended that myeloma patients shield for an initial 12-week period, because they fall in the extremely vulnerable group.[3] A UK retrospective real-world audit of 75 myeloma patients with symptomatic COVID-19 demonstrated a high mortality rate especially in patients aged >80 years.[4]

At the start of the pandemic, leading professional organisations in malignant haematology have issued key general principles about the management of myeloma patients during the pandemic.[5–8] Decisions on therapeutic approaches are being made by the multidisciplinary teams (MDTs) on a case-by-case basis, taking into consideration myeloma disease stage, frontline versus relapse, cytogenetics/FISH, age and co-morbidities.[6,8] All interventions aim to minimise the risk of COVID-19 by reducing hospital visits as well as tailoring immunosuppressive therapy. More recently, the European Myeloma Network published a consensus paper on the management of myeloma during the pandemic.[9]

The new norm consists of limiting patients' physical contact with the hospital, conducting telephone consultations and/or virtual visits and using oral therapies wherever possible.[10]

However, a number of these proposed changes deviate from the accepted standards of care, which have been built on successive randomised trials. For instance, the UK's National Institute for Health and Care Excellence (NICE) issued a guideline on the delivery of cancer therapies during the pandemic, which includes treatment breaks (possibly for longer than 6 weeks).[11] This enables us, for example, to temporarily withhold treatments for standard-risk myeloma patients who achieved a significant response (≥VGPR: very good partial response) with monitoring and to restart treatment in due course.

A number of indications for oral myeloma therapies have also been funded by NHS England (NHSE) as an interim measure during the pandemic.[12] The final decisions on the choice of therapy (parenteral versus oral), treatment breaks, reduced dose intensity or transplant remain at the discretion of the treating clinician.

We support the significant efforts made to date to limit the spread of this disease and to reduce its impact on myeloma patients, and we hope that all these interventions will help to reduce the risk of transmission. However, we have a limited understanding of how these changes will influence clinical outcomes for PCD patients. Moreover, the decision about the best therapy choice during the pandemic in any myeloma setting is also dependent on drug availabilities, which are different in the UK to other countries.

In this letter, the Thames Valley Cancer Alliance (TVCA) Myeloma Group examine the challenges to optimal myeloma outcomes, which may be associated with these new COVID-related adaptations of care in UK routine care, and how clinical outcomes could be measured in the months to come, which we summarise in the accompanying Table 1.

1 | THE NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM) SETTING

Patients fulfilling the CRAB criteria should be offered treatment without delay.[5] In the UK, transplant-eligible (TE) NDMM patients typically receive proteasome inhibitor (PI) bortezomib with cyclophosphamide and dexamethasone (VCD) or bortezomib with thalidomide and dexamethasone (VTD) preferably weekly for 6 cycles until a deep response is achieved.[5] Oral immunomodulatory drug (IMiD) lenalidomide in combination with dexamethasone (LenDex) was recently funded by NHSE as an interim measure for use during the pandemic.[12] However, the LenDex doublet combination may potentially be a less preferable induction therapy option compared to bortezomib triplets, particularly in high-risk disease. Although, two previously published studies described certain cytogenetic abnormalities, and immunohistochemical features associated with a poor myeloma response to bortezomib.[13,14]

Oral LenDex remains an established treatment option in the UK in the transplant-non-eligible (TNE) NDMM setting.

TABLE 1 Myeloma treatment adaptations in the UK during COVID-19, challenges to myeloma outcomes and the measurable outcomes

Myeloma setting	Standard of care	Proposed changes during COVID-19	Challenges for disease management	Measurable outcomes
TE NDMM SLiM-CRAB criteria	Bortezomib-based (VCD or VTD)	LenDex[a] as an oral option, or Bortezomib-based[b]	• Effect on depth or duration of response • Bone marrow suppression with LenDex[d] • Unknown interaction between SARS-Cov-2 and IMiDs	• SARS-CoV-2 infection incidence rate • Outcome of infection (mild/severe/recovery/death) • Incidence of other infections • Viral infection rates (PIs vs. other Tx) • Rates of deviation from standard of care • ORR, disease progression • Influence of deviation from standard of care on QoL
TNE NDMM SLiM-CRAB criteria	Bortezomib-based (VCD or VMP), or LenDex	Oral option: LenDex		
NDMM SLiM-only criteria	Bortezomib-based or LenDex	Watch and wait[b]	• Risk of end organ damage • Risk of increased disease burden	
1st relapse	DVd, or CarDex, or LenDex	Oral option[b]: Len-based, or PomDex (if received prior Len)[a]	• Effect on depth or duration of response • Bone marrow suppression with IMiDs	
2nd relapse	IxaLenDex	IxaLenDex, or PomDex (if received prior Len)[a]	• Effect on depth or duration of response with doublet PomDex compared to triplet IxaLenDex	
Bone protection	Monthly IV bisphosphonates for up to 2 years	3-monthly bisphosphonates in responding NDMM patients	• Risk of future skeletal-related events (SRE)	• Incidence of SRE according to strategy (monthly zoledronic acid vs. other)
Biochemical relapse	Consider treatment if >25% increase in paraprotein/ serum FLC	Watch and wait, unless SLiM-CRAB[b]	• Risk of end organ damage • Risk of increased disease burden	• Rates of disease progression
ASCT	TE NDMM in first remission or selected relapsed MM patients High dose cyclophosphamide priming	Deferral of ASCT[b], unless high-risk patient[c] Filgrastim-only stem cell collection +/− plerixafor[b]	• Risk of disease progression • Missing the optimal window for ASCT • Risk of change in the rate of successful collection with filgrastim-only • Need for hospital visits if plerixafor is required	• Rates of ASCT deferrals • Outcomes of deferrals or delay (remission/progression) • Overall success rate of stem cell collection with filgrastim-only • Plerixafor use rate during collection • Rate of successful collection depending on the choice of induction therapy
AL amyloidosis	VCD 1st-line therapy	Deferral of treatment if limited organ involvement. Oral options preferred (CTD, or MelDex, and the use of PO ixazomib instead of SC bortezomib if possible)[e]	• Risk of ongoing amyloid deposition • Risk of organ failure • Risk of sub-optimal amyloid response to 1st-line oral therapy or to treatment attenuation	• ORR • Rate of progression or death • Organ failure • Rate of ASCT deferrals

Abbreviations: ASCT, autologous stem cell transplant; CarDex, carfilzomib with dexamethasone; CTD, cyclophosphamide with thalidomide and dexamethasone; DVd, daratumumab with bortezomib and dexamethasone; IMiD, immunomodulatory drug; IV, intravenous; IxaLenDex, ixazomib with lenalidomide and dexamethasone; LenDex, lenalidomide with dexamethasone; MelDex, melphalan with dexamethasone; ; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; PO, oral; PomDex, pomalidomide and dexamethasone; QoL, quality of life; RMM, relapsed multiple myeloma; SC, subcutaneous; serum FLCs, serum free light chains; SLiM-only and SLiM-CRAB, criteria for the diagnosis of myeloma; TE, transplant eligible; TNE, transplant non-eligible; Tx, treatment; VCD, bortezomib with cyclophosphamide and dexamethasone; VMP, bortezomib with melphalan and prednisolone; VTD, bortezomib with thalidomide and dexamethasone.

[a]Funded by NHS England during COVID-19 pandemic;

[b]As advised by ([5]);

[c]High risk: includes adverse cytogenetics or patients presenting with clinically aggressive disease, plasma cell leukaemia or extra-medullary disease;

[d]([20]). [e]([18])

In either setting (TE or TNE), the set-up of a home self-administration option for eligible patients can enable the delivery of bortezomib-based regimen (if more appropriate than oral therapies) whilst reducing hospital attendance.

Remote regular monitoring is recommended to manage new myeloma diagnoses presenting with the SLiM-only part of the SLiM-CRAB criteria.[5] However, without systemic therapy, there is a risk of end organ damage during monitoring.

2 | STEM CELL COLLECTION

If stem cell harvest cannot be delayed, it should be performed at the end of induction,[5,9] or after 4 cycles in the case of LenDex, whilst transplant decision is reviewed by the MDT. The filgrastim-only priming strategy can be employed during the pandemic in order to reduce the risk of immunosuppression associated with high dose cyclophosphamide.[5,9] However, the use of salvage plerixafor may be needed in some cases,[5,9] which, in turn, will require hospital visits.

3 | THE RELAPSED MULTIPLE MYELOMA (RMM) SETTING

Daratumumab with bortezomib and dexamethasone (DVd) is widely used as a first relapse therapy in the UK. Oral doublet options LenDex, or pomalidomide with dexamethasone (PomDex, which is recently funded by NHSE as an interim measure during the pandemic for patients previously treated with lenalidomide),[12] may be less efficacious than standard of care triplet DVd.

A network meta-analysis across the whole relapsed population demonstrated that daratumumab-based triplets DVd and DRd (daratumumab with lenalidomide and dexamethasone; not currently approved in the UK) had a higher probability of providing the longest progression-free survival (PFS) than their respective comparators, in patients who received only 1 prior therapy.[15]

With the recent approval of subcutaneous (SC) daratumumab by the European Medicines Agency,[16] which has since also been approved for funding by NHSE under the Cancer Drugs Fund (CDF), it may be possible in the future to deliver the triplet combination DVd at home to eligible patients in subsequent cycles, if a home administration service is set up, provided that patients did not experience infusion-related reactions during their first few doses of SC daratumumab. It would be challenging for patients to self-administer SC daratumumab given that the final volume of the syringe is 15mls, but support from the community nursing home administration team can help overcome this challenge.

For patients treated with carfilzomib plus dexamethasone (CarDex) at first relapse and are tolerating it well, reducing dose intensity from twice-weekly to once-weekly prior to achieving a significant response will reduce hospital visits, but could result in a reduced depth of response.[17]

The all-oral triplet ixazomib with lenalidomide and dexamethasone (IxaLenDex) remains the UK's established treatment option of choice at 2nd relapse in preference to doublet PomDex (recently funded by NHSE in this setting as an interim measure during the pandemic, for patients previously treated with lenalidomide), because there are no head to head trial data comparing these two options .

Patient fitness or frailty, disease presentation and the history of prior therapies, which all determined the aims of myeloma care prior to the pandemic, should continue to be the basis for treatment decisions during the pandemic whilst taking proactive steps to reduce the risk of COVID-19 transmission. Treatment modifications as suggested by expert bodies should be employed according to clinical judgement in individual circumstances.

4 | AUTOLOGOUS STEM CELL TRANSPLANT

Unless myeloma has a higher risk of progression post-induction therapy such as adverse cytogenetics, or has a clinically aggressive presentation (eg plasma cell leukaemia or extra-medullary disease), an MDT decision based on risk versus benefit can be made to defer autologous stem cell transplant (ASCT) if possible,[5,6,8] and best haematological response should be maintained with the continuation of induction therapy, or maintenance lenalidomide.[8] The challenges here include the risk of progressive disease and/or loss of the optimal time window for ASCT.

If an MDT decision is made to proceed with ASCT, exclusion of COVID-19 infection by PCR for SARS-CoV-2 is required, along with strict precautions to prevent COVID-19 transmission.[9]

5 | AL AMYLOIDOSIS PATIENTS

The decision to initiate therapy should be made by the MDT on case-by-case basis, assessing the extent and severity of organ involvement, and balancing risk vs. benefit of deferring treatment.[18] If treatment is required, the International Society of Amyloidosis (ISA) recommends to reduce steroid dose, and to use oral chemotherapy combinations wherever possible such as melphalan with dexamethasone (MelDex), cyclophosphamide with thalidomide and dexamethasone (CTD), in addition to switching from SC bortezomib to oral ixazomib if possible.[18] ASCT can be deferred following a case-by-case MDT discussion, if a deep haematological response is reached with stem cell-sparing chemotherapy.[18]

The risks associated with these strategies in amyloidosis management are ongoing amyloid deposition with the risk of progressive organ failure,[19] in addition to the risk of sub-optimal response to oral treatment options or to dose attenuation.

6 | SUPPORTIVE CARE

The optimal uses of prophylactic antivirals, pneumocystis jirovecii (PCP) prophylaxis, antibacterial prophylaxis with levofloxacin (for 12 weeks in NDMM) and anti-thrombotic agents (with IMiDs) are

recommended during the pandemic, in addition to prophylactic filgrastim in patients with a history of recurrent neutropenia, and erythropoiesis-stimulating agents in anaemic patients in order to prevent the need for blood transfusions and the associated hospital visits.[5,9]

Frequency reduction of bisphosphonates (eg, zoledronic) from monthly to 3 monthly[5,9] especially in NDMM patients who achieved a significant myeloma response, will reduce hospital visits and the associated risk of COVID-19 transmission. However, this strategy may not provide patients with optimal protection from future skeletal-related events (SREs) compared to those who received monthly antiresorptive therapy for a minimum of 2 years.

Monthly SC denosumab is an alternative strategy. However, it is not currently approved in the UK to treat myeloma patients. When it becomes available, it can prevent hospital visits if home administration facilities are available or where patients are educated about self-administration.[9]

7 | AUDITABLE OUTCOMES

The measurable outcomes of the proposed changes in each PCD setting are described in the Table 1. In addition to COVID-19 outcomes, it would be important to establish the extent to which a myeloma patient receiving treatment responds differently to this viral infection compared to a myeloma patient off treatment, or to someone without myeloma. So far, the largest cohort study of cancer patients diagnosed with symptomatic COVID-19 published in Lancet did not identify any evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatment are at an increased risk of mortality from COVID-19 disease compared with those not on active treatment.[2] We can also investigate whether there is a proven association between the use of PIs and increased risk of viral infections, which was an initial concern at the start of the pandemic.

In the context of deviations from standard of care during the pandemic, disease-related outcomes for PCD patients should be compared to data about standards of care reported in clinical trials or similar real-world studies. It would also be useful to assess the impact of reduced dose intensity, therapy suspension, and SREs following frequency reduction of bisphosphonates.

As an exploratory outcome, we could investigate whether the COVID-19 pandemic benefited myeloma patients in any way, such as individualising myeloma care whilst maintaining optimal clinical outcomes. This pandemic placed healthcare care resources under significant strain, but it would also be important to evaluate the extent of improvements in the delivery of myeloma care, and the resultant impact on patients' quality of life, from measures such as home or self-administration of injectable therapies.

8 | FUTURE QUESTIONS

The COVID-19 pandemic is proving to be a period of great uncertainty and PCD patients require close monitoring to study outcomes of COVID-19-related treatment adaptations. Deviation from standard of care for these patients is not a long-term sustainable strategy.

It is unclear how to deal with PCD patients recovering from COVID-19 particularly optimal timing to resume treatment, and the choice of treatment. Issues of prolonged viral shedding as reported with other respiratory viruses, risk of further transmission in healthcare facilities and durability of COVID-19 immunity in patients with immunoparesis require prospective evaluation. Patient-reported outcome measures (PROMs) during the outbreak and the effect of the pandemic on myeloma trial participation also warrant investigation.

KEYWORDS

COVID-19, infection, myeloma, outcome, SARS-CoV-2, therapy

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

FD and KR conceived the article. FD wrote the manuscript, which all authors contributed to, critically reviewed and approved.

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