Achieving long-term disease control in relapsed/refractory multiple myeloma

Expert foreword

Over the past two decades, huge progress has been made in the treatment of multiple myeloma but the quest for a cure continues. New targeted therapies, awareness of patient factors and better understanding of scheduling, dosing and side-effect management have all led to a doubling of the median overall survival. However, many questions remain unanswered, and the best use and delivery of existing treatments is still open to debate.

This article looks at some of these remaining questions, with a key one being optimal treatment response. The achievement of a complete response, as defined by the International Myeloma Working Group, is the goal of treatment; however, with greater understanding of minimal residual disease, its measurement and how it impacts on survival, a deeper response is now recognised as an important aim. Another key factor for survival is maintaining long-term disease control, which may be possible through combination and continuous therapy. Over the past 10 years many studies have been undertaken looking at these paradigms and selected data are summarised here, including studies of maintenance therapy and fixed-duration versus continuous therapy. Other aspects of continuous therapy are also considered, including the ability to maintain efficacious dosing, acceptable tolerability, emergence of cumulative toxicities, whether a regimen is convenient for patients and pressure on healthcare resources.

Looking forward, the future for patients with myeloma is brighter. New treatments, extended periods of remission and an increased awareness of the importance of quality of life through treatment and beyond, have all contributed to these patients living longer, better lives.

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Defining optimal treatment response

Defining the optimal response to treatment in patients with MM requires consideration of both the depth and duration of response. This is because response to therapy can be variable, with some patients achieving deep but short-lived responses, and others achieving more modest responses that are more durable.9

Complete response (CR)—defined by negative immunofixation and a bone marrow plasma cell number below 5%—is a widely accepted measure of depth of response, and is used as a clinically-relevant marker for survival.10 With the advent of IMiDs and PIs, a correlation between CR or very good partial response and improved survival has been observed.11 This is apparent across different stages of MM disease, including in the RRMM setting.11 However, achievement of CR does not preclude relapse, suggesting the presence of residual disease that is undetectable within standard response parameters. Therefore achievement of CR in itself, according to current definitions, might not be the only efficacy goal to consider when treating patients with MM (Figure 2).4,11,12

Minimal residual disease (MRD) is an alternative measure for assessing depth of response in patients with MM, and also has prognostic value.13,14 A negative test for MRD has been associated with significantly prolonged progression-free survival (PFS) compared with MRD-positive status.15 These observations have stimulated efforts to refine existing definitions of response to MM therapies.5

As for the demonstrated relationship between quality of response and survival outcomes,16 durability of the treatment response also appears to have prognostic significance in MM.17 In a study of 668 patients with MM, those who achieved a sustained CR at 3 years experienced significantly longer median survival compared with patients who had not achieved CR or patients who had achieved but lost this response (p<0.0001; Figure 3).8 Crucially, median survival at the 3-year landmark analysis was significantly greater in patients who never achieved CR, compared with those who initially achieved deeper CR but then lost it (p<0.0001).8

The positive association between durable response and extended survival has been reported in other studies, which have also highlighted high-risk disease and persistent MRD as potential predictors of failure to sustain CR.13,14 Thus rather than just aiming for a deep response to treatment, long-term maintenance of treatment response is another important goal of RRMM management.14

Maintaining long-term disease control

Combination therapy

A combination approach to the treatment of MM is the combination of therapies with different mechanisms of action, such as the IMiDs and PIs, in order to achieve a synergistic effect that can lead to deeper and more durable responses.15,16 The way in which different classes of MM agents might interact to elicit a synergistic action has been studied in non-clinical studies; results suggest multiple but overlapping effects that disrupt tumour cell growth and survival.18,19,20 Combination therapy might also be valuable in treating MM due to the subclonal heterogeneity that exists in this disease.17

In the clinical setting, encouraging findings have been reported for the combination of PIs with IMiDs and corticosteroids in patients with MM.21 This triple combination approach has been associated with improved response and PFS in both the newly-diagnosed and RRMM settings.22,23-25 The combined administration of a PI, a corticosteroid and an IMiD enhanced response rates by 13–24%, and achieved higher PFS rates at 2 years compared with combinations without a PI or an IMiD.21,23-25 Such triple combinations are generally well tolerated, with the high anti-tumour activity achieved with synergistic mechanisms facilitating the use of reduced dosing schedules.26 Recent data from phase 3 clinical trials evaluating a number of new agents as part of triple therapy combinations have consistently shown PFS benefits for the new triplet regimen, compared with the respective doublet regimens, with some agents reporting overall survival (OS) benefits where mature data are available.22,23-25 Other regimens, such as the combination of bortezomib and pegylated liposomal doxorubicin have also extended time to progression in RRMM patients compared with single-agent treatment, and this effect is consistent irrespective of patient factors (e.g. prior IMiD therapy, transplantation status, patient age).26

Continuous therapy

The impact of continuous versus fixed-duration therapies on duration of response must also be considered.

The presence of residual disease despite a CR supports the rationale for continuous treatment versus fixed-duration therapy, with the aim of continuously suppressing the survival and/or proliferation of tumour cells.27,28 The results of a recent phase 3 randomised trial of continuous versus fixed-duration therapy in 820 newly-diagnosed MM patients suggest that thalidomide modifies the residual cells in the bone marrow and therefore plays a maintenance role rather than exerting a consolidation effect.27 Additionally, continuous lenalidomide-dexamethasone given until disease progression provided a significant improvement to PFS and OS in newly-diagnosed patients who were ineligible for stem cell transplantation.29

In a frontline setting, continuation of conventional chemotherapy agents, interferon or single-agent corticosteroids, has not proven to be effective in maintaining a response.30 The outcomes of novel agents in the maintenance setting have also been studied in the post-transplantation setting. Treatment with lenalidomide after high-dose autologous stem cell transplantation (HD-ASCT) has been linked to significant improvements in time-to-progression and PFS, with varying effects on OS as compared with placebo.29,31,32 However, it was also associated with increased rates of toxicity and secondary cancers.33 Likewise, a meta-analysis of five post-transplantation studies in 2012 highlighted significant PFS and OS improvements with thalidomide-containing maintenance regimens, but these benefits were gained at the expense of a higher risk of grade 3 or 4 toxicity.34 Long-term follow-up data from the UK Medical Research Council Myeloma IX trial (extended follow-up of 5.9 years) showed that thalidomide maintenance therapy had no impact on median OS.
in patients with favourable cytogenetics, and a negative impact on median OS in those with an adverse cytogenetic profile, versus no maintenance therapy.17 The use of bortezomib as a monotherapy for up to 2 years after HD-ASCT was associated with significantly prolonged PFS (p=0.002), compared with a thalidomide-containing maintenance regimen, with fewer toxicity events requiring treatment discontinuation.32 Of note, the study population enrolled were newly-diagnosed MM patients and patient-related factors (Table 1).26,34–37 These include:

- Efficacy of the agent or regimen, and ability to maintain efficacious dosing
- Acceptable tolerability
- Emergence of cumulative toxicities
- Convenience of the regimen for patients
- Pressure on healthcare resources

Maintaining efficacious dosing

The ability to maintain efficacious dosing can be compromised by adverse events (AEs) or cumulative toxicities39 and dose adjustment may be required in vulnerable patient populations such as those who are elderly and/or have renal or hepatic impairment.2,14,39 Peripheral neuropathy (PN), venous thromboembolism (VTE) and myelosuppression are some of the toxicities seen in patients treated with MM agents in the newly-diagnosed or RR setting.39 The risk of these toxicities are sometimes increased when two or more agents are combined, as in the case of VTE events when corticosteroid and conventional chemotherapy agents are added to IMIDs.39 Management strategies are in place to counter such side effects of therapy, including treatment discontinuation, dose reduction and/or addition of prophylactic and/or supportive medication.39 PN, for example, is usually reversed using these approaches, but there may be permanent damage in some situations.39 In fact, it seems that dose reductions early on may shorten treatment durations and reduce survival in patients with MM.39

The presence of renal insufficiency (as a result of disease progression or other comorbid conditions such as diabetes and hypertension) will frequently require dose adjustments that could limit the efficacy of treatment and potentially affect toxicity.39,41 Of the currently available MM therapies, PIs and thalidomide do not need to be dose-adjusted when given to RRMM patients with renal impairment (RI);42 however, lenalidomide is renally excreted and therefore dose adjustments are needed.26,28 The need for dose adjustment was underlined by a retrospective analysis of the two phase III trials, which showed that RRMM patients with moderate to severe RI who received lenalidomide (plus dexamethasone) with no dose reductions had a greater incidence of thrombocytopenia and shorter OS than patients with mild RI or normal renal function (patients with RI were originally supposed to be excluded per protocol).39 Impaired hepatic function has been known to occur in patients taking concomitant medications for pain or comorbid conditions, as well as being a direct consequence of treatment-related toxicity.28 As for patients with RI, hepatic impairment dictates dose adjustments; however, dosing recommendations are unclear for thalidomide and lenalidomide due to a lack of patient data.39

Dosing adjustments are also likely to be needed in ‘ frail ’ patients with MM, defined as those who are elderly, with comorbidities or disabilities which together may negatively affect treatment outcomes.38 Elderly patients have an increased susceptibility to treatment toxicity. Approximately half of these patients have a severe AE during the early cycles of treatment, possibly due to declining physiological reserve and organ function with age.1,38,39 Strategies to manage toxicity in elderly patients (Figure 5).41 In this way, the most appropriate drug regimen from the available MM agents can be selected and doses adapted accordingly.41

The significant toxicities that can be associated with current MM treatment options may lead to dose reductions and treatment discontinuation and, as a result, compromise the long-term efficacy of these regimes.37

Minimising the impact on patient quality of life

Quality of life (QoL) is complex to judge and is influenced by the balance between treatment toxicity, treatment burden and disease symptoms.24 Painful treatment-related side effects and toxicities can be an important reason for lower QoL in elderly patients who experience a high toxicity burden with treatment.24,28 Neuropathy, in particular, can be a serious concern with long-term use of the first-generation PI bortezomib,26–28 with partial neuropathy continuing to be an issue in clinical practice. A survey from 884 patients with MM cited PN, cytopenias and deep-vein thrombosis as the most worrisome potential side effects of myeloma treatments.40 Additional toxicities of concern include fatigue, gastrointestinal AEs, rash and thrombotic complications.26,28 The detrimental, sometimes insidious, impact of toxicities on patient QoL is beginning to be acknowledged as an aspect of management that needs appropriate long-term supportive care if patients are able to adhere to and benefit from continued treatment.28,29 Patient convenience is another factor for consideration during the use of long-term therapies. Delivery of efficacious therapies could be compromised through reduced adherence, resulting from the

![Figure 4. Continuous treatment (CT) with an IMiD or bortezomib is associated with improved progression-free survival and overall survival compared with fixed-duration therapy (FDT) with these agents; 1-year landmark pooled analysis, n=1,218].

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<thead>
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<th>Table 1. Considerations for long-term treatment</th>
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<td><strong>Treatment considerations</strong></td>
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<td>• Are we likely to be able to maintain efficacious dosing?</td>
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<td>• Is the treatment generally well tolerated?</td>
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<tr>
<td>• Are the side effects of a given regimen manageable?</td>
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<td>• What cumulative toxicities might occur?</td>
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![Figure 5. Three-step strategy to manage toxicity in elderly patients].

1. Assess patient's biological age, comorbidities, frailty and disability
2. Evaluate degree of functional impairment to select appropriate drug regimen and adapt the dosing if required
3. Optimise the supportive care regimen, e.g. pain control, bisphosphonates, anticoagulants

CT = continuous treatment; IMiD = immunomodulatory drug; FDT = fixed-duration therapy; PD1 = first disease progression; HR = hazard ratio
inability of patients to travel to clinics for treatment and to collect their medication. For example, the requirement for injection/infusion of current and selected emerging therapies means that patients must regularly attend hospital clinics in order to receive treatment, e.g. bortezomib, carfilzomib, dexamethasone, currently, and monoclonal antibodies in the future. This could present challenges for older patients with MM who live a long distance from the clinic and/or those who rely on others to transport them to the hospital. At a minimum, the requirement for frequent visits to clinics represents a further disruption to a patient’s everyday life in addition to medication/side effect management.

Patients with MM taking current treatments may therefore face many physical, emotional and logistical challenges that may result in interruption, modification or discontinuation of their therapy.22,23

Maximising limited healthcare resources

Pressure on healthcare resources is difficult to quantify as this varies substantially across different healthcare centres and models of care. In addition, however, the cost of the drug, the use of agents administered in RRMM patients (orally or by injection) can be associated with differential use of day-care resources, pharmacy costs and laboratory resources.24

Prognostic factors, such as low platelet count and worsening performance status, can also generate variations in cost, as can the sequence of treatment.25 Combination of novel agents are increasingly used for the management of RRMM patients,26 but the cost impact of these combination regimes remains to be determined.27

In addition to the issues relating to the long-term use of effective doses and minimising the impact on patient QoL, it is vitally important to ensure optimal and judicious use of continuous therapies in order to maximise limited healthcare resources and budgets.

Looking ahead

At present MM remains incurable and most patients with MM, including those who initially achieve CR, eventually relapse. The aim for MM therapies should be to extend periods of remission before relapse, while maintaining patient QoL. The optimal therapeutic approach to achieving this is through use of regimens that allow patients to both achieve a significant treatment response and maintain their response over a long time period. Continuous, long-term therapies have been linked to improved patient outcomes compared with fixed-duration therapies.28 However, implementing a continuous, long-term treatment approach requires the consideration of several factors, including efficacy, safety, tolerability and patient burden (Table 1).29 Although IMiDs and Ps have demonstrated efficacy and have dramatically improved patient outcomes in recent years, limitations with the current therapeutic options remain, such as tolerability issues and logistical burdens. Additional agents in these classes are currently in development that have the potential to minimise these limitations.

Further improvements in patient outcomes are anticipated through incorporation into clinical practice of new classes of therapies such as the HDAC inhibitor panobinostat (approved for use in combination with bortezomib)30 and the monoclonal antibodies elotuzumab31 and daratumumab.32 However, these agents are administered by injection or as part of a combination regimen involving an injectable agent. As such they might not address the logistical burdens that can limit the continuous use of current therapies. Important advances in the movement towards continuous therapies could also be achieved through increased use of all-or-none regimens that patients can take at home. Further research is needed to fully address the patient- and healthcare-related barriers that prevent the delivery of continuous therapy for sustained efficacy.

References
