Foreword

Three paradigm shifts in clinical outcomes of myeloma have occurred over the last few years. Firstly, the number of therapeutic options available to myeloma patients has increased significantly. Secondly, patients are living longer with myeloma, with a third of newly diagnosed myeloma patients living longer than 10 years in the UK. Thirdly, the depth of remission achieved with treatment combinations in trials is remarkable with remission sustained for many years with continuous therapy approaches, a new treatment paradigm in myeloma. Despite these major leaps in management of myeloma, to translate results observed in Phase 3 clinical trials to the tens of thousands of patients living with myeloma in the UK remains a significant challenge. Myeloma is diagnosed at a median age of 69 years with a vast number of patients living with pre-existing comorbidities. With up to 50% of the UK population on prescribed medication, and rising to higher proportions in older patients, balancing treatment effects versus adverse reactions remains a considerable challenge. Myeloma remains an incurable malignancy with a unique ability to affect multiple organ systems, haematopoietic function, the musculoskeletal system, renal function and immunity. Myeloma is also unique within cancers by causing life-limiting levels of bone destruction with a detrimental impact on the quality of life (QoL) of patients. Apart from the physical morbidity of living with myeloma, there are the emotional fluctuations during the relapsing remitting phases, the feeling of inevitability due to the incurable nature of disease, and the ongoing significant time investment on therapy, which leads to periods of loss of economic activity coupled with considerable strain on carers. Although QoL measurements on therapy within trials show either maintained or improved QoL, these remain poorly instructive of the patient journey on therapy when vast numbers of patients are exposed to these treatments over the longer term. QoL instruments fail to capture all aspects relevant for myeloma patients with heavy skewing toward symptom burden. Additionally, QoL tools have not been applied for longer than 18–24 months despite there being a reasonable expectation that up to 30% of patients would be on continuous therapy for more than three years. This is a call to action that we should redouble our efforts in understanding how we limit the burden of living with myeloma. We should engage forthrightly with patients through focused workshops and support groups to understand how we can better support them on long-term therapy to enhance clinical outcomes.
Multiple myeloma (MM) is an incurable systemic B cell malignancy characterised by the clonal proliferation of plasma cells in the bone marrow, which damage the skeletal system and affect the production of healthy blood cells. About 80% of patients experience symptomatic bone disease, while 73% have anaemia and almost 30% demonstrate renal insufficiency at diagnosis. Another important characteristic of the disease includes impaired immune function leading to severe infections, which can rise during active therapy. Consequently, patients with MM experience burdensome symptoms, which significantly reduce their QoL. The various aspects of the patient burden in MM are shown in Figure 1. In recent years, treatment options for MM have improved substantially, which has led to improved survival; however current use of high-dose chemotherapy with autologous stem cell transplantation (ASCT) and a number of novel agents are associated with adverse events that can affect patient QoL. Toxicity associated with treatment, along with severe bone pain and being severely symptomatic comprise some of the most reported factors that lower QoL.

Figure 1. Living with multiple myeloma

<table>
<thead>
<tr>
<th>Physical effects</th>
<th>Emotional effects</th>
<th>Incurable nature of illness</th>
<th>Ongoing hospital treatment</th>
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<tr>
<td>Bone pain</td>
<td>Low mood</td>
<td>Feeling of inevitability</td>
<td>Loss of economic activity</td>
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<td>Infection</td>
<td>Anxiety</td>
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<td>Fatigue</td>
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<td>Significant time investment</td>
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<td>Neuropathy</td>
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</table>

MM is a malignancy predominantly of the elderly population, with the median age at diagnosis of ≥70 years. In 2013 in the UK, 43% of newly diagnosed patients were over the age of 75. Due to the increasing incidence of MM with age combined with an ageing population, a 77% increase in the number of patients over 65 years is anticipated by 2030. Compared with younger patients, improvements in outcomes for older patients have been limited. The five-year survival for patients <65 years has improved by about 17%, however only 3.3% of the patient population of ≥75 years have demonstrated improvement; more than 60% of patients over the age of 70 die within the first year of diagnosis with MM. The older patient population is particularly vulnerable to adverse events linked to multi-drug combinations, which may lead to dose reductions and treatment discontinuation, altogether leading to poorer survival outcomes. Long-term toxicity of standard treatment is also a concern in patients who experience relapse. Although intolerance to treatment is associated with age, other factors such as comorbidities, functional status and/or dependence, frailty and cognitive impairment may all be contributing factors. Over the last three decades, advances in the prognosis and QoL of MM in the overall population have been seen. However, the progress in outcomes is not as pronounced in the elderly MM population. As survival has been shown to improve mostly in the <70 years age group, it is especially important to consider and develop novel therapeutic agents along with better prognostic markers, in order to improve outcomes for elderly patients with MM. Additionally, controlling the disease, extending survival and maximising patient well being by fully understanding the effects of treatment, are some of the most important elements in managing MM.

Measurement of burden

Providing appropriate support to patients with MM requires that their emotional and psychological needs are addressed. There are numerous available methodologies that can assess disease burden. A qualitative method of hermeneutic phenomenology employed in several studies illustrated that some patients with MM face feelings of loss of body image and fear of disease recurrence. Patients with relapsed myeloma live in a constant state of uncertainty, thereby stressing the need for disease control. Although therapeutic advancements offer better disease control, the psychosocial and holistic needs for a long-term survivor of myeloma are poorly defined, which impacts health-related QoL (HRQoL).

The impact of disease on patients has been well established in several studies. Patients who have undergone stem cell transplant and subsequent treatment have significantly compromised HRQoL related to symptom burden (e.g. progressive work disability, loss of independence, etc.). Their levels of serum cytokines positively correlate with pain, insomnia, and appetite loss, and negatively correlate with physical functioning. Qualitative studies demonstrate that the sudden prospect of mortality is the hardest aspect of MM to overcome, and that younger patients receiving stem cell transplantation and high-dose chemotherapy have a poorer QoL compared with older patients. In the UK, cross-sectional surveys and qualitative interviews have shown that patients with MM as well as their caregivers should receive long-term supportive care that addresses their needs, be screened for psychological disorders and be offered rehabilitation. This highlights that symptom management should be optimised in order to improve QoL. In particular, there is a need to focus more closely on supportive care for patients during active treatment with appropriately validated and sensitive QoL scales. Patients’ QoL may be significantly improved with ongoing psychological support (for both patients and caregivers); optimal and proactive symptom management (especially for pain, fatigue and treatment side effects); and simpler and closer access to hospitals and healthcare professionals. Altogether this would provide to MM patients a greater sense of security, reassurance and control. In addition, it is also known that partners and/
A recent study of nurse-led QoL assessment of myeloma patients concluded that while QoL is an important measurement in myeloma care, the results of measurements are often individual to patients, and tools used in clinical trials are not always easily transferable to clinical practice. As such, in real-life practice, nurses have to adapt their methods of assessment and support to match the needs of the patient as well as practicalities on the ground. At the Oxford University Hospitals NHS Foundation Trust, current practice is to perform a Holistic Needs Assessment for patients, which takes into account physical, emotional, and social needs in addition to a patient’s disease. There are however drawbacks with this as it can be time-consuming; as such there is currently an ongoing effort to introduce the Myeloma Patient Outcome Scale (MyPOS) questionnaire as a way of assessing patients, in addition to using symptom-specific tools.

Depending on the treatment that patients receive, they can be assessed with different tools; for example those receiving bortezomib are monitored for peripheral neuropathy (PN) using a PN tool. Any patient visiting the Day Treatment Unit (DTU) is also assessed for treatment side effects using a questionnaire by the DTU nurses. Side effects are generally assessed by speaking with patients and following up with support calls, telephone assessments, or visits to the DTU. During these assessments the nurse will suggest potential treatments to help manage side effects; the effectiveness of these is further assessed in another follow-up visit.

Patients often encounter several challenges relating to their disease and treatment-related side effects. An important challenge is getting used to the ‘new normal’; i.e. having to deal with fatigue or mobility issues, and coming to terms with their diagnosis – since myeloma is treatable but not completely curable, patients in remission can experience anxiety around each clinic appointment and the potential need for a change or restarting of treatment. The logistical challenges of clinic visits and the sheer number of tablets that patients often need to take are also particularly burdensome, the latter especially so if the patient was not taking medication prior to their myeloma diagnosis. Specific treatment-related side effects that can place a demand on patients include gastric issues such as constipation or diarrhoea, as well as steroid-related effects such as fluid retention and changes in mood. Such side effects have a more pronounced effect on patients when the therapeutic period is extended, for example during continuous treatment.

Due to these challenges faced by patients, one important role of the nurse is to help the patient adjust to this ‘new normal’ and help with symptom and side effect control. Nurses are a constant through the patient’s myeloma journey, and therefore they must build up a relationship with the patient and their family and provide information and support where needed.
or caregivers of MM patients experience anxiety and depression due to the disease. It is therefore important for them to be offered professional support as well as being included in research studies assessing QoL.14

A number of QoL scoring systems have been developed to evaluate the impact of disease and treatment of patients (Table 1). The QLQ-C30, EQ-5D and MyPOS scoring systems were recently used in a multicentre study of 18 centres across the UK to measure the prevalence and severity of symptoms and concerns of patients with MM.17 The MDASI-MM score provided to be a useful tool in interpreting toxicity and clinical benefits of new therapeutic agents, as well as in the management of patients in routine clinical practice.18

| Table 2. Patient groups with the highest burden and their associated characteristics |
|---------------------------------|---------------------------------|---------------------------------|
| Frail patients and those with comorbidities17,19,20 | Patients with myeloma-related morbidity17–23 | Patients with high-risk cytogenetics24,25,74 |
| • Older age | • Refractory disease | • del17p, t(4;14) |
| • Poor performance status | • Renal impairment | • Chromosome instability |
| • Disability | • Bone disease leading to limited mobility e.g.: spinal cord compression, multiple spinal fractures | • Gene expression prognostic signature |
| • Active comorbidities |

Patient groups with the highest burden

**Frail patients and those with comorbidities**

Frailty, presence of comorbidities, myeloma-related morbidity, and high-risk cytogenetics are key predictors of high burden in patients with MM (Table 2).

Due to the improved survival times and increasing life expectancy of the general population, the number of elderly patients with MM is expected to increase. This age group is particularly vulnerable as, along with the frequency of individual chronic conditions that rise with age, the incidence of comorbid conditions (including malignancies) increases significantly as well.19 The severity of comorbidities affects survival outcomes in a progressive pattern, independent of cancer stage.18 The risk of death increases with the number of comorbid conditions, and is associated with polypharmacy and many drug interactions.19 Age, in addition to comorbidities, frailty and disability (the three factors that constitute the performance status) has a cumulative effect on the prognosis of the patient.19 For patients with MM started on conventional chemotherapy, older age, performance status, presence of serum M-protein, low haemoglobin and bone marrow plasma cell infiltration are also recognised as additional independent prognostic factors for poor outcome.20 Frailty has been identified as an independent predictor of disability and is based on weakness, poor endurance, low physical activity and slow gait speed.19 Similar to frailty, physical disability is usually caused by chronic conditions such as cardiovascular disease and orthopaedic problems. Independent of its causes, disability is associated with a higher risk of mortality and hospitalisation.19 All these factors further stress the need for appropriate assessment of concurrent conditions and individualised treatment regimens that would reduce the need for interruptions and optimise therapeutic efficacy.19

Real-world data highlight the burden placed on the elderly and frail population with newly diagnosed or relapsed/refractory MM (RRMM). Retrospective analysis of a US national database of elderly patients with RRMM showed that older patients were less likely to receive intensive therapy than younger patients, and that older age was associated with significantly worse overall survival (OS) following second-line treatment (p<0.01 for age ≥75 vs <75 years).21 In addition, another study in this patient group showed that the presence of comorbidities such as respiratory and cardiovascular disease influences treatment choice in patients with RRMM.22 Among patients receiving second-line treatment, the presence of these comorbidities increased from 48% to 68% during the clinical course, and patients with both or either of these comorbidities demonstrated lower one- and two-year OS, and a shorter time to new treatment compared with patients with MM without these conditions.22

The burden of refractory disease has also been demonstrated by real-world data from US patients, showing that these patients experience greater symptom burden and require more aggressive treatment than relapsed patients.23 Additionally, at the start of second-line treatment, significantly more refractory than relapsed patients had poor genetic features and disease-related end-organ damage.23 Compared with patients with stable or no active disease,
patients with RRMM experience significantly more symptoms, such as severe fatigue, physical limitations and mood changes.\textsuperscript{16} Analysis of data by MyPOS from 18 centres in the UK has shown that patients with refractory or progressive disease demonstrated the highest number of symptoms and the highest overall palliative care concerns compared with other phases of the disease (p<0.001). The most reported symptoms throughout all treatment phases included fatigue (88%), pain (72%) and breathlessness (61%).\textsuperscript{17}

**Patients with high-risk cytogenetics**

Cytogenetic assessment is essential at diagnosis for risk stratification and risk-adapted treatment strategy. This involves evaluation of bone marrow aspirates for deletions, monosomies, trisomies and tetrasomies using chromosome- or centromere-specific probes.\textsuperscript{24} The 17p13 chromosome deletion (del[17p]) is associated with a poor outcome in MM; however, taking into account various factors such as age and stage of the disease produces a heterogeneous outcome for patients with this chromosomal deletion.\textsuperscript{25} The International Staging System (ISS) provides a powerful clinically applicable risk classification tool for survival in MM.\textsuperscript{26} The National Institute for Health and Care Excellence (NICE) guidelines recommend fluorescence in-situ hybridisation to identify adverse risk abnormalities alongside the ISS,\textsuperscript{27} however practices across the UK may vary.

### Current treatment aims and impact on disease burden and QoL

**Depth of response**

With the introduction of novel therapeutic agents (in particular, immunomodulatory drugs and proteasome inhibitors) in MM, trials have demonstrated complete response (CR) rates as high as 40% without resorting to transplantation. Recent studies have shown that CR is not a guarantor of long-term survival. In fact, duration of CR (i.e. making CR a time-dependent variable) may be a better surrogate for survival, especially in high-risk patients with MM who achieve high CR rates but often have a short survival due to early relapse. Sustained CR is, therefore, the new effective independent post-treatment variable for extended survival, while lost CR shows the worst outcome, with no response providing an intermediate prognosis.\textsuperscript{28-30} This pattern of response could be explained by the greater therapeutic sensitivity of rapidly proliferating tumours, which acquire mutations leading to drug resistance.\textsuperscript{28} In general, survival is significantly positively affected when CR is achieved and sustained for a long duration, suggesting that development of new agents for high-risk patients should focus on achieving a sustained CR response, ideally for a minimum of four to five years, beyond which hazard rates decline to those of low-risk disease.\textsuperscript{29}

**HRQoL as a treatment endpoint**

While traditional endpoints in numerous studies and trials have included OS, progression-free survival (PFS), safety, etc., factors such as QoL and patient burden have remained complementary measures of effectiveness of treatment. However, they are now moving to the foreground as increasingly important to consider, particularly in the absence of curative therapy, as is the case with MM. The US Food and Drug Administration (FDA) has emphasised HRQoL as a significant endpoint for approval of new anti-cancer therapies.\textsuperscript{31} A systematic review recently highlighted the complementary value of HRQoL and confirmed that little HRQoL analysis has been carried out for agents currently used in clinical practice.\textsuperscript{3-33} While the majority of trials confirm that HRQoL should influence clinical decision-making, HRQoL data had limited impact on published treatment guidelines so far. Studies have shown that in order to translate statistically significant differences in HRQoL to clinically meaningful differences that may impact patients’ management, the minimal important difference (MID) should be considered. However there is a lack of consensus on what this minimal difference should be.\textsuperscript{31} Currently, MID varies by context and population.\textsuperscript{31} HRQoL differences are further influenced by lack of comparative trials, differences in methodologies used, pathology and time of assessment (Table 3).\textsuperscript{3} Both statistical and descriptive tools should be used to interpret the clinical values of HRQoL from trials, with reporting tools such as the Consolidated Standards of Reporting Trials Patient-Reported Outcomes (CONSORT PRO).\textsuperscript{31}

Even where HRQoL is measured in trials, further aspects such as the study design also need to be taken into account to assess their reliability. Open-label studies including QoL endpoints can have a significant bias toward the investigational arm, making objective interpretation a challenge. Therefore whenever possible double-blind studies should be performed, as this is considered the gold-standard.

**Treatment effects on QoL**

When evaluating new treatment, HRQoL generally provides a strong prognostic tool for survival and is particularly important in relapsed patients with MM who have limited survival benefits. RRMM patients receiving bortezomib in the APEX study had significantly better mean Global Health Status compared with patients receiving dexamethasone.\textsuperscript{32} Improved HRQoL with bortezomib is at least partially explained by improved survival; patients demonstrated better physical health, cognitive, and emotional functioning scores, as well as lower dyspnoea and sleep symptom scores.\textsuperscript{32} The FIRST trial compared the HRQoL in patients with MM receiving lenalidomide plus low-dose dexamethasone (Rd) versus melphalan, prednisone and thalidomide (MPT) treatments.\textsuperscript{33} The HRQoL was assessed using the QLQ-MY20, QLQ-C30, and EQ-5D tools and although both treatment combinations statistically improved symptoms, when MID was applied, clinical significance of HRQoL improvement
The burden of living with myeloma and the challenges of coping with treatment was confirmed only in the Rd treatment arm. Generally, Rd was well tolerated and demonstrated better adherence, while patients on MPT experienced more grade 3–4 side effects such as neutropenia, leukopenia, constipation and peripheral neuropathy. These led to more frequent treatment discontinuation than adverse events experienced on the Rd arm.\(^3\) From previous studies, it appears that addition of thalidomide to MP increases grade 3–4 toxicity.\(^3\) Overall, the HRQoL results of this trial have established the continuous lenalidomide plus low-dose dexamethasone regimen as a new standard of care for initial therapy for patients with MM ineligible for ASCT.\(^3\)

Another observational study of European patients with RRMM investigated the difference in QoL affected by either second- or third-line treatment with bortezomib or lenalidomide, assessed from baseline to 6 months or until study discontinuation.\(^3\) HRQoL was measured using several tools and evaluated against distribution-based MID. Results of the study have shown that HRQoL could be maintained under continued treatment in both cohorts, however, higher progression and treatment discontinuation rates were observed in the bortezomib arm, with study discontinuation associated with clinically significant deteriorations in HRQoL.\(^3\) The authors of this study have proposed to address HRQoL separately at early discontinuation for all current and future therapies approved in MM.\(^3\) Importantly, with the advent of triplet therapy becoming the new standard in RRMM, it is reassuring that clinical trials of new drugs are not showing significant detriment of HRQoL when compared to their doublet counterpart.\(^3\)–\(^5\)

### Burden associated with current treatments

#### Treatment-induced toxicity

As has been described, treatments for MM are associated with toxicities that can impact on QoL.\(^3\) A common treatment for MM is high-dose chemotherapy followed by ASCT, however this course of treatment is associated with substantial morbidity and small risk of mortality; patients can experience pain, fever, nausea, vomiting, diarrhoea, mucositis, organ toxicity, sleep disturbances and infections.\(^3\) Baseline symptom burden is usually the most important predictor of symptom burden after ASCT. Author experience suggests

### Table 3. Guidance in collecting and analysing HRQoL in patients with MM treated with novel agents

<table>
<thead>
<tr>
<th>Instruments</th>
<th>Study design</th>
<th>Reporting and analysis</th>
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</thead>
<tbody>
<tr>
<td>Internationally validated questionnaires, to be used in their entirety</td>
<td>Intention-to-treat principle</td>
<td>Compliance reporting:</td>
</tr>
<tr>
<td>Questionnaires measuring the impact of treatment toxicity</td>
<td>Preferably randomised double-blind trial</td>
<td>• Compliance rates regarding questionnaire completion at each assessment time point and per study arm</td>
</tr>
<tr>
<td>Questionnaires measuring the impact of treatment toxicity</td>
<td>If study design is a randomised, open-label trial, baseline questionnaire to be completed before randomisation</td>
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<tr>
<td>Prospective design</td>
<td></td>
<td>• Statistical between-group comparisons at individual measurement time points, assessing data interpretability independent of absolute compliance levels</td>
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<tr>
<td></td>
<td></td>
<td>• Between-group comparisons of individual patient categories (study drop-outs vs non-compliant vs compliant patients) in terms of patient and disease characteristics and inclusion of treatment interaction terms</td>
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</table>

**HRQoL**, health-related quality of life; **MID**, minimal important difference; **MM**, multiple myeloma.

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that it usually takes at least 2 months for patients’ symptoms to improve; 3 weeks to leave hospital after the transplant and another 5 weeks to recover at home. To assess symptom burden of ASCT, patients often use the blood and marrow transplantation module of the MDASI tool before hospitalisation, during conditioning, on day of transplantation, at nadir (the time of lowest white blood cell count) and on day 30 post-transplantation.\textsuperscript{36,39} Interestingly, there does not appear to be a significant difference in the QoL burden between young and elderly patients post-ASCT.\textsuperscript{42} Agents such as thalidomide, bortezomib and lenalidomide or the continuous bortezomib-dexamethasone regimen mentioned previously are currently strong candidates for treatment in newly diagnosed patients who are not suited for ASCT and high-dose therapy.\textsuperscript{40} Triplet regimens combining an immunomodulatory drug and steroid with either a proteasome inhibitor or a monoclonal antibody are expected to become new standards of care over the next decade. Alternating regimens consisting of immunomodulatory drugs, proteasome inhibitors, and potentially other novel agents might also become a treatment option.\textsuperscript{40}

Despite new or improved benefits, tolerability and logistical challenges associated with novel agents remain. Prolonged exposure to novel agents may increase toxicities and cause treatment discontinuation, while more traditional drugs such as melphalan are not suitable as maintenance therapy due to limited efficacy and tolerability. In transplant-ineligible patients, standard induction therapy consists of three novel agents, while for particularly frail patients, the regimen may need to be reduced to two-drug combinations. The route of administration (oral, subcutaneous or intravenous) also plays an important role in maintenance therapy and must be considered alongside toxicity; e.g. both bortezomib and thalidomide are associated with peripheral neuropathy.\textsuperscript{41,43} While continuous lenalidomide proved to significantly improve PFS regardless of age, haematologic grade 4 adverse events including neutropenia still affect over a third of patients on this regimen, and led to a 16% discontinuation rate in a newly diagnosed MM study.\textsuperscript{44} Cytogenetic risk due to del(17p) and/or t(4;14) also interferes with survival: for example, bortezomib with thalidomide and dexamethasone (VTD) appear to improve CR and prolong PFS,\textsuperscript{45} but despite this, progression is inevitable, stressing the need for effective therapies.

**Optimising therapy**

As previously mentioned, efficacy must be balanced with risk of toxicity of therapy and QoL. A number of factors influence treatment outcomes in older patients with MM, in part due to the heterogeneity of ageing (Figure 2).\textsuperscript{4} Older adults are particularly vulnerable to multi-drug combinations and often need dose reductions or cessation of therapy altogether. In addition to age, frailty and comorbidities affect the treatment regimen prescribed as well as its effectiveness, therefore for older patients, symptom control may be prioritised over OS. Supportive care is especially important to ensure optimal outcomes in this group of patients. Route of drug administration is, again, another factor that can affect tolerability and adherence to treatment, thus influencing outcomes.\textsuperscript{4} The feasibility of administering a drug at home is also worth consideration as it would substantially reduce the time travelling to and spent at an infusion centre, therefore having the potential to minimise risks (e.g. infections, bone fractures) and optimise patient experience. The prospect of home service should however, be weighed against the risk of adverse events that would not be proactively monitored.\textsuperscript{46} Patients with MM will eventually experience relapse, and become resistant to at least one drug from their initial regimen.\textsuperscript{46}

Maintenance therapy may be an option to keep the patient symptom-free following induction therapy. However there are concerns that prolonged treatment may induce chemotherapy relapse and thus negatively affect OS.\textsuperscript{47} Furthermore, since some agents are delivered via intravenous infusion, treatment may be difficult to maintain over the long term. Agents such as lenalidomide, however, have shown promise as maintenance therapy in MM, with reductions in risk of disease progression and death demonstrated in a recent meta-analysis.\textsuperscript{48} Results from the Myeloma XI study further demonstrated significant improvements in PFS associated with maintenance lenalidomide in patients of all ages.\textsuperscript{49} Bortezomib has further proven to be effective in prolonging survival; of note,
higher doses could be maintained if administered subcutaneously, once per week and with effective adverse event management. Bortezomib with melphalan and prednisone comprise frontline therapy for elderly patients and those not suited for high-dose therapy. In transplant-eligible patients, as part of induction and maintenance therapy, bortezomib improves OS and PFS in patients with del(17p) (without overcoming the risk) and those who present with renal failure. There are several ongoing clinical trials assessing the impact of both current and new therapies when given as maintenance, on outcomes of transplant-eligible and ineligible MM patients. Overall, optimising treatment is essential in minimising the disease burden in patients with MM. Using tools such as the ISS, cytogenetics and gene signature profiling, as well as molecular and immunophenotypic assessments of minimal residual disease can help to identify patients most at risk of relapse and develop optimal and personalised treatment algorithms that will maximise benefit of currently available novel therapeutic agents.

**New therapies/treatment approaches may help reduce patient burden**

Continuous therapies have shown promising efficacy in the treatment of MM. While the norm used to be a fixed duration of induction/primary treatment or a drug given at relapse for a fixed duration of time, followed by a drug-free period until relapse, long-term treatment now has the potential of maintaining/prolonging remission. This can be achieved by continuously suppressing myeloma cells and attaining minimal residual disease negativity, thus preventing or postponing relapse. Several studies of long-term treatment with agents such as thalidomide, lenalidomide and bortezomib have shown positive survival outcomes. Considering the future of continuous therapies, the development of oral agents may help lengthen the time patients are on treatment and hopefully help toward maintaining long-term outcomes. Outcomes, however, need to be improved in patients with high-risk cytogenetics, a group with poor survival rates. Thalidomide negatively impacts OS in these patients, lenalidomide maintenance does not provide a PFS or OS benefit, and results with bortezomib in induction and maintenance settings in patients with high-risk cytogenetics have been mixed. A pooled analysis of fixed vs continuous therapies, including PIs and IMiDs, has shown a survival benefit to continuous versus fixed therapy in patients with del(17p), t(4;14) or t(14;16).

In terms of treatment combinations, doublet and triplet therapies are well established at improving outcomes in myeloma. Building on this, an array of new treatments against a lenalidomide and dexamethasone backbone have shown better outcomes than lenalidomide and dexamethasone alone in the relapsed/refractory setting; with new agents showing impressive benefits in PFS and response rate in both standard and high-risk patients as compared with doublet comparators.

Patients with genetically and clinically defined high-risk myeloma (based on disease stage, chromosomal abnormalities, cancer biology and gene expression) may require more aggressive combination and long-term maintenance therapy that may include new immune-based treatments or new PIs and a more targeted approach. New therapeutic agents should also be targeted at improving safety, tolerability and preservation of QoL in the long term, especially in frail patients and those with comorbidities. In transplant-ineligible patients, goals of treatment should include achieving high-quality responses with effective combinations that include novel agents, as well as sustaining the response with maintenance therapy with longer follow-up periods.

In the pursuit of building on existing benefits, new agents should aim to further minimise symptoms, financial and logistical burden, while maximising QoL. Future studies should also focus on comparisons of therapies in terms of route of administration and its effects on patients’ QoL; any bias should be eliminated or minimised through more randomised, double-blind settings exploring the effect of new therapies on patients’ overall well being.

**Conclusions**

Multiple myeloma is an incurable disease with considerable psychological, physical, financial and logistical burden for the patient. While new therapeutic agents are significantly improving outcomes such as PFS and OS, more attention should be directed at preserving and optimising patients’ QoL. Dynamic QoL measures should be incorporated into standard practice when patients are on therapy, thus mitigating ongoing symptom/disease burden for the patient. Patient-reported outcome measure tools that are simple to use should be developed and used, perhaps routinely, to inform treatment outcomes. In terms of treatments themselves, associated toxicities and burdens need to be minimised so that dose reductions and discontinuations are avoided, as these can negatively impact efficacy. Simplified routes of administration of novel agents for MM would further alleviate the burden associated with the disease and improve long-term outcomes.

“Peripheral neuropathy] feels like I’m walking on cushions. [I] have to look down and check my feet are on the floor as I can’t tell; [I] feel wobbly and unsteady on my feet – like walking on something uneven”  
Patient with multiple myeloma
The burden of living with myeloma and the challenges of coping with treatment

References


The burden of living with myeloma and the challenges of coping with treatment.