The role and value of maintenance therapy following autologous stem cell transplant in multiple myeloma

Expert Foreword

Advances in treatment for multiple myeloma (MM) over the last 10 years mean that patients are now living longer; MM is increasingly considered a chronic disease, necessitating a long-term approach to therapy. Emerging data suggest that prolonged treatment may delay relapse and extend survival. One strategy for optimising initial therapy in newly diagnosed patients with MM involves maintenance therapy post-autologous stem cell transplantation (ASCT), which aims to lengthen primary remission via long-term disease control. Such an approach is becoming more widespread in clinical practice, especially with the approval of lenalidomide in this setting in 2017.

Integrating maintenance therapy into practice is complex given that patients with MM are generally older (median age of diagnosis of ~69 years), often have existing comorbidities, and have a high burden of disease. Thus, maintenance therapy not only needs to demonstrate prolonged survival but also must be convenient, and must not substantially impair patient quality of life, cause cumulative or late-onset toxicity or contribute to the development of resistant clones at relapse. As yet, an ideal maintenance therapy has not been found. It is additionally unclear how long maintenance therapy should be given in clinical practice to achieve optimal treatment outcomes due to a lack of systematic analysis; some studies treat until disease progression and others cease treatment at two years. In general, it is likely that treatment will need to be individually tailored to patients taking into account the efficacy and tolerability of maintenance treatments, along with patient preferences.

Introduction

MM is a haematological cancer characterised by periods of active disease and remission. Despite advances in treatment and improvements in patient outcomes over the last 50 years,1 relapse remains inevitable and the duration of remission tends to decrease with each increasing line of therapy.2 Variation in genetic composition and secondary genetic events within the tumour are thought to be responsible for relapse in many cases due to the proliferation of resistant subclones.3
Current standard of care for MM comprises induction therapy and ASCT in patients who are transplant-eligible, followed by observation. More recently maintenance treatment, with or without prior consolidation, has been suggested as an addition to this pathway.\(^4\) The aim of maintenance treatment is to increase the duration of disease quiescence via continuous suppression of clonal proliferation, ultimately leading to long-term disease control.\(^4\) However, the benefits of extended treatment must be balanced with the risk of potential side effects and the lifestyle implications associated with dosing regimens and appointment requirements, which can impact patient quality of life (QoL). The efficacy and tolerability as well as the optimal duration of maintenance therapy continue to be evaluated as the field of MM treatment evolves.

### Maintenance therapy as part of the evolving continuous treatment paradigm

The treatment paradigm in MM is moving towards continuous or long-term therapy instead of short-term, fixed-duration approaches.\(^5\) Based on emerging data which suggest that continuous or prolonged treatment may delay disease progression and extend survival,\(^6-8\) Maintenance therapy has emerged as an option to potentially delay progression and prolong survival in newly diagnosed MM (NDMM).\(^9-10\) First-line treatment for NDMM is dependent on whether patients are eligible for high-dose therapy plus ASCT. For those who are transplant-eligible, use of post-ASCT maintenance is increasing, although it is not yet widespread despite lenalidomide obtaining approval in 2017 by the United States Food and Drug Administration\(^11\) and the European Union in this setting.\(^12\)

Lenalidomide has been studied as post-ASCT maintenance in several Phase III trials.\(^13-17\) A recent meta-analysis of three of these trials demonstrated statistically significant improvements in progression-free survival (PFS) (hazard ratio [HR]: 0.48; 95% confidence interval [CI]: 0.41–0.55) and overall survival (OS) (HR: 0.75; 95% CI: 0.63–0.90; p=0.001) with lenalidomide maintenance vs placebo or observation, supporting its utility in this setting.\(^9\) To date, lenalidomide is the only agent approved specifically in the post-ASCT maintenance setting; however, due to the heterogeneity of MM\(^18\) and the differing requirements of patients there is a need to study and validate additional agents with various mechanisms of action.

### Early agents used as post-ASCT maintenance

A number of different agents have been investigated in the post-ASCT maintenance setting, including melphalan and prednisone, interferon-\(\alpha\), and corticosteroids.\(^19\) However, these early maintenance agents often were found to be toxic, making extended therapy difficult due to patient discontinuations.\(^19\) Interferon-\(\alpha\) had an unfavourable toxicity profile characterised by mood swings and flu-like symptoms, which, coupled with the limited OS benefit\(^19\) and the absence of a PFS benefit compared with steroids,\(^20\) resulted in cessation of investigation of interferon-\(\alpha\) as a maintenance option for MM.\(^21\) Similarly, dexamethasone was not recommended as a post-ASCT maintenance option by the International Myeloma Working Group due to lack of compelling evidence.\(^22\) In contrast, studies using thalidomide as post-ASCT maintenance demonstrated prolonged PFS; however, the OS benefit from these studies was unclear, with conflicting results reported, and poorer outcomes in patients with high-risk disease.\(^23-26\) Furthermore, thalidomide was associated with a poor toxicity profile, including dose- and time-dependent peripheral neuropathy (PN), which resulted in a higher prevalence of this side effect after 6–12 months of treatment. An increased risk of deep vein thrombosis, pulmonary embolism, constipation, somnolence, and loss of balance has also been identified with thalidomide maintenance, and a higher risk of arrhythmias and bradycardia has been seen in elderly patients.\(^19\) Consequently, thalidomide maintenance has typically been limited to 7–24 months’ duration, with tolerability remaining poor; treatment discontinuation rates of up to 84% have been reported.\(^19\)

### Current post-ASCT maintenance options

Lenalidomide is the only agent approved for post-ASCT maintenance in MM for responding patients or those with stable disease, but is not indicated as maintenance therapy in the non-transplant setting.\(^27\) Lenalidomide maintenance has shown a significant PFS advantage in several large, Phase III trials, and an OS advantage in some individual trials and in a meta-analysis of three Phase III trials of post-ASCT maintenance in NDMM patients.\(^8,14,16,17\) In this meta-analysis, lenalidomide maintenance significantly delayed disease progression (HR: 0.48)\(^9\) and prolonged OS vs placebo or observation (HR: 0.75, p=0.001).\(^6\) Table 1 summarises results of the individual trials included in this meta-analysis. Recent results from the Myeloma XI trial corroborate these findings, revealing an extension in PFS with lenalidomide maintenance compared to observation (HR: 0.46 [95% confidence interval (CI) 0.41–0.53]; p<0.0001). Median OS was not significantly different in the intention-to-treatment population (HR: 0.87 [95% CI 0.73–1.05]; p=0.15); but a significant OS benefit was seen with lenalidomide maintenance vs observation or placebo in the transplant-eligible subgroup (HR: 0.69 [95% CI 0.52–0.93]).\(^15\)

Although lenalidomide maintenance has shown significant improvements in PFS and OS in the post-ASCT setting in MM, 29.1% of patients in the lenalidomide maintenance group discontinued treatment as a result of treatment-emergent adverse events vs 12.2% in the placebo or observation group.\(^9\) The most common TEAEs leading to treatment discontinuation in the lenalidomide maintenance and placebo or observation groups were blood and lymphatic system disorders (4.3% vs 2.1%, respectively) and general disorders and administration site conditions (4.7% vs 1.5%, respectively).\(^2\) Lenalidomide maintenance has been associated with an increased risk of thromboembolic events thus meaning it may not be an appropriate choice for patients with clotting disorders who are unable to take the thromboprophylactic medications which is recommended whilst on lenalidomide treatment.\(^27\) Furthermore, lenalidomide maintenance has been linked with a potential elevated risk of secondary primary malignancies (SPMs), as well as, diarrhoea and fatigue.\(^5,13,28\) A meta-analysis of seven Phase III trials of lenalidomide maintenance in NDMM, revealed a small but elevated risk of haematological SPMs with lenalidomide maintenance vs no lenalidomide maintenance, with cumulative 5-year incidences of 3.1% versus 1.4% (HR: 3.8, p=0.029) and cumulative 5-year incidences of solid tumour SPMs were 3.8% vs 3.4%.\(^29\) This increase was found to be primarily driven by co-exposure to lenalidomide and oral melphalan (HR: 4.86, p<0.0001, vs melphalan alone).\(^29\)
Table 1. Results from meta-analysis of three Phase III trials of post-ASCT lenalidomide maintenance in NDMM patients, and from individual contributing studies

<table>
<thead>
<tr>
<th>Trial/analysis</th>
<th>Meta-analysis(^a)</th>
<th>CALGB 100104(^{5,28})</th>
<th>IFM 2005-02(^{25,27})</th>
<th>GIMEMA RV-MM-PI-209(^{4,17})</th>
</tr>
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<tbody>
<tr>
<td>Comparison (patient no.)(^{19})</td>
<td>R (n=586) vs placebo/obs (n=590)</td>
<td>R (n=224) vs placebo (n=221)</td>
<td>R (n=306) vs placebo (n=302)</td>
<td>R (n=56) vs observation (n=67)</td>
</tr>
<tr>
<td>Mean DOT, mos</td>
<td>28 vs 22</td>
<td>31.0 vs 18.1(^{15,18})</td>
<td>25(^v) vs 20(^9)</td>
<td>35 vs 29(^{29})</td>
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**PFS**

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<th>Median, mos</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<tr>
<td></td>
<td>52.8 vs 23.5</td>
<td>0.46 (0.41–0.55)</td>
<td>Not reported</td>
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**OS**

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<th></th>
<th>Median, mos</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<tr>
<td></td>
<td>NR vs 86.0</td>
<td>0.75 (0.63–0.90)</td>
<td>0.001</td>
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</table>

DOT data was taken from meta-analysis unless available from individual study reports.

*Median DOT reported. Median DOT in placebo group was 20.7 months in crossover patients and 14.5 months in non-crossover patients. \(^{19}\)119 patients stopped R maintenance without progression (minimum DOT of 27 months; mean 36 months) after the observation of an imbalance of SPMs in the R arm.\(^5\)Data shown for the post-transplant patients only, from report of meta-analysis. \(^a\)ASCT and non-ASCT cohorts combined.

CALGB, Cancer and Leukemia Group B; CI, confidence interval; DOT, duration of treatment; GIMEMA, Gruppo Italiano Malattie Ematologiche dell’Adulto; HR, hazard ratio; IFM, Intergroup Francophone du Myélome; mos, months; N/A, not applicable; NR, not reached; Obs, observation; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, lenalidomide; SPM, secondary primary malignancy.

**In addition to efficacy and tolerability, other factors must be considered when considering maintenance therapy that will meet the needs of a variable population. Ease of administration and a limited side-effect profile, including limited acute and chronic toxicity, are key desirable characteristics of post-ASCT maintenance therapy, making it feasible for an agent to be given long-term (up to 2 years or until progression) without substantially impairing patients’ QoL or limiting their lifestyle.**

Furthermore, maintenance may contribute to the emergence of more resistant clones at relapse which has been attributed to the selection of treatment-resistant clones resultant from intra-clonal heterogeneity that characterises MM.\(^9\) Poorer post-relapse survival (1.1 vs 2.7 years in thalidomide and control groups, respectively; \(p=0.01\)) in patients with adverse cytogenetics has been found in some trials of thalidomide maintenance.\(^24\) In addition, the use of lenalidomide maintenance until disease progression may result in lenalidomide-refractory disease, although the definition of lenalidomide refractoriness in this context remains to be determined. Of note, many second and third-line treatment options are based upon a lenalidomide-dexamethasone backbone, although the definition of lenalidomide refractoriness in this context remains to be determined. Of note, many second and third-line treatment options are also often studied in combinations that include lenalidomide, hence lenalidomide-refractoriness may also limit the eligible patient population for these studies. Agents should ideally offer similar benefit in all patient subgroups, which has yet to be shown with IMiD-based maintenance therapy; thalidomide maintenance in patients with high-risk cytogenetics has been shown to result in poorer OS.

<table>
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<th>HR (95% CI)</th>
<th>P-value</th>
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<td>NR vs 86.0</td>
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<td>0.001</td>
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\(\text{DOT} = \text{duration of treatment}\)
The role and value of maintenance therapy following autologous stem cell transplant in multiple myeloma (p=0.009) compared to their counterparts without high-risk cytogenetic abnormalities. With regards to extending outcomes, depth of response to treatment (e.g., complete vs partial response [CR vs PR]) is strongly associated with improved long-term outcomes, in particular the achievement of minimal residual disease (MRD)-negative status by sensitive flow cytometry or polymerase chain reaction methodologies. However, only a proportion of patients achieve CR and/or MRD-negative status following induction therapy and ASCT. Therefore, for these patients, there is a need for a maintenance agent that can deepen responses in maintenance as well as sustaining an existing response.

As with conventional fixed-term therapies, combination treatment has been shown to confer additional benefit to treatment outcomes compared with their single or double-agent counterparts. Therefore, looking to the future there may be prospects for combination maintenance regimens including lenalidomide that could further improve patient outcomes in MM. Recent results from a trial of bortezomib-lenalidomide-dexamethasone (PAD) vs vincristine-doxorubicin-dexamethasone (VAD) induction and then bortezomib vs thalidomide, respectively, as post-ASCT maintenance for 2 years (Table 2). Of 413 patients who started PAD induction, 229 went on to receive bortezomib maintenance; best response rates increased over the course of treatment, from 62% ≥VGPR and 21% CR post-ASCT, to 76% ≥VGPR and 36% CR post-maintenance. Notably, among patients with the high-risk cytogenetic abnormality del(17p), response rates in the PAD-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAD-bortezomib arm</th>
<th>VAD-thalidomide arm</th>
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<tbody>
<tr>
<td>Patients receiving maintenance, n</td>
<td>229</td>
<td>270</td>
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<tr>
<td>Response upgrade during maintenance, %</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Overall best response rate, % (ITT)</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>≥VGPR rate, %</td>
<td>76</td>
<td>56</td>
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<tr>
<td>CR/nCR rate, %</td>
<td>49</td>
<td>37</td>
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**Outcomes**

- **Median PFS, months (initial)**
  - 35
  - HR: 0.75 (95% CI 0.62–0.90); P=0.002
- **Median PFS, months (updated)**
  - 34
  - HR: 0.76 (95% CI 0.65–0.89); P<0.001
- **5-year OS, % (initial)**
  - 61
  - On multivariate analysis HR: 0.77 (95% CI 0.60–1.00) P=0.049
- **5-year / 96-month OS, % (updated)**
  - 65/48
  - HR: 0.89 (95% CI, 0.74–1.08) P=0.24

**Proteasome inhibitors in the post-ASCT maintenance setting**

Limited data exist regarding proteasome inhibitor (PI)-based maintenance treatment in MM. Although bortezomib maintenance has shown efficacy in patients with high-risk cytogenetics, demonstrated ability to increase depth of response over time and has not been associated with an increased risk of SPMs, incorporation into routine clinical practice has been limited by the incidence of toxicities, discontinuation rates, and route of administration. Bortezomib has been investigated as a component of maintenance therapy in Phase III studies in the post-ASCT and the non-ASCT settings. In the HOVON65/GMMGHD4 study patients were randomly assigned to receive bortezomib-doxorubicin-dexamethasone (PAD) vs vincristine-doxorubicin-dexamethasone (VAD) induction, and then bortezomib vs thalidomide, respectively, as post-ASCT maintenance for 2 years (Table 2). Of 413 patients who started PAD induction, 229 went on to receive bortezomib maintenance; best response rates increased over the course of treatment, from 62% ≥VGPR and 21% CR post-ASCT, to 76% ≥ VGPR and 36% CR post-maintenance. Notably, among patients with the high-risk cytogenetic abnormality del(17p), response rates in the PAD-
bortezomib arm were similar to those in the overall population: 49% CR or near-CR and 76% ≥VGPR in all 413 patients and 52% and 72%, respectively, in 25 patients with del17p.40 PFS and OS with PAD–bortezomib were also similar in patients with or without del17p.50

Similarly, in the GEM05MAS65 Phase III trial, 260 transplant-ineligible patients received bortezomib-melphalan-prednisone (VMP) or bortezomib-thalidomide-prednisone (VTP) induction, 178 of whom received bortezomib-thalidomide (VT) or bortezomib-prednisone (VP) maintenance.48 Best response rates increased over the course of treatment, with the CR rate increasing from 24% pre-maintenance to 46%/39% post-VT/VP maintenance (P=NS); overall 19% of patients deepened their response during bortezomib-based maintenance.48

Despite the demonstrated activity of bortezomib-based maintenance, discontinuation rates are high. In the HOVON65/ GMMG-HD4 trial, only 48% of patients completed 2 years of bortezomib maintenance, with 32% discontinuing due to progression/relapse and 12% discontinuing maintenance prematurely due to toxicities.49 No increased risk of SPMs with PAD–bortezomib vs VAD–thalidomide was observed, with a 7% incidence in each arm after a median follow-up of 96 months.51 Similarly, in GEM05MAS65, 57% and 59% of patients receiving VT and VP maintenance, respectively, discontinued the trial; discontinuations were due to toxicity in 13% and 9% of patients, respectively, due to PN and cardiac events.46 Furthermore, the burden of repeated IV/SC administration could limit the feasibility of long-term bortezomib maintenance treatment.10 Although SC administration is more tolerable and home administration is feasible,10 repeat infusions and clinic visits are a burden to patients, impacting their QoL.30

### Determining the optimal duration of maintenance therapy

Whilst numerous studies have investigated therapeutic options for maintenance therapy, there is a lack of randomised trials assessing the optimal duration of maintenance therapy. Previous studies have observed increased rates of SPMs with lenalidomide-based maintenance regimens and significant discontinuation rates due to toxicity with lenalidomide- and bortezomib-based maintenance.19 The IFM trial was prematurely terminated after 2 years, despite having been planned to continue until disease progression, due to the rate of SPMs.4 However, there are no data to suggest that termination after 2 years is effective in preventing secondary cancer development with the median time to develop SPM determined to be 15 months after the start of maintenance therapy.4 Of note, it has been suggested that the SPM development identified with lenalidomide-based maintenance is due to a synergistic effect with alkylator therapy, as the increased risk of secondary cancer was not evident in the FIRST trial of lenalidomide monotherapy.4

Data from the Myeloma XI study and from a recent pooled analysis has demonstrated that maintenance therapy does not have a negative effect on the efficacy of subsequent therapies, as highlighted by a longer PFS2 in patients who received lenalidomide maintenance vs those in the observation group.6,15 Indeed a recent study of bortezomib-lenalidomide-dexamethasone maintenance in high-risk patients continued for 3 years, demonstrated good efficacy and tolerability, and no Grade 3/4 neuropathy.45 Novel disease assessment techniques, specifically MRD assessment, may further support the investigation and individualisation of optimal maintenance treatment duration. It is important however to ensure that lifestyle implications and patient preferences are considered in addition to balancing efficacy and tolerability of maintenance treatment, thus making shared decision-making and adequate patient education integral to effectively optimise treatment on an individual basis.

### Conclusion

Despite advances in patient outcomes with MM in recent years,1 a cure remains elusive and critical unmet needs persist. As OS improves, MM can increasingly be considered a chronic disease with inevitable relapse and duration of remission decreasing with each subsequent line of therapy, thus response to initial treatment must be capitalised upon. Maintenance therapy aims to extend primary remission via long-term disease control. Lenalidomide is currently the only treatment approved for maintenance therapy and, although providing significant PFS and OS benefit to post-ASCT patients, is limited by tolerability and toxicity risks, and reduced efficacy in certain patient populations.18,55 Investigation of other agents and combinations in the maintenance setting is ongoing, with several therapies showing promising efficacy, suggesting the potential to further improve patient outcomes in MM.14 Currently, the optimal duration of maintenance therapy is uncertain and must be clarified prior to general recommendation.3 Strategies employed in clinical studies include treatment continuation until disease progression or unacceptable toxicities, whilst others terminate treatment at 2 years. It is as yet unclear which confers the greatest benefit and further investigation is required. QoL implications in these trials must also be investigated to ensure that the dosing regimen, side effect profile and psychological implications of long-term therapy are acceptable for patients, and the value and duration of maintenance treatment must be determined on an individual basis.
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References


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