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United Kingdom Myeloma Forum position statement on the use of consolidation and maintenance treatment in myeloma

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SUMMARY

Therapeutic advances and the availability of novel agents have significantly improved outcomes in myeloma; yet, it remains incurable and strategies to improve survival continue to be sought. One approach is to prolong the duration of response and increase progression-free survival (PFS) through consolidation or maintenance treatment with regimens that have low toxicity profiles, and do not negatively impact on quality of life. Data from several studies with thalidomide, lenalidomide and bortezomib consistently show improvements in response and PFS, although results have still to be confirmed with respect to overall survival (OS). Despite the promising data, the optimal use of consolidation and maintenance treatment in terms of regimen, dose and duration has yet to be defined. Given the evidence to date, the UK Myeloma Forum believes that both maintenance and consolidation therapy should be considered as treatment options for patients with myeloma. Patients should be encouraged to enrol in clinical studies. This document reviews the current position of maintenance and consolidation for patients with myeloma treated in the UK.

INTRODUCTION

Myeloma is a haematological malignancy involving the clonal expansion and accumulation of plasma cells within the bone marrow. Clinically, it is characterised by skeletal destruction, renal complications, anaemia and increased risk of infection.

Before the introduction of alkylating agents in the 1960s, the prognosis for patients with myeloma was poor. However, advances in treatment, particularly over the last two decades, have considerably improved outcomes for patients with median overall survival (OS) increasing from approximately 3 years to over 5 years. Much of this can be attributed to the introduction of high-dose therapy and autologous stem cell transplantation (HDT-ASCT), and the emergence of the novel agents such as thalidomide, bortezomib and lenalidomide [1–3].

Despite this, myeloma remains an incurable disease. Following a period of remission, all patients relapse because residual myeloma cells persist even when a complete response to treatment has been achieved. Consequently, salvage treatment is necessary when relapse does occur. The course of myeloma is therefore defined by a pattern of recurrent remission and relapse. However, remission periods become increasingly shorter with subsequent treatments because of acquired drug resistance and clonal selection. Patients ultimately become refractory to further treatment [4, 5].

Studies have shown the prognostic relevance of high response rates particularly in the transplant setting, with achievement of a complete response being one of the strongest predictors of improved long-term outcomes [6–8]. To that end, optimising treatments that produce the deepest responses as early as possible in the disease course has become a priority in recent years [9, 10].

One proposed approach is to continue treatment following initial therapy in the form of consolidation or maintenance. Although sometimes used interchangeably, by definition, these are two different treatment approaches with distinct objectives: consolidation treatment is administered over a short period with the aim of maximising the response obtained with the previous treatment, whereas maintenance treatment is administered long term and intended to sustain control of minimal residual disease and reduce the risk of progression.

In reality, this distinction for maintenance is imprecise as maintenance strategies often have a consolidation effect by improving responses and may only be given for relatively short periods due to the lack of tolerability. Ideally, consolidation or maintenance treatment should have an acceptable safety profile and maintain quality of life, be convenient to administer and crucially, not compromise treatment at relapse.

Despite the potential to improve patient outcome, consolidation and maintenance treatment has yet to be incorporated into routine clinical practice and no specific guidelines on their use in the United Kingdom are currently available. Evidence is still being sought on their benefit to patients. Added to that, questions remain on which agent/regimen is most effective and no head-to-head study of consolidation versus maintenance treatment has yet been performed to assess whether one approach is better than the other.

TREATMENTS

The first attempts involved maintenance treatment with melphalan and prednisolone but this did not improve progression-free survival (PFS) or OS [11]. Subsequent studies with corticosteroid and interferon-α produced mixed results [12–15] but because of their associated toxicities, they were not developed further.

The introduction of the novel agents renewed interest in the concept of consolidation and maintenance treatment and in this context have been studied extensively over the last few years.

Thalidomide

Studies have largely focused on the role of thalidomide as a maintenance treatment in the transplant setting [16–21]. Data across the various studies consistently show improved progression-free survival (PFS); however, the evidence for a benefit of thalidomide maintenance post-ASCT with respect to OS is conflicting.

This lack of agreement in OS data may be due to differences in study design: two studies involved tandem ASCT [17, 18], single-agent thalidomide maintenance was used in some studies [16, 18, 19] and in combination in others [17, 20, 21], and used as induction as well as maintenance treatment [16, 18, 19].

Thalidomide maintenance is often poorly tolerated particularly because of peripheral neuropathy. This was highlighted in the Myeloma IX study where the median duration for thalidomide maintenance was only 9 months and 6 months in the intensive and nonintensive arms, respectively, and the median tolerated dose was only 50 mg daily [19].

Although results are variable, meta-analyses show that thalidomide maintenance exerts a modest but statistically significant survival benefit in patients with myeloma who have undergone HDT-ASCT [19, 22].

Importantly, a number of additional observations were obtained from the studies. Firstly, an improvement in the depth of response was reported in most trials [16–18, 21]. Interestingly, in the IFM99-02, the survival benefit was only apparent in patients who had achieved less than a very good partial response (VGPR) post-ASCT [17]. This suggests that thalidomide may improve survival by additional cytoreduction rather than suppression of minimal residual disease. The MRC Myeloma IX study showed that 28% of patients positive for minimal residual disease after induction treatment became minimal residual disease negative with thalidomide maintenance [9, 23].

Secondly, the effects of thalidomide maintenance appear to be influenced by cytogenetic characteristics. In both the IFM99-02 and HOVON-50 study, subgroup analyses revealed that patients with del (13q) showed no improvement in event-free survival (EFS) following thalidomide maintenance ($P = 0.2$) [17] or worse PFS (HR: 1.38, 95% CI 1.04–1.84, $P = 0.03$) [18].

The Myeloma IX study also found that thalidomide maintenance outcomes were associated with cytogenetic abnormalities. Patients were classified as having either favourable or adverse cytogenetic abnormalities determined by interphase fluorescence in situ hybridisation (iFISH) analysis. Favourable iFISH was defined by the presence of hyperdiploidy, t(6 : 14) and t(11 : 14), and the absence of the adverse iFISH abnormalities: t(4 : 14); t(14 : 16), t(14 : 20); gain (1q); del(17p) and del(1p32).

Patients with favourable cytogenetics benefitted from thalidomide maintenance treatment with significantly improved PFS ($P = 0.004$) and a trend towards increased OS [19]. However, those with adverse cytogenetics had an adverse outcome, showing no improvement in PFS compared to those who did not receive maintenance (9 months *vs.* 12 months, $P = 0.48$) and worse OS ($P = 0.009$) [24].

In contrast, the Total Therapy 2 study found a significant OS benefit with thalidomide maintenance in patients with metaphase cytogenetic abnormalities detected by karyotype analysis [25]. The discrepancy between this and the other data may be due to the different approaches in detecting cytogenetic abnormalities. The evidence to date indicates that thalidomide maintenance does not appear to be of value in patients with adverse cytogenetics [26, 27].

Thalidomide maintenance treatment in the nontransplant setting has also been studied at length. Several studies compared thalidomide maintenance versus no maintenance after initial treatment with melphalan, prednisolone and thalidomide [28–30]. Despite differences in dose, schedule and duration of treatment, all studies demonstrated significant improvements in overall response rates (ranging from 17% up to 30%) and PFS (ranging from 2 to 7 months) with thalidomide maintenance compared to no maintenance. However, only the HOVON-49 study reported a significant improvement in OS (40 months *vs.* 31 months, $P = 0.05$) [29].

In the nonintensive arm of the Myeloma IX study, thalidomide maintenance was compared with no maintenance after initial treatment with cyclophosphamide, thalidomide and low-dose dexamethasone or melphalan and prednisolone. PFS was significantly increased from 9 months to 11 months with thalidomide maintenance (HR: 1.35, 95% CI 1.06–1.73, $P = 0.014$) but OS was not different between the two groups (38 months *vs.* 39 months: (HR: 1.00, 95% CI 0.73–1.38, $P = 0.995$) [19].

Other studies compared different thalidomide combinations. In one study, patients were randomised to either thalidomide and interferon-α or interferon-α alone maintenance treatment following treatment with thalidomide plus dexamethasone or melphalan plus prednisone (MP). Thalidomide and interferon-α maintenance led to a significantly longer PFS compared with interferon alone (27.7 months *vs.* 12.2 months, $P = 0.006$) but not OS (52.6 *vs.* 51.4 months, $P = 0.81$) or quality of response (8% *vs.* 3% of patients) and was associated with greater toxicity than interferon-α maintenance [31]. Thalidomide in combination with bortezomib as maintenance treatment is discussed later.

Overall, the evidence points to a clear advantage of thalidomide maintenance in terms of PFS both in the transplant and nontransplant settings. However, concerns remain with thalidomide maintenance treatment for two reasons: reports of shorter postrelapse survival in some studies [16, 18, 19] and the increased incidence of peripheral neuropathy associated with prolonged thalidomide treatment.

Unfortunately, toxicity remains a major issue for thalidomide maintenance as highlighted by the Myeloma IX study that reported 52.2% of patients discontinued thalidomide treatment before progression because of paraesthesia (26.6%); drowsiness (6.8%); constipation (4.1%), eczema/rash (4.1%); haematological events (1.4%); infection (1.0%); thrombosis (1.0%); and tremor (1.0%). As a result, the median duration of treatment was only 7 months overall (range 0–50 months) [18]. Dose is critical as the median tolerated dose was 50 mg and doses above 200 mg were largely unachievable. However, toxicity of treatment may not translate into inferior quality of life and may lead to a better patient experience with treatment [32].

Some of these hurdles may be overcome by reducing the length of thalidomide treatment and using low doses of 50–100 mg. The improvement in quality of response supports a consolidation effect, and indeed, outcomes have been favourable in those studies where thalidomide was given over a limited period [33, 34]. Further studies will help determine whether thalidomide may be more useful as a consolidation treatment.

Lenalidomide

Lenalidomide was first tested in a pilot phase II study [35] as a consolidation and maintenance treatment post-ASCT with promising results before further testing in phase III studies. Lenalidomide maintenance has proven to be considerably better tolerated than thalidomide maintenance as shown, for example, in the CALGB 100104 study where less than 10% of patients discontinued lenalidomide treatment because of toxicity [36].

The IFM 2005-02 study included 614 patients who received induction with bortezomib and dexamethasone or vincristine, doxorubicin and dexamethasone (VAD), and dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) if they had a suboptimal response prior to a single or double HDT-ASCT. Patients received consolidation treatment with lenalidomide (25 mg/day on days 1–21 for two 28-day cycles) and then randomisation to either single-agent lenalidomide maintenance treatment (10–15 mg/day) or placebo for a median of 32 months [37]. Lenalidomide consolidation treatment improved the rate of CR and VGPR post-ASCT (58% increasing to 69%, $P < 0.001$) and maintenance improved the rate of CR or VGPR compared to placebo ($P = 0.009$). Patients receiving maintenance treatment had a significantly longer median PFS (41 months *vs.* 23 months; HR: 0.5, $P < 0.001$) [37]. This benefit was consistent across all subgroups of patients irrespective of response to HDT-ASCT and prognostic factors such as β2-microglobulin levels and cytogenetic profile (± del 13q). However, there was no difference in the 4-year OS rate (73% with lenalidomide and 75% with placebo).

The design of the CALGB 100104 study, although similar in principle, differed from the IFM 2005-02 study as the induction regimen was not mandated; there was no DCEP prior to ASCT, only a single ASCT, and there was no consolidation step. Importantly, maintenance treatment was continued until disease progression, whereas it was stopped after 24 months in the IFM 2005-02 study due to concerns about second primary malignancies (SPM). This is discussed in greater detail later. After a median follow-up of 34 months, lenalidomide maintenance (5–15 mg/day) significantly delayed the time to progression (TTP) compared to placebo (median TTP 46 months *vs.* 27 months, $P < 0.001$) [36]. In addition, there was a significant improvement in OS: 35 (15%) deaths were recorded in the maintenance group *vs.* 53 (23%) deaths in the placebo group ($P = 0.03$).

Lenalidomide maintenance treatment has also been investigated in the nontransplant setting in the MM-015 study [38]. Newly diagnosed patients were randomised to receive either nine cycles of melphalan, prednisolone and lenalidomide (MPR) followed by lenalidomide maintenance (MPR-R) at 10 mg daily on days 1–21 of each 28-day cycle, or nine cycles of MPR or MP without lenalidomide maintenance. Response rates were significantly higher with lenalidomide-containing regimens (MPR-R, 77%; MPR, 68%; MP, 50%, $P < 0.001$ and $P = 0.002$, respectively, compared to MP) [38]. Median PFS was significantly longer with

MPR-R (31 months) than with MPR (14 months; HR: 0.49, $P < 0.001$) or MP (13 months; HR: 0.40, $P < 0.001$). Further analysis showed that lenalidomide maintenance resulted in a 66% reduced risk of progression compared to no maintenance (HR: 0.34, $P < 0.001$). At a median follow-up of 41 months for OS, there was no difference in the 4-year OS rate between the groups (58–59%).

Finally, lenalidomide maintenance has been investigated in patients previously randomised to receive induction treatment with six cycles of melphalan, prednisolone and Velcade (MPV) or tandem ASCT (https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001610-16) [39]. After a median follow-up of 32 months from start of maintenance, lenalidomide improved PFS (41 months *vs.* 18 months, $P < 0.0001$) and improved 3-year OS (81% *vs.* 72%, $P = 0.04$) compared to no maintenance.

All these studies are currently undergoing long-term follow-up. Of note, an improvement in PFS has been observed with lenalidomide maintenance; yet, only one study has reported an OS benefit. As the data mature, they will determine whether further improvements are made and whether lenalidomide maintenance can indeed prolong OS. Although the optimal dose has yet to be defined, most strategies have used doses of 10–15 mg daily for 21 days of a 28-day cycle.

Lenalidomide maintenance treatment appears to be better tolerated than thalidomide. In the IFM 2005-02 study, the rate of grade 3 or 4 peripheral neuropathy was similar in both groups [37]. However, there was a higher incidence of grade 3 or 4 haematological events (58% *vs.* 23%, $P < 0.001$), mainly due to neutropenia but febrile neutropenia was rare (1%). Fatigue can also be a problem. The issue of increased second primary malignancies is discussed below.

Currently, lenalidomide maintenance is being investigated in both the transplant and nontransplant setting in the Myeloma XI study either as a single agent at 10 mg daily for 21 days of a 28-day cycle, or in combination with the histone deacetylase (HDAC) inhibitor vorinostat (http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=7072). A detailed examination of the association between genetic abnormalities and clinical outcomes forms an integral part of this study. The European Myeloma Network trial (EMN02) is assessing bortezomib lenalidomide dexamethasone (VRD) consolidation and lenalidomide maintenance versus no consolidation and lenalidomide maintenance after single, tandem or no transplant for myeloma (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2528). Results of these trials should help determine the best use of lenalidomide as a maintenance/consolidation treatment so that in future, they will be targeted to those who are likely to benefit.

Bortezomib

Bortezomib has been investigated to a lesser extent than IMiDs as a consolidation or maintenance treatment possibly because of its greater potential for cumulative toxicity and the inconvenience of administering it intravenously. Nevertheless, data suggest it should be strongly considered especially now that it can be administered subcutaneously [40].

Single-agent bortezomib consolidation after HDT-ASCT has been investigated in a randomised Phase III study [41]. Given over the course of 21 weeks, results demonstrate and increased CR rate from 35% to 45% with bortezomib consolidation ($P < 0.05$) with an improvement in PFS from 20 to 27 months ($P = 0.02$). The 2-year overall survival was 90% in both groups.

A phase II study of 39 patients showed that four 28-day cycles of bortezomib consolidation combined with thalidomide and dexamethasone (VTD) increased the CR rate from 15% to 49% in patients who achieved at least a VGPR after high-dose therapy and ASCT [42]. Furthermore, qualitative nested PCR and quantitative RT-PCR demonstrated an increase in molecular remission from 3% to 18%, and PFS was significantly longer in these patients [42].

Bortezomib consolidation is further supported by the Italian study by Cavo *et al.* [43] in which VTD was used as both induction and consolidation treatment after double ASCT. With two cycles of treatment, VTD consolidation significantly enhanced CR ($P = 0.009$) and nCR ($P = 0.004$) rates, whereas TD consolidation did not ($P = 0.052$ and $P = 0.11$, respectively). After a median follow-up of 30.4 months, 3-year PFS was significantly longer for the VTD compared to TD group (60% *vs.* 48%, $P = 0.04$). Due to the design of the study, it was not possible to distinguish how much of this benefit was due to bortezomib used in induction

or in the consolidation step of the study. To date, there is no improvement in OS.

Bortezomib as a maintenance treatment was evaluated in the HOVON 65MM/GMMG-HD4 study, given (1.3 mg/m^2) every 2 weeks for 2 years following induction with PAD (bortezomib, adriamycin and dexamethasone) and single or double ASCT [44]. This was compared to maintenance treatment post-transplant with thalidomide (50 mg once per day for 2 years) after VAD induction (vincristine, adriamycin and dexamethasone).

All outcomes were significantly better in the PAD arm: CR including nCR after induction was 49% *vs.* 34%, $P < 0.001$; PFS after a median follow-up of 41 months was 35 months *vs.* 28 months (HR: 0.75, 95% CI 0.62–0.90, $P = 0.002$), and in multivariate analysis, OS was significantly improved (HR: 0.77, 95% CI 0.60–1.00, $P = 0.049$).

Outcomes were found to be associated with cytogenetic factors. Patients with del(17p13) derived a particular benefit from bortezomib with superior median PFS of 22 *vs.* 12 months (HR: 0.49, 95% CI 0.26–0.86, $P = 0.01$) and OS of 54 *vs.* 24 months (HR: 0.36, 95% CI 0.18–0.74, $P = 0.003$). However, for patients with del (13q14), PFS was worse in both treatment arms than those without the deletion. OS was similar in the PAD arm regardless of whether they had del (13q14) or not but was significantly improved for those with the deletion compared to the VAD arm (median OS 59 months *vs.* 49 months; HR: 0.60, 95% CI 0.42–0.97, $P = 0.007$).

Overall, the study demonstrated that bortezomib maintenance can be tolerated long term. However, because of the design of the study, the benefit of bortezomib as maintenance treatment could not be distinguished from the benefit obtained during induction.

Bortezomib maintenance was also examined in the PETHEMA/GEM study comparing VTD to TD and VBMCP/VBAD/B prior to a single ASCT [45]. Patients were randomised to receive alpha interferon, thalidomide or bortezomib 1.3 mg/m^2 given on days 1, 4, 8, 11 every 3 months, in addition to thalidomide (VT). Maintenance treatment was continued for 3 years. After a median follow-up of 24 months from start of maintenance, PFS was significantly longer with VT compared to thalidomide alone or alpha interferon (78% *vs.* 63% *vs.* 49%, $P = 0.01$). However, there was no significant difference in OS.

In the nontransplant setting, Mateos *et al.* [46] reported the outcomes of a study of 260 elderly patients who received induction treatment with bortezomib, melphalan and prednisolone (VMP) or bortezomib, thalidomide and prednsiolone (VTP) followed by maintenance with bortezomib plus thalidomide (VT) or prednisolone (VP). After a median follow-up of 38 months, the CR rate increased from 24% after induction to 42% (VT, 46%; VP, 39%). There was no significant difference in PFS or OS between the two groups; however, CR achievement was associated with a significantly longer PFS ($P < 0.001$) and 5-year OS ($P < 0.001$).

Maintenance with VT was also evaluated in a study comparing VMPT/VT with VMP [47]. Patients receiving VMPT followed by VT achieved a significant benefit in PFS at 3 years (56% v 41%, $P = 0.008$) but no differences in OS were reported.

Bortezomib is known to promote osteoblast function and so inhibit myeloma bone disease. A phase II study (Velcade Consolidation Bone Study; http://clinicaltrials.gov/show/NCT01286077) assessing bone mineral density following bortezomib consolidation post-transplant is ongoing, and the results are awaited.

Overall, bortezomib-based consolidation and maintenance treatments provide significant benefit in terms of increasing response rate and prolonging PFS, but benefit in terms of OS has yet to be confirmed. Given the limited data and heterogeneity of existing studies, the optimal use of bortezomib (in terms of dose, scheduling, duration and drug combination and as consolidation or maintenance) remains unclear. Further prospective studies are warranted.

POTENTIAL ISSUES

Despite the accumulating evidence showing the benefits of consolidation and maintenance treatment in terms of disease control, prolonged use of thalidomide, lenalidomide and bortezomib does, however, has a number of drawbacks.

Long-term treatment is often limited by tolerability and the impact it has on quality of life. In many cases, it is the primary reason treatment is prematurely discontinued. The risk of cumulative toxicity is also a potential issue, especially for patients in remission. This is particularly so for thalidomide with a significant proportion of patients discontinuing within a year of starting it as maintenance treatment.

Treatment side effects that require vigilance include peripheral neuropathy (associated with thalidomide and bortezomib), myelosuppression (lenalidomide), excessive fatigue (thalidomide and lenalidomide) and thromboembolic events (thalidomide and lenalidomide). However, these are generally predictable, preventable and can be easily managed provided they are detected early. In most cases, dose reduction, adjustments to schedule and appropriate supportive care, implemented at the right time, will enable long-term treatment to be achieved [48]. The introduction of subcutaneous administration of bortezomib should help reduce the incidence and severity of associated neuropathy [40].

An unexpected finding has been the increased incidence of second primary malignancies (SPM) associated with lenalidomide maintenance in newly diagnosed patients. This was observed both in the nontransplant setting after prior treatment with lenalidomide in combination with melphalan [38] and also post-transplant [36, 37]. Overall, the incidence of SPM from the three studies was 7.6% in those receiving lenalidomide maintenance compared to 2.9% in controls [data from Celgene Corporation]. The increased risk of SPM was observed in both haematological malignancies (mainly myelodysplastic syndrome and acute myeloid leukaemia) and to a lesser degree in solid malignancies. The cause of increased SPM risk is not clear but may be influenced by treatment-related factors, such as the potential interaction of melphalan with lenalidomide.

In a recent meta-analysis, the risk of haematological SPM was higher in patients receiving lenalidomide maintenance after prior exposure to melphalan, than those without melphalan [49]. Disease-related factors are also relevant with an increased risk of AML/MDS seen in patients with IgG and IgA (but not IgM) MGUS [50]. However, differences in the incidence of solid *versus* haematological malignancies, the use of induction regimens in these trials and trial entry criteria mean it is not possible to draw any firm conclusions about the risk of SPM. Indeed, a retrospective review of patients treated in the Total Therapy 2 and 3 studies showed no difference in SPM rates in patients receiving either thalidomide or lenalidomide maintenance [51], and a large population-based study found no increase in SPM rates after the introduction of novel therapies [52].

Further prospective randomised studies of lenalidomide versus placebo that include SPM as a defined end-point will help determine whether there is a true association or not. Based on the current available data with a marked improvement in PFS (and OS in one study) and a small risk of SPM, this would support the use of lenalidomide maintenance in selected patients.

Another potential issue is the observation from some studies of a shorter survival time after relapse in patients who received thalidomide maintenance treatment [16, 18, 19]. One possible explanation is that long-term treatment results in the selection of a drug-resistant tumour clone. This requires further investigation and highlights the need to select appropriate treatment at progression. This was demonstrated in the Myeloma IX study, which showed a significantly longer survival in patients who had received thalidomide maintenance treatment and then had subsequent access to novel agents at relapse compared to those who were treated only with further thalidomide or conventional chemotherapy agents [19].

At present, thalidomide, bortezomib and lenalidomide do not have marketing authorisation for maintenance treatment after induction in newly diagnosed patients, and there are no National Institute for Health and Care Excellence (NICE) guidelines recommending their availability in this setting. A recent European Union (EU) application for lenalidomide maintenance treatment for newly diagnosed patients with myeloma who have not progressed following initial treatment with melphalan, prednisolone and lenalidomide or following ASCT was withdrawn on the recommendation that more data were needed.

Access to consolidation or maintenance treatment therefore remains in the context of a clinical study. In the United Kingdom, patients in the Myeloma XI study who have achieved a partial response or less after initial treatment are randomised to receive bortezomib consolidation in the form of the VCD regimen. Patients are later randomised to lenalidomide maintenance treatment either as a monotherapy or in combination with vorinostat. Bortezomib consolidation up to a maximum of eight cycles (if tolerated) on the outcome of ASCT is also being assessed in a noncommercial Phase II study. Preliminary data from both studies should be available within the next year.

The financial impact of long-term treatment with novel agents also warrants careful assessment. The cost of some of these agents is substantial, and supportive treatment costs and laboratory testing must

also be factored. At present, the net price of a 28-capsule pack of thalidomide (50 mg) = £298.48; a 3.5 mg vial of bortezomib = £762.38, equivalent to £3049.52 a cycle, and for lenalidomide, depending on concentration (5–25 mg capsule), a 21-capsule pack ranges from £3570–£4368 (British National Formulary).

THE FUTURE

The goal of consolidation and maintenance treatment is to prolong PFS and preferably OS, and to maintain patient's quality of life. Thalidomide, lenalidomide and bortezomib have all shown clinical activity in this context but in order for them to become integrated into clinical practice, further evidence must be sought to determine how best they can be implemented.

This includes understanding whether subgroups (e.g. by cytogenetic profile) of patients might benefit more from continuous treatment with a particular agent; which dosing regimen, schedule and combination are effective yet tolerable; how long treatment should last and the consequences on treatment options at relapse.

Answers to these questions should help determine the value of consolidation/maintenance treatment in the pathway of care for patients with myeloma.

Current recommendations for the use of consolidation and maintenance treatment

Maintaining results of successful induction treatment is an important goal in myeloma. Data from several studies with thalidomide, bortezomib and lenalidomide consistently show improvements in response rates and PFS, although results still have to be confirmed with respect to OS.

It is important to note that at present, none of these novel drugs evaluated for consolidation or maintenance is approved for these indications. Furthermore, which regimen, tolerability, dose, duration and risk groups are likely to benefit have yet to be defined. In addition, there is a paucity of data regarding the impact on quality of life of these agents in this setting. Watchful waiting therefore remains the standard of care.

We would therefore encourage patients and their treating physicians to enrol them in clinical studies investigating maintenance and consolidation regimens. In the United Kingdom, there is the national Myeloma XI study and also some investigator-initiated studies.

Thalidomide maintenance improves PFS, and in some studies, OS could be considered in selected patients. It is important to establish the FISH-defined cytogenetic risk before offering thalidomide maintenance. Thalidomide maintenance should not be offered to patients with FISH-defined poor risk cytogenetics due to its inferior outcome compared to controls in this patient group. It could be considered in patients who have failed to achieve a VGPR without FISH-defined adverse features. Long-term use of thalidomide is not feasible and should be limited to <1 year due to toxicity.

Lenalidomide maintenance is well tolerated and active in most risk groups, and improves PFS as shown in three large randomised clinical studies. However, exposure to this agent confers an increased risk of SPM but it is likely this risk is low compared to the potential benefit in terms of antimyeloma effects. It is important to wait for more mature survival data before making specific recommendations for lenalidomide maintenance treatment. In the United Kingdom, it is unlicensed and the cost of treatment needs to be considered before adopting its widespread use.

Data regarding bortezomib maintenance/consolidation are encouraging. However, because of the design of these studies, the benefit of bortezomib as maintenance cannot be distinguished from the benefit obtained during induction treatment. There is also limited data on the use of bortezomib as a single agent in patients not previously exposed. It is important to await further data before adopting its widespread use.

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