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Maintenance treatment of multiple myeloma: evidence from recent clinical trials

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Donna E Reece
Princess Margaret Hospital,
610 University Avenue, Suite 5-207, Toronto, ON M5G 2M9, Canada
Tel.: +1 416 946 2824
Fax: +1 416 946 6546
E-mail: donna.reece@uhn.on.ca

Maintenance therapy with novel agents has recently been investigated in both transplant-eligible and -ineligible myeloma patients. In Phase III trials, thalidomide, lenalidomide and bortezomib have consistently improved progression-free survival after autologous stem cell transplantation, with variable effects on overall survival. In elderly patients, induction regimens combining melphalan and prednisone with novel agents, followed by maintenance with thalidomide, combinations of bortezomib with thalidomide or prednisone, and lenalidomide have also extended progression-free survival. However, to date, no survival advantage has emerged. Longer follow-up is awaited to assess the long-term consequences of maintenance therapy as well as to identify subgroups of patients in whom maintenance might be most appropriate.

Keywords: maintenance therapy • myeloma • novel agents • stem cell transplantation

Maintenance therapy has had its major role in the management of childhood acute lymphoblastic leukemia, in which prolonged outpatient chemotherapy makes a significant contribution to the cure of this hematologic malignancy [1]. More recently, the use of maintenance therapy in diseases that are not considered curable, such as follicular lymphoma, has emerged as a beneficial strategy in prolonging the progression-free survival (PFS), and has been adopted as a standard of care in many centers [2]. The first maintenance strategy in multiple myeloma involved continuation of oral melphalan after achievement of the maximal response, that is, the plateau phase. In part due to the cumulative toxicity of this drug, this approach was abandoned in favor of reinstitution of the drug at the time of disease progression [3]. Other efforts have utilized older agents, such as IFN-α and corticosteroids, with variable results and toxicity concerns [4–7]. The availability of more effective drugs in myeloma has generated a renewed interest in maintenance therapy in this disease, and a number of Phase III trials have now been reported.

A recent myeloma consensus panel has defined maintenance therapy in this disease as any treatment administered after the completion of induction therapy in patients whose disease is either responsive or nonprogressive at that time, with the goal of prolonging survival [8]. Maintenance therapy has been evaluated most extensively after high-dose therapy and autologous stem cell transplantation (ASCT), a modality which can prolong time to progression (TTP), PFS and overall survival (OS) in younger patients, but which is not considered curative. However, more recently, clinical trials using maintenance therapy in elderly patients have been initiated and early results are now available. Finally, some investigators have reported studies in which induction therapy containing various combinations is given to all age groups, but ASCT is optional as part of initial therapy (although it may be utilized at the time of relapse); in many of these studies, patients may remain on all or part of the original combination as long as remission continues. This approach is more difficult to

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critically assess due to the lack of uniform management. Therefore, this paper will evaluate the potential role of maintenance therapy with novel agents in ASCT and non-ASCT patients separately, with a focus on results of Phase III trials.

Maintenance therapy after ASCT

In the 1990s, newly diagnosed myeloma patients usually received induction with several cycles of high-dose dexamethasone-based therapy, such as vincristine, doxorubicin and dexamethasone (VAD) or dexamethasone alone followed by ASCT. Phase III trials indicated that the median PFS with this approach was on the order of 2–2.5 years [9,10]. After the novel agents thalidomide, bortezomib and lenalidomide demonstrated efficacy in relapsed/refractory myeloma, they were introduced earlier in the disease course. One of their applications in ASCT patients included their use as post-transplant maintenance therapy.

Thalidomide

Thalidomide was the first novel agent studied as maintenance therapy and has now been evaluated in seven randomized trials (Table 1) [11–18]. As noted in Table 1, these trials differ with respect to the risk group studied, type of induction therapy, number of transplants (single or tandem), thalidomide dose and duration, and control arm. Most of these early maintenance trials evaluated thalidomide maintenance in patients who did not receive novel agents upfront [11–13,17]. However, thalidomide was part of the induction regimen in three of the trials, none of which demonstrated a survival advantage with thalidomide maintenance [14,16,17]. This observation raises the question of whether thalidomide is most efficacious when it is introduced for the first time post-transplant, at the time of potential minimal residual disease.

All of these trials show a benefit in terms of a longer time until myeloma progression, with, as noted above, variable effect on OS. The magnitude of the benefit is on the order of 6–12 months (Table 1). However, a major disadvantage of thalidomide is its toxicity profile; in most trials patients could only tolerate the drug for less than 1.5–2 years. Sedation, constipation, rash, risk of venous thromboembolism (VTE) and peripheral neuropathy can all occur, leading to dose reductions and discontinuations. The side effects of corticosteroids, if included as either alternate day prednisone/prednisolone or pulse dexamethasone, may also be problematic. The National Cancer Institute of Canada (NCIC) study rigorously evaluated toxicity and quality of life during maintenance thalidomide and prednisone compared with observation alone, and the findings were recently reported at the 2010 American Society of Hematology meeting. Although 4 years of maintenance therapy at a dose of oral thalidomide 200 mg/day and prednisone 50 mg every other day was planned in the treatment arm, the median time to thalidomide discontinuation was 16.1 months, with the first dose reduction of thalidomide observed at a median of 3.4 months and of prednisone at 5.5 months. The quality of life was clearly impacted negatively by the treatment [18]. Even when lower doses of thalidomide were used, as in the Hemato-Oncologie voor Volwassenen Nederland (HOVON) trial by Lokhorst *et al.*, 33% of the patients stopped the drug due to toxicity, with grade 2 peripheral neuropathy noted in 33% and grade 3–4 in 10% [16]. The British Medical Research Council (MRC) IX study also reported limited tolerability of thalidomide maintenance at doses of 50–100 mg/day [17].

Given the heterogeneity of these trials, the optimal dose and duration of thalidomide has not been established. In practicality, the dose is often limited by patient tolerance and should likely be started at the lower end of the spectrum. Moreover, the observation that 1 year of therapy produced a PFS and survival benefit in the trial reported by Spencer *et al.* suggests that this duration is a minimum goal [12].

One important concern is the identification of patient subsets most likely to benefit from maintenance therapy. In a *post hoc* analysis of the Intergroupe Francophone du Myelome (IFM) trial by Attal *et al.*, the advantage of maintenance therapy was limited to patients who had achieved less than a very good partial remission, defined as at least a 90% reduction in serum monoclonal protein and whose myeloma cells lacked the cytogenetic abnormality del 13q by FISH [11]. However, it should be noted that high-risk patients were ineligible for this trial; specifically, patients could have no more than one adverse feature, either high β-2 microglobulin or del 13q. Another finding of this trial was that the depth of response was improved in a high proportion of patients, indicating that thalidomide was actually exerting a therapeutic, rather than a simple stabilizing (or maintenance), effect [11]. The HOVON-50 trial, which compared a comprehensive program of thalidomide, adriamycin, and dexamethasone induction, ASCT and thalidomide maintenance with another program consisting of VAD followed by ASCT and interferon maintenance, reported that del 13q detected by conventional cytogenetics did not confer an adverse effect in thalidomide-treated patients [17]. On the other hand, the MRC IX trial found that patients with del 17p (*p53* deletion) by FISH had a particularly poor outcome if thalidomide maintenance was used [19]. Finally, the trial by Barlogie *et al.,* which observed a better PFS when continuous thalidomide was added to an aggressive

Table 1. Phase III trials of thalidomide maintenance after autologous stem cell transplant.

Author, year (trial name/location)	Patients (n)	Thal included in induction	Thal maintenance dose (mg/day)	Comparator	Duration of maintenance	CR rate (%) Thal†/Thal‡	PFS (%) or EFS (year) Thal†/Thal‡	Overall survival (%) (year) Thal†/Thal‡	Ref.
Attal *et al.*, 2006§ (IFM 95–02)	597	-	Thal 400	Obs	Until progression	67/55¶	52/36¶ (3 year)	87/77¶ (4 year)	[11]
Spencer *et al.*, 2006 (Australia)	243	-	Thal 200 and Pred	Pred	12 months	63/40¶	42/23¶ (3 year)	86/75¶ (3 year)	[12]
Maiolino *et al.*, 2008 (Brazil)	212	-	Thal 200 and Dex	Dex	12 months	N/A	42/25¶	65/74	[13]
Barlogie *et al.*, 2006 (Total therapy 2)	668	+	Thal 400	No Thal	Until progression	62/43¶	62/43¶ (5 year)	57/44 (8 year)	[14,15]
Morgan *et al.*, 2010 (MRC IX)	492	+	Thal 100	Obs	Until progression	N/A	N/A§	NA††	[17]
Lokhorst *et al.*, 2010 (HOVON-50)	556	+	Thal 50	IFN	Until progression	31/23¶	34/22¶ (median, in months)	73/60 (median, in months)	[16]
Stewart *et al.*, 2010 (NCIC MY.10)	325	-	Thal 200 and P	Obs	48 months	N/A	32/14¶ (4 year) 28/17† (median, in months)	5/5 (median, in years)	[18]

†Thalidomide included in pre-ASCT induction regimen.

‡Thalidomide not part of pre-ASCT induction regimen.

§Trial included only good-risk patients.

¶Statistically significant.

#Includes non-ASCT patients; benefit in favorable FISH subgroup only.

††Survival benefit predicted in patients who received effective antimyeloma therapy at relapse.

ASCT: Autologous stem cell transplant; CR: Complete remission; Dex: Dexamethasone; EFS: Event-free survival; HOVON: Hemato-Oncologie voor Volwassenen Nederland; IFM: Intergroupe Francophone du Myelome; MRC: Medical Research Council; N/A: Not available; NCIC: National Cancer Institute of Canada; Obs: Observation; P: Prednisone; PFS: Progression-free survival; Pred: Prednisolone; Thal: Thalidomide.

program of intensive induction, tandem transplantation and post-transplant chemotherapy consolidation, initially reported no survival benefit, due to a shorter survival after myeloma relapse in the thalidomide arm, although complete remission (CR) rates were higher and PFS was longer [14]. However, an updated analysis later described a significantly better survival in the thalidomide-treated patients considered high-risk due to the presence of cytogenetic abnormalities defined by conventional karyotyping [15]. The different definitions used to identify high-risk patients make it difficult to derive firm conclusions regarding the best use of thalidomide maintenance, although avoidance of this agent in patients with del 17p seems prudent.

A statistical exercise performed in the UK MRC IX trial, in which the combination of oral cyclophosphamide, dexamethasone and thalidomide (CTD) was utilized as induction therapy pre-ASCT (with an attenuated schedule called CTDa studied in elderly nontransplant patients), projected a significantly longer survival in recipients of thalidomide maintenance if they subsequently had access to novel agents at the time of myeloma progression, but not in those who were treated only with further thalidomide or older cytotoxic agents [17]. The lack of a survival advantage in several of the thalidomide-maintenance studies has largely been attributed to a compromised survival after subsequent salvage treatment in the thalidomide arm. This was found in the first report of the Arkansas trial [14], as well as in the HOVON-50 [16] and NCIC trials [18], but has not been reported in others. This discrepancy may in part reflect the heterogeneity of therapy administered after myeloma recurrence, as treatment was not mandated by the trial and not all jurisdictions had uniform access to the most effective novel agents, bortezomib and lenalidomide, to offer to relapsed patients during the study period. The importance of optimal postrelapse therapy was emphasized by the MRC IX analysis described above, in which a survival benefit of thalidomide was contingent on the availability of alternative novel agents at progression [17]. On the other hand, the NCIC trial examined the availability of alternative novel agents at disease progression, and found similar access to lenalidomide and bortezomib in both arms of the study; the survival was still not significantly improved in the thalidomide arm, although it was marginally longer (hazard ratio compared with observation: 1.29; 95% CI: 0.89–1.88; p= 0.188) [18].

Since myeloma patients experience longer survival with more effective approaches, the risk of late complications of therapy, particularly second malignancies, needs to be considered. This issue had received little attention until the recent reports of second cancers after lenalidomide maintenance appeared, as discussed below. There is minimal information available regarding the risk of second malignancies in patients treated with other agents, such thalidomide, after ASCT. However, Barlogie *et al*. noted a 5-year cumulative incidence of 4% for secondary myelodysplastic syndrome (MDS)-associated cytogenetic abnormalities in both arms of the Total Therapy 2 trial, in which patients were randomized to receive maintenance with interferon plus dexamethasone, with or without the addition of thalidomide after tandem transplants [20]. In the NCIC trial of thalidomide and prednisone versus observation alone after a single ASCT, fatal second cancers occurred in only one of 166 (0.6%) of thalidomide patients versus two of 166 patients (1.2%) in the observation arm [18]. No mention is made of secondary cancers in the other reviewed randomized trials of thalidomide.

One potential problem with assessing the incidence of late complications in randomized trials, particularly in those in which the control arm is observation or placebo only, is the lack of detailed follow-up after progressive myeloma has developed, since these patients may be removed from the study and followed only for survival rather than toxicity. Therefore, the occurrence of second cancers may be underestimated, whereas those patients in the arm treated with immunomodulatory derivatives, who remain in remission longer, will be more carefully and frequently evaluated for late complications.

■ Lenalidomide

The oral immunomodulatory derivative lenalidomide has a more potent antimyeloma effect and is better tolerated than thalidomide. It lacks the sedation, constipation and peripheral neuropathy effects that often accompany thalidomide use. However, it is associated with potential myelosuppression and increased risk of VTE when used in combination with other agents. Two Phase III trials have recently reported the outcome of patients given lenalidomide as a single agent after ASCT (Table 2) [21,22]. In the IFM trial, patients ≤65 years of age with disease stabilization were randomized within 6 months post-ASCT to maintenance lenalidomide 10–15 mg/day versus placebo; all patients first received two cycles of full-dose lenalidomide 'consolidation' (25 mg) before the assigned treatment. In the US Cancer and Leukemia Group B (CALGB) trial, patients ≤70 years of age without disease progression on days 90–100 post-ASCT were randomized to either the maintenance dose of lenalidomide versus placebo [21,22]. Many patients in these trials had received induction therapy with more modern regimens (Table 2). In both trials, lenalidomide was given until progression. The findings were similar in that

Table 2. Phase III trials of lenalidomide maintenance after autologous stem cell transplant.

Author, year (trial name)	Patients (n)	Pre-ASCT induction	Number of ASCT(s)	PFS/TTP		Overall survival at 3 years (%)	Ref.
				Median PFS/TTP (months)	Overall PFS/TTP at 3 years (%)		
Attal *et al.*, 2010 (IFM 2005–02)	614	VAD or BD	1 or 2	Lenalidomide: 42 Observation: 24	Lenalidomide: 60† Observation: 33	Lenalidomide: 81 Observation: 81	[21]
McCarthy *et al.*, 2010 (CALBG 100104)	568	Lenalidomide: 32% Bortezomib: 42% Thalidomide: 16%	1	Lenalidomide: 42.3 Observation: 21.8	Lenalidomide: ~50† Observation: ~25	Lenalidomide: ~80 Observation: ~80	[22]

†Statistically significant.

ASCT: Autologous stem cell transplant; BD: Bortezomib plus dexamethasone; PFS: Progression-free survival; TTP: Time to progression; VAD: Vincristine, doxorubicin and dexamethasone.

the median PFS/TTP was significantly longer with lenalidomide compared with the placebo, namely an unprecedented median of 42 months in the lenalidomide arm in each trial, although this advantage did not confer a survival benefit. Of note, however, the CALGB trial was unblinded after the second analysis by the Data Safety and Monitoring Board to allow the control patients to crossover to open-label lenalidomide, an event which complicates the interpretation of any survival advantage.

The primary toxicities with lenalidomide were neutropenia and thrombocytopenia, as expected, with a modest increase in infections, including febrile neutropenia. In the most recent analysis, 2% of patients in the IFM trial and 13% in the US study discontinued the drug due to toxicity, compared with 4 and 6%, respectively, in the placebo arms **(Table 3)**. The incidences of peripheral neuropathy and VTE were very low.

One unexpected finding in these trials that was presented at the 2010 American Society of Hematology meeting, was the possible increase in the number of secondary malignancies, including secondary MDS and acute myelogenous leukemia. In total, 15 out of 231 (6.4%) patients treated with lenalidomide versus six out of 229 (2.6%) patients treated with placebo in the CALGB trial, and 16 out of 307 (5.2%) versus three out of 307 (0.9%), respectively, in the IFM study, exhibited secondary malignancies. These numbers are preliminary and should be treated with caution at this point. It should also be noted that the some of secondary cancers in the French study were only basal cell skin cancers, which are typically innocuous, and some of the CALGB patients were diagnosed with a secondary cancer after randomization but before actually commencing maintenance lenalidomide.

Although the overall incidence is relatively low, these observations raise the question of whether continuous immunosuppression with a potent immunomodulatory derivative may predispose to the development of other cancers, analogous to the effect of the antirejection drugs used for immunosuppression in organ transplantation and/or other medical conditions [23]. Alternatively, lenalidomide could exert a direct carcinogenic effect, or, lastly, the longer survival of myeloma patients diagnosed and treated in the modern era may simply allow the leukemogenic or carcinogenic effects of prior cytotoxic therapy to emerge. The latter explanation is analogous to the explanation of the findings when alkylating agent-based chemotherapy such as nitrogen mustard, vincristine, procarbazine and prednisone, particularly when given with radiotherapy, was administered to Hodgkin's disease patients in earlier decades [24]. A final and accurate determination of the risk of secondary malignancies is awaited, since

Table 3. Toxicity of lenalidomide maintenance after autologous stem cell transplantation.

Toxicity	IFM 2005–02 (%) [20]		CALGB 100104 (%) [21]	
	Lenalidomide	Placebo	Lenalidomide	Placebo
Neutropenia	31	6	42	7
Thrombocytopenia	8	3	12	6
Febrile neutropenia	8	4	7	2
Documented infection	8	4	7	2
Discontinuation of study drug	6	4	13	2
Secondary malignancy	6.8	1.6	6.5	2.6

CALGB: Cancer and Leukemia Group B; IFM: Intergroupe Francophone Myelome.

antimyeloma benefit of lenalidomide maintenance is considerable. Until the factors predisposing to secondary cancers have been defined, some groups have proposed that the duration of lenalidomide maintenance be limited to 1 or 2 years.

Another potential concern regarding the routine use of lenalidomide maintenance relates to the treatment options available when disease progression occurs. So far, no reports have been published evaluating the results when the lenalidomide dose is increased and dexamethasone is added at the time of relapse, although such an approach would clearly increase therapeutic choices once low-dose lenalidomide becomes ineffective. Available data, although limited, suggest that thalidomide may not be effective after resistance to lenalidomide develops [25,26], so relapsed treatment would be potentially limited to only bortezomib-based therapy and clinical trials using investigational agents.

In summary, these two trials are the first to convincingly show that the median TTP after ASCT can be extended to over 3 years, specifically to 3.5 years. This result was observed when lenalidomide was given after either a single or tandem transplant. However, to date, no survival advantage has been realized, and the final determination of benefit will depend on long-term outcome and toxicity considerations, the development of further novel agents effective for myeloma progressing on this highly efficacious immunomodulatory derivative and the identification of subgroups most likely to benefit from maintenance.

■ Bortezomib

Only two Phase III trials of bortezomib-maintenance therapy have been reported in the setting of ASCT. The Nordic Myeloma Study Group has conducted a randomized Phase III trial of post-transplant bortezomib, and preliminary results were reported by Mellqvist *et al.* in 2009 [27]. They termed post-transplant bortezomib consolidation therapy, rather than maintenance therapy, and it was given in the usual biweekly 21-day schedule for three cycles followed by a weekly program on days 1, 8 and 15 of a 28-day cycle for four more cycles in the study arm. The control arm received no therapy. Induction therapy was not specified, patients could have undergone one or two prior autotransplants, and randomization occurred 3 months post-ASCT. Dose reductions of bortezomib were needed in 21% of patients, with ≥grade 3 neutropenia noted in 22%, thrombocytopenia in 9%, sensory neuropathy in 3% and neurologic pain in 5%. At 6 months after randomization, the rate of CR/near complete remission (nCR) increased from 23 to 54% in the bortezomib arm, compared with 21–35% in the control arm ($p < 0.005$), while significantly fewer relapses were observed in the bortezomib group [27]. So far, no data regarding PFS or OS is available.

The second trial, the HOVON 65/GMMG-HD4 study, compared two approaches: VAD induction, ASCT and low-dose thalidomide 50 mg/day for 2 years (arm A) with bortezomib, doxorubicin and dexamethasone (PAD) induction, ASCT and then bortezomib given every 2 weeks for 2 years (arm B). As in the Nordic Myeloma Study Group trial, one or two autotransplants were allowed as per institutional policy. Both maintenance approaches increased response rates after ASCT, but myeloma responses were significantly higher at every time point of the study in arm B. The best response included CR/nCR in 49%, ≥very good partial remission in 76% and ≥PR in 91% of bortezomib-treated patients compared with 34, 55 and 83% of those in arm A, respectively. The toxicity profile of maintenance bortezomib compared favorably with maintenance thalidomide, with less grade 2 (26 vs 14%) and grade 3–4 (15 vs 9%) peripheral neuropathy. Importantly, both the PFS and OS rates were significantly better in the PAD arm (3-year PFS: 48 vs 42% and OS: 78 vs 71%). Patients with high-risk cytogenetic, increased serum creatinine and with a high International Staging System stage derived particular benefit from the inclusion of bortezomib. Despite the better outcomes in patients with t(4;14) and del 17p in the PAD plus bortezomib maintenance arm, the results were still inferior to those in patients lacking these adverse features: the 3-year

PFS for t(4;14) patients was 32% versus 22% for the PAD-bortezomib group and VAD-thalidomide group, respectively. For del 17p, the 3-year PFS was 27% versus 16% in the two therapeutic arms, respectively. In contrast, the 3-year PFS was 48% for all patients treated with PAD plus bortezomib and 42% for those receiving thalidomide, adriamycin and dexamethasone plus thalidomide [28].

Despite the efficacy of this agent, it has the disadvantages of intravenous administration and the risk of treatment-emergent peripheral neuropathy. The future use of subcutaneous bortezomib [29], as well as the intermittent dose schedules used in maintenance, may both decrease neurotoxicity and mitigate the inconvenience of intravenous administration.

It should be mentioned that the contribution of maintenance therapy may be difficult to determine in trials designed to evaluate an entire transplant approach in which the induction and post-ASCT regimens are specified, such as in the HOVON studies cited above. A similar situation pertains when highly effective induction therapy, which contains agents such as bortezomib and/or lenalidomide, is given, since the induction regimen itself may improve the TTP, PFS and OS independent of post-ASCT maintenance therapy [30].

The consistent observation that the administration of effective antimyeloma agents prolongs response duration in myeloma is not surprising. However, these agents are costly and associated with potential toxicity, and the question arises of whether deferring their use until the time of disease progression would achieve the same survival advantage but restrict drug use to those who definitely warrant therapy. As an example, one older study found that a strategy of ASCT delayed until the time of first progression produced a similar OS to the use of transplant at diagnosis. Although, the time without symptoms, treatment, and treatment toxicity (TWiSTT) was less favorable with the deferred approach [31]. To address the question of the optimal time post-ASCT in which novel agents should be introduced, Phase III trials would need to compare the use of the agent as maintenance therapy versus its mandated use at the time of progression. Such studies would be problematic, as they would require prolonged follow-up in a rapidly evolving field, characterized by the availability of even newer agents and regimens. Also, such a trial would have less appeal in the high-risk subgroups, in which novel agents have already been shown to extended PFS and OS to some extent after ASCT [28].

Consolidation therapy after ASCT

The term consolidation has been introduced to describe relatively intensive, short-term, post-ASCT therapy, and two recent myeloma trials have integrated such an approach – the IFM-2005–02 trial discussed above, using single agent lenalidomide for 2 months, and the Gruppo Italiano Malattie e Matologiche dell'Adulto (GIMEMA) Italian Myeloma Network trial. In the latter study, patients randomly were assigned to three induction cycles of bortezomib, thalidomide and dexamethasone (VTD) or thalidomide and dexamethasone (TD), followed by tandem ASCT, and two cycles of consolidation with the same regimen utilized in induction. Dexamethasone maintenance was then given until progression. The VTD arm had a significantly higher complete or near CR and 3-year PFS rates (68 vs 56%; p = 0.0057); OS was comparable in the two groups, 86 and 84%, respectively. Multivariate analysis identified a low β-2 microglobulin, absence of t(4;14) with or without del 17p, treatment on the VTD arm and achievement of CR/nCR as significant favorable factors for PFS [32]. The concept of consolidation therapy in myeloma will be more fully evaluated in the ongoing North American Clinical Trials Network trial. In this trial, all patients undergo an initial ASCT and are then subsequently randomized to proceed directly to lenalidomide maintenance versus a second ASCT followed by lenalidomide maintenance versus consolidation with bortezomib, lenalidomide and dexamethasone (VRD) followed by lenalidomide maintenance.

Maintenance therapy in non-ASCT patients

Until recently, oral melphalan and prednisone (MP) given for 6–12 cycles to achieve plateau phase was the standard therapy for older myeloma patients. More prolonged administration of melphalan did not improve survival, and toxicity is particularly high with this drug. Instead, the standard of care became to reinstitute melphalan at the time of disease progression. With the advent of novel agents, two general approaches have evolved for the management of elderly patients: the addition of one of the newer drugs (thalidomide, bortezomib or lenalidomide) to the MP backbone (with or without maintenance therapy with novel agents) or the continuous administration of an immunomodulatory derivative alone (usually lenalidomide) and dexamethasone without a treatment hiatus. As discussed in more detail below, these strategies have in general extended the median TTP from the range of 12–15 months with MP, to approximately 24 months [33].

Thalidomide was the first novel agent to be combined with MP, and there are five randomized trials comparing MP with melphalan, prednisone and thalidomide (MPT) that have now been published [34–39]. These trials utilized different doses and durations of melphalan and thalidomide, and three involved continuation of thalidomide as single-agent maintenance therapy after completion of MPT (Table 4) [34,37–39].

Table 4. Randomized trials of melphalan and prednisone versus melphalan, prednisone and thalidomide in elderly myeloma patients.

Author (year)	Patients (n)	Regimens (induction-maintenance)	Maintenance duration	Initial dose of thalidomide (mg/day)	Overall response rate (CR/nCR; %)	Median PFS/EFS (months)	Median overall survival (months)	Ref.
Palumbo *et al.* (2006, 2008)	331	MPT-T MP	Until progression	100	76 (28)† 48 (7)	21.8† 14.5	45 47.6	[34,35]
Facon *et al.* (2007)		MPT MP	None	≤400	76 (18)† (2)	27.5† 17.8	51.6† 33.2.	[36]
Hulin *et al.* (2009)	229	MPT MP	None	100	62 (7)† 31 (1)	24.1† 18.5	44† 29	[37]
Wijermans *et al.* (2010)	333	MPT-T MP	Until progression	200 –	66† 45	13† 9	40† 30	[38]
Waage *et al.* (2010)	363	MPT-T MP	Until progression	200–400 –	57 (13)† 40 (4)	15 14	29 32	[39]

†Statistically significant.

CR: Complete remission; EFS: Event-free survival; M: Melphalan; nCR: Near complete remission; P: Prednisone; PFS: Progression-free survival; T: Thalidomide.

All showed higher response rates with MPT. Four of these trials, including two with thalidomide maintenance, reported a significant improvement in PFS in the thalidomide arm, but only three observed a significant survival benefit with this agent [36–38]. Maintenance thalidomide was used in only one of the studies with a survival benefit, the HOVON-49 study by Wijermans *et al.*, so conclusions regarding the necessity of this approach to prolong PFS or OS cannot be made with certainty [38].

Single-agent lenalidomide was given as maintenance in another study by Palumbo *et al.*, following induction with MPR (Table 5) [40]. This study compared three treatment arms: MP alone for nine cycles, MP plus lenalidomide (MPR) for nine cycles and MPR for nine cycles followed by lenalidomide maintenance until myeloma progression (MPR-R). The findings highlight the contribution of lenalidomide maintenance, as the median PFS was 13, 14 and 31 months, in the three arms, respectively [40]. To date, no differences in OS have emerged. Grade 4 neutropenia was observed in 8, 32 and 36%, respectively, but febrile neutropenia was rare. Secondary solid malignancies were noted in 1% of patients treated with MP, versus 3% with MPR and <1% with MPR-R. The incidence of MDS was also low at 0, 1 and <1% in these groups, respectively, and acute myelogenous leukemia was diagnosed in 0, 1 and 2%, respectively.

Finally, maintenance therapy with novel agents has been evaluated after four melphalan- and bortezomib-containing induction regimens in two trials (Table 5). Neither of these studies evaluated bortezomib alone as maintenance therapy, but rather involved maintenance with either bortezomib plus thalidomide (VT) – in the trial by Mateos *et al.* [41] and third study by Palumbo *et al.* [42] – and bortezomib plus prednisone (VP) – in the Mateos trial. As expected, patients who continued maintenance with novel agent(s) after induction therapy demonstrated a longer PFS than those who discontinued therapy after induction. However, a survival benefit was not observed in the arms receiving maintenance therapy. The overall outcome of the VT maintenance trials mirrors that of the MPR-R results: PFS in elderly patients was extended to the longest median PFS reported to date (2.5 years) but without an identifiable survival benefit.

Of note, despite the more advanced age of patients, only 5% of patients receiving VP and 8% of those given VT in the Mateos trial discontinued the planned 3 years of maintenance therapy due to adverse events [41]. These data seem inconsistent with the short time that thalidomide, even at similar doses of 50 mg/day, was tolerated in younger individuals post-ASCT. Details regarding the duration of maintenance VT is not available from the Palumbo trial.

As in younger patients, given the expense and potential toxicity of maintenance therapy with novel agents, identification of patients most likely to benefit is a worthwhile endeavour. Mateos *et al.* explored the influence of high-risk cytogenetics (t[4;14], t[41;16] and del 17p) by FISH in 231 of the 260 patients in their trial. They noted that this subset of high-risk patients had a shorter PFS after the first randomization to induction therapy, as well as after the second randomization to maintenance VT or VP; specifically, their PFS after randomization to maintenance was 17 months versus 27 for standard risk patients (p = 0.001) with no difference between the two maintenance regimens [41]. Similarly,

Table 5. Results of maintenance therapy in elderly myeloma patients treated with lenalidomide or bortezomib regimens.

Author (year)	Patients (n)	Regimens (induction-maintenance)	Maintenance duration	Grade 3–4 adverse events (during maintenance; %)	Toxic deaths (%)	PFS/EFS median (months)	Overall survival	Ref.
Palumbo *et al.* (2010)	459	MPR-R MPR MP	Until progression	~7	N/A	31† 14 13	92–93% (at 1 year) 75–82% (at 2 years)	[40]
Mateos *et al.* (2010; PETHEMA)	290	VMP-VP MTP-VP VMP-VT MTP-VT	<3 years	2 (PN) 7 (PN)	1 1 (during maintenance)	32 24	74% for VMP-VP or VT (at 3 years) 65% for VTP-VP or VT (at 3 years)	[41]
Palumbo *et al.* (2010)	511	VMP VMPT + VT	2 years	– 8	4 3	27.3† 56% (at 3 years)	87% (at 3 years) 89% (at 3 years)	[42]

†Statistically significant.

EFS: Event-free survival; Heme: Hematological; M: Melphalan; N/A: Not available; P: Prednisone; PETHEMA: Programa para el Tratamiento de Hemopatías Malignas; PFS: Progression-free survival; PN: Pripheral neuropathy; R: Lenalidomide; T: Thalidomide; V: Bortezomib.

in the VMPT-VT versus VMP trial of Palumbo *et al.*, VMPT-VT did not significantly improve PFS in patients who had high-risk cytogenetics, ISS stage 3 disease or who were male [42]. Subset analysis is not available yet for the MPR-R trial in which lenalidomide was utilized.

In contrast to the approach for younger patients, none of these studies in elderly patients have evaluated the use of the novel agent introduced for the first time after induction with MP alone. Instead, novel agents were integrated into the induction regimen and subsequently continued as maintenance therapy. Introduction of the novel agent only after completion of the induction phase would reduce the costs of therapy, but there is concern that use of less effective initial antimyeloma therapy would undermine the results, and fewer patients would survive without progression to experience the benefit of novel drugs given as maintenance.

Summary & conclusion

Maintenance therapy with each of the three novel agents has been shown to extend PFS after ASCT in randomized trials. Although a survival benefit has been noted in some of the trials of thalidomide maintenance, the toxicity is quite bothersome with this drug. On the other hand, use of thalidomide after ASCT leaves two other effective regimens, lenalidomide and/or bortezomib, available to offer at relapse. Lenalidomide avoids most of the unpleasant side effects of thalidomide and clearly extends PFS, but a survival benefit has not been observed to date in the two Phase III trials, likely in part due to the efficacy of this agent as a second-line therapy when combined with dexamethasone [43]. Outstanding questions relate to an accurate estimate of the risk of secondary malignancies, as well as the best management and anticipated survival after myeloma has progressed on low doses of lenalidomide. Less information is available on the use of bortezomib maintenance after ASCT. However, the results of the HOVON-65/GMMG-HD4 trial, in which this agent was given both before and after ASCT, are encouraging and represent one of the few trials in which a survival advantage has been reported in the arm giving maintenance therapy with a novel agent. The three-arm randomized Clinical Trials Network trial is designed to evaluate the relative contributions of a second planned ASCT or triple-agent consolidation therapy to maintenance lenalidomide.

The use of these agents for maintenance therapy in elderly patients has also demonstrated benefit in terms of PFS. However, no clear survival benefit has been apparent, and it is uncertain whether prolonged therapy in a more fragile population will become a standard of care. Identification of the patients most likely to benefit from maintenance therapy is desirable for all patient groups.

Executive summary

- The identification of more effective antimyeloma agents has led to a renewed interest in developing maintenance strategies, given after induction therapy to patients with nonprogressive disease, to prolong survival.
- Each of the novel agents, thalidomide, bortezomib and lenalidomide, have been evaluated as maintenance therapy in both younger transplant-eligible and older transplant-ineligible myeloma patients in Phase III trials.

Maintenance therapy after autologous stem cell transplantation

- Seven randomized trials of thalidomide maintenance, using different doses and regimens, have been reported. Progression-free survival is significantly prolonged with this agent, with a variable effect on overall survival.
- Thalidomide maintenance is limited by the toxicities associated with this drug, particularly peripheral neuropathy.
- The newer immunomodulatory derivative lenalidomide is better tolerated as a maintenance agent, and two Phase III trials report an excellent progression-free survival of 42 months when low doses are used after autologous stem cell transplantation (ASCT). Longer follow-up will be needed to assess the survival benefit and assess the risks of prolonged therapy with this agent, as secondary malignancies have been noted in these trials.
- Intravenous bortezomib has been evaluated in two randomized trials. The Hemato-Oncologie voor Volwassenen Nederland (HOVON)-65 trial found that bortezomib given as part of induction therapy, and again as maintenance therapy every 2 weeks after ASCT, prolonged progression-free and overall survival compared to older induction therapy and thalidomide maintenance after ASCT. The second trial administered more frequent doses of bortezomib after ASCT and has demonstrated encouraging preliminary results.
- Consolidation therapy is a term referring to more intensive therapy given post-ASCT, and may be followed by lower-dose maintenance therapy with the same or alternative drugs.

Maintenance therapy in non-ASCT patients

- A number of trials have evaluated the addition of novel agents to the oral melphalan and prednisone regimen, which was the mainstay of myeloma therapy for several decades.
- The use of thalidomide, borezomib plus thalidomide, and lenalidomide after induction has been observed to significantly prolong progression-free survival compared to melphalan and prednisone alone. However, in each of these trials, patients in the maintenance also received novel agents as part of the induction regimen, in addition to melphalan and prednisone. Thus, the contribution of maintenance therapy alone to the improved results is difficult to determine.
- To date, the use of maintenance therapy in elderly patients has not yet conferred a survival advantage in the Phase III trials.

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