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Role of Consolidation/Maintenance Therapy in Multiple Myeloma

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Abstract

Multiple myeloma is a highly treatable but still incurable malignancy. Many advances have been made in the treatment of this disease, particularly thanks to the introduction of the immunomodulatory drugs, thalidomide and lenalidomide, and the proteasome inhibitor, bortezomib. Different trials have supported the inclusion of consolidation/maintenance therapy as part of a sequential approach after induction therapy and transplantation (for eligible patients). This therapeutic strategy aims to maintain or even improve response obtained after induction, and ultimately to prolong survival. The role of consolidation/maintenance therapy has been assessed in patients eligible and ineligible for transplantation, and proved to be a valuable option. The improved outcome reported with consolidation/maintenance therapy should, however, be balanced against the toxicity profile of such an approach. Prolonged exposure to a drug might in fact increase toxicity, and prompt management of adverse events is necessary.

Introduction

Multiple myeloma is the second most common hematologic malignancy worldwide. It accounted for 20,580 new cancer cases in the United States in 2009, including 11,680 cases in men, 8900 cases in women, and 10,580 deaths overall. Multiple myeloma is mainly a disease of the elderly; the median age at diagnosis is 70 years, with 37% of patients younger than 65 years of age, 26% aged 65 to 74 years, and 37% older than 75 years.[1]

For the past 10 years, the median overall survival (OS) for patients with multiple myeloma has considerably increased thanks to the use of autologous stem cell transplantation (ASCT) and the introduction of the immunomodulatory drugs, thalidomide and lenalidomide, and the proteasome inhibitor, bortezomib.[2 and 3] In particular, in a large analysis of 2981 patients with newly diagnosed myeloma, patients diagnosed in the past decade had a 50% improvement in OS compared with those who had been diagnosed earlier (44.8 vs. 29.9 months; $P < .001$). [2] Today, new and various treatment options including novel agents are now available for transplant-eligible and -ineligible patients.

Consolidation (2-4 cycles of combination therapies) and maintenance (continuous therapy, usually with single agents, until disease progression) are commonly used in clinical practice to improve outcome after induction therapy.[4] Although many trials support the use of consolidation/maintenance to maintain response achieved after induction therapy and to improve patient survival, prolonged exposure to new drugs might increase toxicities. Therefore, appropriate management of treatment-related side effects is crucial (Table 1).

Table 1. Toxicities Associated With New Drugs and Related Management

Toxicity	Drug	Action	Dose Adjustment
Hematologic			
Neutropenia	R, V	G-CSF until neutrophil recovery in case of uncomplicated Grade 4 AE or Grade 2-3 AEs complicated by fever or infection	25% to 50% drug reduction
Thrombocytopenia	R, V	Platelet transfusion if the event reaches Grade 4	25% to 50% drug reduction
Anemia	R, V	Erythropoietin or darbepoietin if hemoglobin level is $\leq$ 10 g/dL	25% to 50% drug reduction
Nonhematologic			
Infection	T, R, V	Trimetoprin-cotrimoxazole for *Pneumocystis carinii* prophylaxis during high-dose dexamethasone. Acyclovir or valacyclovir for HVZ prophylaxis during bortezomib-containing therapy	25% to 50% drug reduction
Neuropathy	T, V	Neurological assessment before and during treatment. Immediate dose reduction is recommended	T: 50% reduction for Grade 2 neuropathy; discontinuation for Grade 3; resume at a decreased dose if neuropathy improves to Grade 1; V: 25%-50% reduction for Grade 1 with pain or Grade 2 peripheral neuropathy; dose interruption until peripheral neuropathy resolves to Grade 1 or better with restart at 50% dose reduction for Grade 2 with pain or Grade 3 peripheral neuropathy; treatment discontinuation forGrade 4 peripheral neuropathy
Thrombosis	T, R	Aspirin 100-325 mg if no or 1 individual/myeloma thrombotic risk factor is present. LMWH or full dose warfarin if there are 2 or more individual/myeloma risk factors and in all patients with thalidomide-related risk factors	Stop drug temporarily, use full anticoagulation, then resume treatment
Skin disorder	T, R	Steroids and antihistamines	Interruption in case of Grade 3-4 AE; 50% reduction in case of Grade 2 AE
Gastrointestinal disorder	T, R, V	Appropriate diet, laxatives, physical exercise, hydration, antidiarrhetics	Interruption in case of Grade 3-4 AE; 50% reduction in case of Grade 2 AE
Renal impairment	R	Correct precipitant factors (dehydration, hypercalcemia, hyperuricemia, urinary infections, and concomitant use of nephrotoxic drugs)	Reductions based on creatinine clearance: • 30-60 mL/min → R: 10 mg/d; • < 30 mL/min and no dialysis needed → R: 15 mg every other day; • < 30 mL/min with dialysis required → R: 5 mg on dialysis days, after dialysis

Abbreviations: AE = adverse event; G-CSF = granulocyte-colony stimulating factor; HVZ = herpes-varicella-zoster; LMWH = low-molecular-weight heparin; R = lenalidomide; T = thalidomide; V = bortezomib.

Consolidation/Maintenance Approaches in the Era of Novel Agents

The high efficacy of thalidomide, lenalidomide, and bortezomib, both upfront and at relapse, has provided the basis to evaluate these agents as consolidation/maintenance therapy. The major objective is to maintain outcome after induction, prolong duration of response, and ultimately prolong survival. The first maintenance therapies date back to 1975 and simply consisted of continuing chemotherapy after successful induction treatment with melphalan-prednisone (MP).[5, 6 and 7] Response duration was prolonged, but no survival benefit was detected, and this approach was no longer used. Single-agent interferon was also assessed as maintenance therapy.[8] Two metaanalyses reported a survival improvement of approximately 6 months with continuous interferon administration,[9 and 10] however, studies led to controversial and conflicting results, and this approach was not pursued further because of its toxicity profile.

To date, different trials assessing the role of consolidation/maintenance therapy with novel agents have been performed, and results are promising.

Young Patients

For patients younger than 65 years, different effective treatment options including novel agents are available. These patients generally receive full-dose induction treatment followed by high-dose melphalan (melphalan 200 mg/m^2) and single or double ASCT. Various studies assessed consolidation/maintenance approaches after induction and transplantation in these patients.

Thalidomide-Based Strategies

Large phase III studies have evaluated the role of continuous thalidomide as either a single agent or in combination with glucocorticoids, and only 3 of 5 trials detected an OS improvement (Table 2).[11, 12, 13, 14, 15, 16, 17 and 18] Initial thalidomide doses ranged from 50 mg to 400 mg in the 5 studies. In the study conducted by the French group, thalidomide was found to improve the best response achieved after randomization (P < .001). The 3-year event-free survival (EFS) was 52% for the maintenance arm compared with 37% for no maintenance (P < .009). The respective 4-year OS rates were 87% and 75% (P < .04). Drug-related toxicity led to thalidomide discontinuation in 78 patients (39%), and peripheral neuropathy was the major cause. [11] In the Total Therapy 2 study, the addition of thalidomide at induction and at maintenance resulted in superior median EFS (6 years vs. 4 years; P = .001). The 8-year OS estimate was 57% among the 323 patients randomized to thalidomide compared with 44% for the 345 in the control arm (P = .09). [12] In the Australian study, thalidomide was administered as consolidation therapy after ASCT. Thalidomide was given for 12 months in addition to continuous prednisolone. This approach improved progression-free survival (PFS; at 3 years, 42% vs. 23%; P < .001) and OS (at 3 years, 86% vs. 75%; P = .004) compared with prednisolone alone. In particular, the PFS enhancement was independent of response achieved after ASCT. Thalidomide was associated with an increased incidence of Grade 3 to 4 peripheral neuropathy (10% for the thalidomide arm vs. 0% for the control arm; P < .001) but there were no differences between arms for thromboembolic events. [13] Another study assessed thalidomide maintenance given at 50 mg in comparison with interferon alpha maintenance. Although thalidomide improved the response before and after ASCT, prolonged EFS and PFS, this benefit did not translate into a statistically significant longer survival. Thalidomide maintenance was stopped in 33% of patients because of toxicity, with 9% of patients experiencing a Grade 3 neuropathy. [14] In the study conducted by Morgan and colleagues, transplant-eligible patients (intensive pathway) received induction with either CTD (cyclophosphamide-thalidomide-dexamethasone) or CVAD (cyclophosphamide-vincristine-adriamycin-dexamethasone). Patients were then randomized for maintenance therapy with thalidomide or placebo. Median PFS was longer for patients receiving thalidomide maintenance (30 vs. 23 months; P = .003), with no significant difference in OS (3-year OS, 75% vs. 80%; P = .26). Of note, patients with adverse interphase fluorescence in situ hybridization did not report either a PFS or OS advantage using thalidomide maintenance. Toxicities were inevitably higher for patients receiving thalidomide maintenance compared with those who did not, in particular 52% of patients (intensive and nonintensive pathways) interrupted maintenance because of treatment-related toxicity. [15]

Table 2. Main Maintenance Strategies for Young Patients

Novel Agent	Schedule	CR	PFS/TTP/EFS	OS	Reference
Thalidomide					
	Pa: 90 mg at 4-week intervals; T: 400 mg/d, reduced to maximum 50 mg/d for treatment-related toxicity	NR	52% at 36 months	87% at 48 months	Attal et al[11]
	T: 400 mg/d until relapse	50%[a]	50% at 72 months	57% at 96 months	Barlogie et al[12]
	T: 100 mg/d increased to 200 mg/d if tolerated; Po: 50 mg qod	NR	42% at 36 months	86% at 36 months	Spencer et al[13]
	T: 50 mg/d until relapse	31%	50% at 34 months	50% at 73 months	Lokhorst et al[14]
	T: 50 mg/d increased to 100 mg/d after 4 weeks	NR	50% at 30 months	75% at 36 months	Morgan et al[15]
Lenalidomide					
	R: 10-15 mg on days 1-21 until disease progression	NR	50% at 46 months	88% at 36 months	McCarthy et al[16]
	R: 10-15 mg on days 1-21 until disease progression	29%	50% at 41 months	73% at 48 months	Attal et al[17]
Bortezomib					
	V: 1.3 mg/m^2 intravenously every 2 weeks for 2 years	36%	50% at 35 months	61% at 60 months	Sonneveld et al[18]

Abbreviations: CR = complete response; EFS = event-free survival; OS = overall survival; Pa = pamidronate; PFS = progression-free survival; Po = prednisolone; qod, every other day; R = lenalidomide; T = thalidomide; TTP = time to progression; V = bortezomib.
[a]Percentage at 3 years.

Recently, the role of VTD (bortezomib-thalidomide-dexamethasone) vs. TD (thalidomide-dexamethasone) consolidation after double ASCT has been assessed. After 2 cycles of treatment, VTD consolidation increased the complete response (CR)/near CR rate from 63% to 73%, but 3-year PFS was only marginally improved (60% vs. 48%; P = .042). [19] Grade 2 to 3 peripheral neuropathy (8.1% vs. 2.4%) was higher in patients receiving VTD than in those treated with TD, although no other significant differences between treatment groups in the overall frequency of toxicities or the frequency of Grade 3 to 4 adverse events were seen.

Because of the increased risk of neuropathy and treatment discontinuation with prolonged exposure to thalidomide, lenalidomide might be preferred as maintenance therapy.

Lenalidomide-Based Strategies

Two randomized phase 3 studies have assessed the role of lenalidomide maintenance compared with no maintenance after ASCT.[16 and 17]

In the CALGB study,[16] patients received maintenance therapy approximately 100 days after transplantation, with no previous consolidation treatment. Median time to progression (TTP) was significantly improved in patients receiving maintenance (46 vs. 27 months; P < .001), and an OS enhancement was detected as well (3-year OS: 88% vs. 80%). Toxicities were higher with lenalidomide, particularly Grade 3 neutropenia (32% vs. 12%; P < .001). Second primary malignancies (SPMs) occurred in 8% and 3% of patients in the 2 treatment arms, respectively.

In the IFM 05-02 study,[17] patients received 2 months of consolidation therapy within 100 days of ASCT (lenalidomide at 25 mg on days 1-21 for two 28-day cycles) and were subsequently randomized for maintenance with lenalidomide vs. placebo. Median TTP was longer for the lenalidomide group (41 vs. 23 months; P < .001), although there was no difference in terms of OS

(3-year OS: 80% vs. 88%; P = .29). The rate of Grade 3 or 4 peripheral neuropathy was similar in the 2 study groups, and thromboembolic events were more frequent in patients taking lenalidomide (6% vs. 2%; P = .01). The incidence of SPMs was 8% in the lenalidomide group and 4% in the placebo group.

Despite the recent concerns about the risk of SPMs with prolonged exposure to lenalidomide, the benefits associated with lenalidomide maintenance seem to outweigh the increased risk of SPMs and thus this approach remains a valuable option.

Bortezomib-Based Strategies

Bortezomib is another attractive option in this setting, although further investigation as maintenance therapy is needed. Particularly, lower doses should be used to decrease the risk of peripheral neuropathy.

The HOVON-65/GMMG-HD4 study has recently compared the combination PAD (bortezomib-doxorubicin-dexamethasone) followed by bortezomib maintenance for 2 years with VAD (vincristine-doxorubicin-dexamethasone) followed by thalidomide maintenance for 2 years.[18] After a median follow-up of 41 months, median PFS was 35 months for the PAD group and 28 months for the VAD group (P = .002). In patients with renal impairment, the bortezomib-based sequential approach improved PFS compared with VAD followed by ASCT and thalidomide maintenance, and PFS improved from 13 to 30 months (P = .004).

In a landmark analysis, superior outcome was reported with bortezomib maintenance, which led to longer PFS and OS. There was no difference in SPMs between the 2 treatment groups, thus showing that bortezomib does not increase the risk of SPMs.[18] However, these results should be interpreted with caution because no randomization for maintenance was planned, and patients assigned to bortezomib maintenance had already received this drug at induction. The better tolerability of bortezomib during maintenance and the lower discontinuation rate might explain the outcome advantage.

This study, and the other trials already described, underline the concept that the most appropriate therapy for young and transplant-eligible patients should consist of a sequential approach including induction with effective drug combinations followed by ASCT and subsequent consolidation/maintenance therapy.

Elderly Patients

Patients older than 65 years of age are usually not considered eligible for high-dose therapy followed by ASCT. For these patients, and for younger patients with comorbidities who would not tolerate ASCT, gentler approaches are needed. To date, the combinations VMP (bortezomib-MP) and MPT (MP-thalidomide) are considered the standard of care in this setting, and they have replaced the former standard MP.[20, 21 and 22] New drugs are being tested in these patients, and various trials have also assessed the role of consolidation/maintenance approaches for elderly patients.

Thalidomide-Based Strategies

Thalidomide is a favorable option for maintenance therapy in the elderly because it is administered orally. Still, prolonged exposure might cause neurotoxicity. Four studies have evaluated the role of continuous thalidomide after MPT induction (Table 3).[15, 23, 24, 25, 26, 27, 28, 29 and 30] In the Italian study,

thalidomide was given continuously at a dose of 100 mg/d. Median PFS was 25 months with thalidomide maintenance and 15 months with no maintenance (P < .001). Median OS was 47.6 months vs. 45 months (P = .79), respectively, with 10% and 1% of patients experiencing a neurologic toxicity. [23 and 24] In the Dutch study, maintenance consisted of 50 mg/d thalidomide. [25] Median EFS was 13 months with MPT vs. 9 months with MP alone (P < .001), and a borderline OS advantage favoring MPT followed by thalidomide maintenance was detected (40 vs. 31 months; P = .05). However, Grade 3 to 4 neurologic events were quite high in the thalidomide arm (23% vs. 4%). In the Nordic study, thalidomide was given at 200 mg/d until relapse. [26] Thalidomide did not significantly improved median PFS (15 vs. 14 months; P = .84), nor a significant OS difference between the 2 treatment arms (29 vs. 32 months; P = .16). Grade 3 to 4 peripheral neuropathy was detected in 6% of patients who received thalidomide and 1% of those who did not.

Table 3. Main Maintenance Strategies for Elderly Patients

Novel agent	Schedule	CR	PFS/TTP/EFS	OS	Reference
Thalidomide					
	T: 100 mg/d until relapse	16%	50% at 22 months	50% at 45 months	Palumbo et al [23,24]
	T: 50 mg/d until relapse	NR	50% at 13 months	50% at 40 months	Wijermans et al[25]
	T: 200 mg/d until progression	13%	50% at 15 months	50% at 29 months	Waage et al[26]
	T: 100 mg/d until relapse	9%	50% at 21 months	50% at 26 months	Beksac et al[27]
	T: 200 mg/d until progression or intolerance; I: 3 MU 3 times a week	NR	50% at 28 months	50% at 53 months	Ludwig et al[28]
	T: 50 mg/d increased to 100 mg/d after 4 cycles (if tolerated) until progression	NR	50% at 11 months	50% at 38 months	Morgan et al[15]
Lenalidomide					
	R: 10 mg on days 1-21 until disease progression	NR	50% at 31 months	70% at 36 months	Palumbo et al[29]
	R: 25 mg on days 1-21; P: 50 mg qod for four 28-day cycles followed by R: 25 mg on days 1-21 until disease progression	40%	69% at 24 months	86% at 24 months	Palumbo et al[30]
Bortezomib					
	V: 1.3 mg/m^2 twice weekly, on days 1, 4, 8, 11, every 3 months; P: 50 mg qod for up to 3 years	39%	50% at 32 months	50% at 60 months	Mateos et al[31]
	V: 1.3 mg/m^2 twice weekly, on days 1, 4, 8, 11, every 3 months; T: 50 mg/d for up to 3 years	46%	50% at 39 months	69% at 60 months	Mateos et al[31]
	V: 1.3 mg/m^2 every 14 days; T: 50 mg/d for 2 years	38%	56% at 36 months	89% at 36 months	Palumbo et al[32]

Abbreviations: CR = complete response; EFS = event-free survival; I = interferon α-2b; OS = overall survival; P = prednisone; PFS = progression-free survival; qod = every other day; R = lenalidomide; T = thalidomide; TTP = time to progression; V = bortezomib.

Two other studies assessed the effect of thalidomide maintenance after conventional therapy in patients not eligible for transplantation.[15 and 28] PFS was improved in both studies, but no OS advantage was seen, probably because of a slight increase in toxicity. In one trial,[28] patients were randomized to thalidomide-interferon or interferon alone maintenance after induction with either TD or MP. Thalidomide-interferon maintenance was associated with enhanced median PFS (27.7 vs. 13.2 months; P = .0068), no survival difference was seen between the 2 maintenance arms (52.6 vs. 51.4 months; P = .81). Toxicity was higher with thalidomide-interferon, with a Grade 3 to 4 neuropathy rate of 7% vs. 0% (P = .0015). In the Medical Research Council Myeloma IX trial, [15] patients ineligible for transplantation (nonintensive pathway) received MP or CTD attenuated and were then randomized to receive thalidomide maintenance or no maintenance. Thalidomide maintenance improved PFS (11 vs. 9 months; P = .014), and the advantage was particularly evident in those who received thalidomide also at induction. No significant OS difference was found (P = .995).

The trials described suggest that the optimal dose of thalidomide in elderly myeloma patients should be between 50 and 100 mg/d. To reduce peripheral neuropathy, thalidomide administration should not be excessively prolonged.[11] Thalidomide maintenance should be interrupted when > Grade 1 peripheral neuropathy occurs so that the patient's quality of life is not negatively affected. Despite the PFS advantage reported in these trials, longer follow-up is needed to detect a survival advantage with thalidomide maintenance.

Lenalidomide-Based Strategies

Similar to thalidomide, lenalidomide is a valuable option for maintenance in the elderly because of the oral administration.

Recently, a phase III study evaluated lenalidomide maintenance after MPR-R (melphalan-prednisone-lenalidomide) vs. no maintenance (MPR or MP inductions only).[29] A landmark analysis from the start of maintenance was performed and results indicated that lenalidomide maintenance after MPR significantly extended median PFS compared with MPR alone (26 vs. 7 months; $P < .001$). Yet, no clear survival advantage was noted with maintenance, and longer follow-up is needed. Grade 3 to 4 neutropenia was reported in 7% of patients receiving lenalidomide maintenance, and thrombocytopenia in 6%. SPMs were more frequent with MPR-R and MPR (7%) compared with MP (3%). However, the PFS benefit associated with lenalidomide maintenance outweighs the increased risk of SPMs.

A phase II study evaluated lenalidomide plus prednisone as consolidation therapy followed by lenalidomide alone as maintenance therapy, after PAD induction and reduced-intensity transplantation with melphalan 100 mg/m^2.[30] This sequential approach resulted in a 2-year PFS of 69% and a 2-year OS of 86%. Lenalidomide used in combination with prednisone as consolidation and used as single agent as maintenance significantly improved response achieved after induction, with CR rate increasing from 12% to 40%. Neutropenia remained the major toxicity, with a grade 3 to 4 event occurring in 16% of patients.

Data support the use of lenalidomide maintenance therapy in elderly patients with myeloma, despite the recent concerns about SPMs. In addition, the lack of neurologic toxicity, makes lenalidomide an appropriate option for continuous treatment in this setting.

Bortezomib-Based Strategies

The Spanish group assessed the effect of bortezomib maintenance therapy in combination with either thalidomide (VT) or prednisone (VP) after induction with VMP or bortezomib-thalidomide-prednisone.[31] The dose of bortezomib was 1.3 mg/m^2 on days 1, 4, 8, and 11 scheduled for 3 years. VT showed longer median PFS than VP (39 vs. 32 months), but this difference was not statistically significant; similarly, no significant difference in OS was seen between the 2 maintenance approaches. Peripheral neuropathy is the major toxicity associated with bortezomib, and was reported in 9% of VT patients and 3% of VP patients, although in most of the patients peripheral neuropathy had previously developed during induction therapy and worsened with maintenance.[31]

The role of VT maintenance was also evaluated after the 4-drug induction regimen, VMP plus thalidomide (VMPT-VT), in comparison with standard VMP with no maintenance.[32 and 33] Of note, in both treatment arms, the schedule of bortezomib was reduced from twice- to once-weekly administration to decrease neurologic toxicity.[34] During maintenance, bortezomib was administered at 1.3 mg/m^2 every 14 days, thalidomide at 50 mg/d for 2 years or until progression.[32 and 33] After a median duration of maintenance of 14.4 months, 45% of patients achieved a CR. The 1-year

landmark analysis of PFS in patients completing the 9 induction cycles showed a 2-year PFS of 63% in the VMPT-VT group and 40% in the VMP group, demonstrating that maintenance with VT reduced the risk of disease progression 51% (P = .0003). VT maintenance had also a favorable safety profile: 3% of patients experienced Grade 3 to 4 hematological toxicity, 5% Grade 3 to 4 peripheral neuropathy, and 7% discontinued because of adverse events. [33]

Another phase III study assessed bortezomib as single agent given continuously at the dose of 1.6 mg/m^2 twice weekly after induction with bortezomib-dexamethasone, VTD, or VMP.[35] Response after induction slightly improved, but toxicities were also higher, with a Grade 3 to 4 peripheral neuropathy rate of 5%.

The data presented show that bortezomib maintenance is feasible and effective in elderly patients, and a reduced dose should be adopted to reduce neurologic toxicity.

Conclusion

Maintenance therapy is an effective strategy to prolong remission duration and survival in young and elderly patients. In the era of novel agents, various maintenance approaches have been tested and were associated with a PFS advantage. In young patients, maintenance therapy for 2 years or lenalidomide or thalidomide until disease progression improves PFS. These new drugs proved to have a positive effect also on OS, although the IFM 05-02 did not detect a survival advantage with continuous lenalidomide. As single agents, thalidomide, lenalidomide, or bortezomib maintenance proved to be well tolerated, and they can be safely used as part of a sequential approach after induction and transplantation. In elderly patients, thalidomide maintenance is a valuable option after MPT, yet peripheral neuropathy remains a major drawback. Lenalidomide has the advantage of the lack of neurologic toxicity, and it is a valuable option after MPR induction. Bortezomib maintenance seems to be most beneficial when used with a reduced schedule to decrease peripheral neuropathy.

Overall, when choosing a consolidation/maintenance approach, physicians should carefully balance the potential benefits and risks associated with this strategy. Head-to-head comparisons are warranted to better guide physicians in the choice of the best consolidation/maintenance option. Future trials will also assess the role of second-generation novel agents, such as carfilzomib, pomalidomide, MLN 9708, elotuzumab, and bendamustine as maintenance therapy,[36] either alone or in combination.

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