

# Optimal maintenance and consolidation therapy for multiple myeloma in actual clinical practice

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Multiple myeloma is an incurable malignant plasma cell-originating cancer. Although its treatment outcomes have improved with the use of glucocorticoids, alkylating drugs, and novel agents, including proteasome inhibitors (bortezomib and carfilzomib) and immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide), relapse remains a serious problem. Strategies to improve outcomes following autologous stem cell transplantation and frontline treatments in non-transplant patients include consolidation to intensify therapy and improve the depth of response and maintenance therapy to achieve long-term disease control. Many clinical trials have reported increased progression-free and overall survival rates after consolidation and maintenance therapy. The role of consolidation/maintenance therapy has been assessed in patients eligible and ineligible for transplantation and is a valuable option in clinical trial settings. However, the decision to use consolidation and/or maintenance therapy needs to be guided by the individual patient situation in actual clinical practice. This review analyzes the currently available evidence from several reported clinical trials to determine the optimal consolidation and maintenance therapy in clinical practice.

**Keywords:** Multiple myeloma; Maintenance; Consolidation; Proteasome inhibitors; Immunologic factors

## INTRODUCTION

Multiple myeloma (MM) is a plasma-cell neoplasm characterized by skeletal destruction, renal failure, anemia, hypercalcemia, and other systemic symptoms, including disrupted heart function [1-4]. In the past, the combination of melphalan and prednisone was the standard treatment for MM. However, improved survival has more recently been achieved by incorporating novel agents [1]. In 1996, Attal et al. [5] demonstrated the clinical significance of autologous stem cell transplantation (ASCT) as a consolidation therapy in eligible patients. They reported that a high-dose therapy combined with stem-cell support improves the response rate, event-free survival (EFS), and overall survival (OS).

Seven years later, Attal et al. [6] confirmed the clinical impact of consolidation therapy using tandem ASCT in patients with MM. Compared with a single ASCT, double transplantation improves OS in patients with newly diagnosed MM, suggesting a beneficial role of consolidation therapy. Novel agents, such as immunomodulatory derivatives (IMiDs) and proteasome inhibitors (PIs), have been incorporated into induction therapies, which has resulted in unprecedented rates of complete response (CR) that rival those previously seen with conventional chemotherapy and subsequent ASCT [7,8]. Moreover, an improvement in the depth of response has been observed following consolidation therapy with novel agents. Usmani et al. [9] attempted total therapy (TT), including induction, transplant, consolidation, and maintenance therapy, in patients with

MM and presented the long-term outcomes. Based on Cox model-adjusted statistics, OS, progression-free survival (PFS), and CR duration all improved with transitions from TT1 to TT2 and TT3; improvement was also evident from time-to-progression estimates, 4-year conditional survival data, and cumulative relative survival.

The excellent activity shown by IMiDs and/or PIs before ASCT has led to their investigational use as consolidation and maintenance therapy after ASCT [10-12]. Consolidation therapy is defined as a distinct course of therapy aimed at increasing the depth of response. It consists of a limited number of cycles of a single agent or combination therapy or a second transplant step. Maintenance therapy is then applied for a prolonged period  $\geq 12$  months and typically for at least 2 to 3 years and even until progression. The overall aim of this therapy is to maintain the depth of response achieved in previous treatments by applying novel treatments usually at a lower dose than that used during either induction or consolidation. The current strategies for treating patients with transplant-eligible MM include induction, ASCT, and consolidation and maintenance therapy, whereas those for transplant-ineligible patients include induction and consolidation and maintenance therapy. However, cost-effectiveness, compliance, toxicities, and quality of life (QoL) must be considered in actual clinical practice, in addition to improvements in survival and response during maintenance therapy. This review focuses on maintenance and consolidation therapy, offering an overview of the different strategies available for patients with MM who are treated in a clinical trial setting as well as in actual clinical practice.

## CONSOLIDATION THERAPY IN PATIENTS ELIGIBLE FOR TRANSPLANTATION

Consolidation therapy generally has a short duration and aims to increase the frequency and depth of response obtained with previous treatments, including high-dose melphalan and ASCT [13]. Novel agents, such as thalidomide, lenalidomide, and bortezomib, have been successfully combined with cytotoxic drugs and have been widely investigated as induction therapy prior to ASCT [14-18]. The combinations of thalidomide-dexamethasone (TD), bortezomib plus dexamethasone (VD),

and doxorubicin or cyclophosphamide with TD have been assessed in terms of increased overall response rate, including CR. However, increasing the depth of response to the level of undetectable minimal residual disease (MRD) and maintaining a sustained CR are stronger predictors of a favorable long-term outcome than attainment of CR [19,20]. The impact of consolidation therapy on clinical outcomes for transplant-eligible patients with MM is discussed below and summarized in Table 1 [8,21-25]. Patients in the Gruppo Italiano Malattie EMatologiche dell'Adulto trial were randomized to receive either TD or bortezomib, thalidomide plus dexamethasone (VTD) induction therapy, followed by double ASCT and two consolidation cycles of assigned chemotherapy [8]. After induction, CR/near complete response (nCR) rates were similar in the VTD (63.1%) and TD (54.7%) groups. After consolidation, the CR/nCR (73.1% vs. 60.9%) rate was significantly higher in VTD-treated patients. Mellqvist et al. [21] compared consolidation therapy with single-agent bortezomib with no consolidation in a phase 3 trial. The rates of very good partial response (VGPR) and PFS were significantly higher in the bortezomib group than in the consolidation therapy group (71% vs. 57%,  $p < 0.01$ ; 27 months vs. 20 months,  $p = 0.05$ , respectively). Ladetto et al. [22] implemented treatment with VTD in patients who achieved at least VGPR after vincristine/adriamycin/dexamethasone (VAD)/double ASCT; the CR rate increased from 15% to 40%. Attal et al. [23] presented results of the Intergroupe Francophone du Myelome (IFM) 2005-02 trial. In their study, patients who underwent ASCT received two cycles of lenalidomide monotherapy as consolidation with further randomization to lenalidomide maintenance versus no maintenance. Lenalidomide consolidation resulted in improved responses; CR increased from 14% to 20% ( $p < 0.001$ ) and VGPR increased from 58% to 69% ( $p < 0.001$ ). In the IFM 2008 study, Roussel et al. [24] assessed the efficacy of two VRD cycles (bortezomib, lenalidomide, and dexamethasone) after previous VRD induction treatment and single ASCT. They found that consolidation increased the VGPR rate by 26%.

**Table 1. Consolidation therapy after autologous stem cell transplantation for newly diagnosed multiple myeloma**

Study	Type of trial	Treatment scheme	No. of patients	Response rate	EFS or PFS	OS
<b>Bortezomib-based</b>						
Cavo et al. (2012) [8]	Phase III	VTD vs. TD	160 vs. 161	CR/nCR preconsolidation: 63% vs. 55% ( $p = \text{NS}$ ) CR/nCR postconsolidation: 73% vs. 61% ( $p = 0.020$ )	3-yr PFS: 60% vs. 48% ( $p = 0.042$ )	3-yr OS: 90% vs. 88% ( $p = \text{NS}$ )
Mellqvist et al. (2013) [21]	Phase III	Bortezomib consolidation vs. no consolidation	187 vs. 183	$\geq$ VGPR preconsolidation: 40% vs. 39% ( $p = \text{NS}$ ) $\geq$ VGPR postconsolidation: 71% vs. 57% ( $p = 0.009$ )	Median PFS: 27 mon vs. 20 mon ( $p = 0.05$ )	3-yr OS: 80% vs. 80% ( $p = \text{NS}$ )
Leleu et al. (2013) [25]	Retrospective comparison	VTD consolidation vs. no consolidation	121 vs. 96	CR postconsolidation: 52% vs. 30% ( $p = 0.001$ )	Median TTP: NR vs. 25 mon ( $p = 0.005$ )	4-yr OS: 84% vs. 91% ( $p = \text{NS}$ )
Ladetto et al. (2010) [22]	Phase II	VTD consolidation	39	CR pre-VTD: 15% CR post-VTD: 49%	Median PFS: 60 mon	3-yr OS: 89%
<b>Lenalidomide-based</b>						
Attal et al. (2012) [23]	Phase III	Len consolidation + Len maintenance vs. Len consolidation + placebo	307 vs. 307	CR preconsolidation: 58% CR postconsolidation: 69% ( $p < 0.001$ )	NR after consolidation	NR after consolidation
Roussel et al. (2014) [24]	Phase II	RVD consolidation	31	sCR/CR pre-VRD: 47% sCR/CR post-VRD: 50%	3-yr PFS: 77%	3-yr OS: 100%

EFS, event-free survival; PFS, progression-free survival; OS, overall survival; VTD, bortezomib, thalidomide plus dexamethasone; TD, thalidomide plus dexamethasone; CR, complete response; nCR, near complete response; NS, non-specific; VGPR, very good partial response; TTP, time to progress; Len, lenalidomide; NR, not reached; RVD, lenalidomide, bortezomib plus dexamethasone; VRD, bortezomib, lenalidomide, and dexamethasone.

## MAINTENANCE THERAPY IN PATIENTS ELIGIBLE FOR TRANSPLANTATION

Maintenance therapy is generally administered for a long duration and aims to improve PFS with minimal toxicity and without interfering with the QoL. The paradigm for transplant-eligible patients consists of induction, stem-cell mobilization, and ASCT, followed by consolidation and/or maintenance [26]. Maintenance therapy consists of prolonged therapy of either a fixed duration or until progression to a sustained response. The ideal maintenance therapy is easily delivered, such as per oral, and a schedule administered intravenously is convenient for patients. This portion of the review focuses on maintenance therapy following ASCT for patients with transplant-eligible MM. The clinical outcomes of maintenance therapy for patients with transplant-eligible MM are summarized in Table 2 [17,23,27-37].

### Thalidomide

Thalidomide maintenance studies have reported improved EFS or PFS compared with those with no maintenance. In the IFM study, Attal et al. [27] randomized 400 patients after ASCT to receive thalidomide versus no maintenance and demonstrated an improved 3-year EFS (52% vs. 37%,  $p < 0.009$ ) and an improved 4-year OS (87% vs. 75%,  $p < 0.04$ ). A single-institution study from Arkansas demonstrated a significant benefit of thalidomide vs. no thalidomide maintenance. The 5-year EFS was 64% for thalidomide and 43% for no maintenance ( $p < 0.001$ ), and the 8-year OS was 57% for thalidomide versus 44% for no maintenance ( $p = 0.09$ ) [28]. The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON)-50 study compared thalidomide and interferon- $\alpha$  (IFN- $\alpha$ ) maintenance and demonstrated that thalidomide improved median EFS (34 months vs. 22 months,  $p < 0.001$ ) but resulted in a non-significant increase in median OS (73 months vs. 60 months,  $p = 0.77$ ) [17]. The Medical Research Coun-

**Table 2. Maintenance therapy after autologous stem cell transplantation for newly diagnosed multiple myeloma**

Study	Type of trial	Treatment scheme	No. of patients	Median follow-up, mon	EFS or PFS	OS
<b>Thalidomide-based</b>						
Attal et al. (2006) [27]	Phase III	Pamidronate + thal vs. pamidronate vs. no maintenance	201 vs. 196 vs. 200	39 vs. 39 vs. 40	3-yr EFS: 52% vs. 37% vs. 36%	4-yr OS: 87% vs. 74% vs. 77%
Spencer et al. (2009) [31]	Phase III	Thal + PRD vs. PRD	243	36	3-yr PFS: 42% vs. 23%	3-yr OS: 86% vs. 75%
Maiolino et al. (2012) [32]	Phase II	Thal + dexa vs. dexa	56 vs. 52	27	2-yr PFS: 64% vs. 30%	2-yr OS: 85% vs. 70%
Barlogie et al. (2008) [28]	Phase III	Thal + IFN- $\alpha$ + dexa vs. IFN- $\alpha$ + dexa	323 vs. 345	72	5-yr EFS: 56% vs. 45%	5-yr OS: 67% vs. 65%
Lokhorst et al. (2010) [17]	Phase III	Thal vs. IFN- $\alpha$	268 vs. 268	52	Median PFS: 34 mon vs. 25 mon	Median OS: 73 mon vs. 60 mon
Stewart et al. (2013) [30]	Phase III	Thal + PRD vs. no maintenance	166 vs. 166	48	Median PFS: 28 mon vs. 17 mon	4-yr OS: 68% vs. 60%
Morgan et al. (2012) [29]	Phase III	Thal vs. no maintenance	245 vs. 247	46	Median PFS: 30 mon vs. 23 mon	3-yr OS: 75% vs. 80%
<b>Bortezomib-based</b>						
Sonneveld et al. (2012) [33]	Phase III	Bortezomib 1.3 mg/m <sup>2</sup> every 2 wk vs. thal 50 mg/day	160 vs. 161	74	Median PFS: 36 mon vs. 27 mon	Median OS: NR vs. 84 mon
Rosinol et al. (2012) [34]	Phase III	VT vs. T vs. IFN- $\alpha$ -2b	89 vs. 87 vs. 90	34.9	Median PFS: 56.2 mon vs. 35.3 mon vs. 28.2 mon	4-yr OS: 74% vs. 70% vs. 65%
<b>Lenalidomide-based</b>						
Attal et al. (2012) [23]	Phase III	Len 10 mg/day vs. placebo	307 vs. 307	45	Median EFS: 40 mon vs. 23 mon	4-yr OS: 73% vs. 75%
McCarthy et al. (2012) [35]	Phase III	Len 10 mg/day vs. placebo	230 vs. 230	34	Median TTP: 46 mon vs. 27 mon	3-yr OS: 88% vs. 80%
Palumbo et al. (2014) [36]	Phase III	Len 10 mg/day vs. placebo	126 vs. 125	51.2	Median PFS: 41.9 mon vs. 21.6 mon	3-yr OS: 88% vs. 79.2%
Gay et al. (2015) [37]	Phase III	Len 10 mg/day + PRD vs. Len 10 mg/day	117 vs. 106	52	Median PFS: 37.5 mon vs. 28.5 mon	3-yr OS: 83% vs. 88%

EFS, event-free survival; PFS, progression-free survival; OS, overall survival; thal, thalidomide; PRD, prednisone; dexa, dexamethasone; IFN- $\alpha$ , interferon- $\alpha$ ; NR, not reached; VT, bortezomib plus thalidomide; T, thalidomide; Len, lenalidomide; TTP, time to progression.

cil of the United Kingdom Myeloma IX study examined transplant and non-transplant approaches to treat newly diagnosed patients with MM. Thalidomide maintenance for the transplant arm resulted in a median PFS of 22 months versus 15 months for the no-maintenance arm ( $p < 0.0001$ ). Median OS was 60 months in both groups ( $p = 0.70$ ) [29]. Median PFS only improved due to thalidomide maintenance in patients with low-risk disease according to the cytogenetic analysis at diagnosis

(29 months vs. 18 months,  $p = 0.01$ ), but no OS benefit was observed. Thalidomide plus glucocorticoids has been investigated as maintenance after ASCT [30-32]. An Australian study compared 243 patients receiving 1 year of thalidomide with prednisolone until progression to patients receiving prednisolone alone until progression [31]. The 3-year PFS was 42% for the thalidomide/prednisolone (TP) arm and 23% for the prednisolone-only arm ( $p < 0.001$ ). The 3-year OS was 86% for the TP

arm and 75% for the prednisolone-only arm ( $p = 0.004$ ). The National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group maintenance study randomized 332 patients with MM receiving a single ASCT to TP versus observation after ASCT [30]. The PFS of patients who received TP was superior to that of observation (4-year estimates: 32% vs. 14%,  $p < 0.0001$ ). At a median follow-up of 4 years, the OS was 68% for thalidomide and prednisone and 60% for observation ( $p = 0.18$ ). Thalidomide maintenance may be an effective option for patients with transplant-eligible MM, and thalidomide should be administered at the minimal effective dose and possibly for no longer than 1 year.

### Bortezomib

The HOVON and German Multicenter Myeloma Group randomized 827 symptomatic patients and those with newly diagnosed MM to either VAD or bortezomib, doxorubicin, and dexamethasone (PAD) [33]. The study was reported at a median follow-up of 41 months. Median PFS of the PAD-P (bortezomib maintenance) arm was 36 months, and that of the VAD-T (thalidomide maintenance) arm was 27 months ( $p = 0.002$ ). The Spanish Myeloma group (Grupo Espanol de Mieloma PETHEMA) conducted a 386-patient trial that randomized newly diagnosed patients with MM into induction treatments of VTD versus TD versus alternating chemotherapy of vincristine, carmustine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, or dexamethasone [34]. All three groups were randomized to maintenance therapy for 3 years with IFN- $\alpha$  versus thalidomide or bortezomib plus thalidomide (VT). At a median follow-up of 2 years from initiating maintenance therapy, the 3-year PFS of the VT maintenance treatment was significantly longer than that of the thalidomide or IFN- $\alpha$  (78% vs. 63% vs. 49%,  $p = 0.01$ ). No difference in OS was observed among the three arms (Table 2).

### Lenalidomide

Three phase 3 studies have examined lenalidomide maintenance therapy after ASCT (Table 2) [23,35,36]. The Cancer and Leukemia Group B (CALGB) 100104 study randomized 462 patients with newly diagnosed MM who had received various induction regimens to 10 mg of lenalidomide daily (dose range, 5 to 15 mg) versus pla-

cebo until progression after single ASCT [35]. The 3-year PFS was 66% for the lenalidomide arm and 39% for the placebo arm ( $p < 0.001$ ). The 3-year OS for the lenalidomide arm with a median follow-up of 34 months was 88%, and that of the placebo arm was 80% ( $p = 0.028$ ). The IFM 05-02 study examined 605 patients randomized to lenalidomide in the same dose range as that used in the CALGB 100104 versus placebo study until progression after single (79%) or double ASCT (21%). Four-year PFS rates were 43% for the lenalidomide-arm and 22% for the placebo-arm patients ( $p < 0.001$ ); no difference in OS was detected between the arms. The 4-year OS rate was 73% for the lenalidomide arm and 75% for the placebo arm ( $p = 0.7$ ). A third lenalidomide maintenance study compared melphalan, prednisone, and lenalidomide (MPR) vs. tandem ASCT with high-dose melphalan [36]. The chemotherapy and tandem ASCT maintenance patients were combined and compared with the chemotherapy and tandem ASCT patients who did not receive lenalidomide maintenance. At a median follow-up of 51.2 months from chemotherapy or tandem ASCT, median PFS was 41.9 months for the lenalidomide maintenance patients and 21.6 months for patients who did not receive maintenance ( $p < 0.0001$ ). The 3-year OS estimate was 88.0% for the lenalidomide arm and 79.2% for the no-maintenance arm ( $p = 0.14$ ). Gay et al. [37] examined maintenance therapy with lenalidomide plus prednisone versus lenalidomide alone following cyclophosphamide, lenalidomide, prednisone versus tandem ASCT in 389 patients with newly diagnosed MM. At a median follow-up of 52 months from chemotherapy or tandem ASCT, PFS did not differ between maintenance treatments with lenalidomide plus prednisone versus with lenalidomide alone (37.5 months vs. 28.5 months,  $p = 0.34$ ). Three-year OS in the 223 patients eligible for maintenance did not differ between the lenalidomide plus prednisone and lenalidomide alone groups (83% vs. 88%,  $p = 0.21$ ).

### SOUTH KOREAN STUDY OF THALIDOMIDE MAINTENANCE IN CLINICAL PRACTICE

Some concerns have been raised about applying thalidomide maintenance in patients with MM who are eligible for ASCT in an actual clinical setting. Lee et al. [38]

reported on the clinical impact of thalidomide maintenance after ASCT in a South Korean clinical practice. The 3-year PFS rates of patients treated with and without maintenance were 55.4% and 37.2%, respectively ( $p = 0.005$ ). The 3-year OS rates of patients treated with and without maintenance were 88.0% and 84.0%, respectively ( $p = 0.105$ ). The 3-year OS rates after relapse or progression of patients treated with and without maintenance were 50.4% and 55.3%, respectively ( $p = 0.661$ ). In particular, patients who showed less than a CR after ASCT and who had undergone maintenance therapy had superior survival rates to those who had not received such therapy. Among the patients who showed less than CR after ASCT, the 3-year PFS rates with and without maintenance therapy were 68.4% and 23.3% ( $p < 0.001$ ), respectively. Thalidomide maintenance after ASCT can be helpful to prolong PFS in fit patients with MM. Long-term exposure to thalidomide during maintenance therapy may not affect survival after relapse or progression from salvage chemotherapy. Finally, patients who have shown less than CR after ASCT might have the option of undergoing thalidomide maintenance.

## MAINTENANCE THERAPY IN PATIENTS INELIGIBLE FOR TRANSPLANTATION

Patients  $\geq 65$  years of age do not tolerate intensive therapy and are usually ineligible for ASCT. Combinations with novel agents, such as thalidomide, lenalidomide, and bortezomib, are widely adopted for newly diagnosed and relapsed patients with MM. The clinical outcomes of maintenance therapy for patients with transplant-ineligible MM are summarized in Table 3 [39-51].

### Thalidomide

Thalidomide can be a suitable option for prolonged use because it is administered orally. Continuous thalidomide therapy after induction with melphalan-prednisone-thalidomide (MPT) has been evaluated for transplant-ineligible patients in six trials (Table 3). In one study, 100 mg/day thalidomide was given continuously. Median PFS was 22 months for patients who received thalidomide and 15 months for those who did not ( $p < 0.001$ ). Median OS rates were 48 and 45 months for the two arms, respectively ( $p = 0.79$ ) [39]. In another study,

200 mg/day thalidomide was administered at induction and was reduced to 50 mg/day during maintenance. Median EFS was 13 months for patients who received thalidomide and 9 months for those who did not ( $p < 0.001$ ). A marginally significant OS advantage favoring thalidomide maintenance was also detected, with median OS of 40 months versus 31 months ( $p = 0.05$ ) [40]. In another study, 200 mg/day thalidomide was administered continuously until relapse [41]. Median PFS (15 months vs. 14 months,  $p = 0.84$ ) and OS (29 months vs. 32 months,  $p = 0.16$ ) were similar between patients who received thalidomide and those who did not. Finally, another study randomized 820 patients including those who were and were not eligible for ASCT to thalidomide maintenance or no maintenance. Patients ineligible for ASCT had received MP or cyclophosphamide-TD induction [29]. In these patients, thalidomide maintenance improved PFS (23 months vs. 15 months,  $p < 0.001$ ), but median OS was not different between the two arms ( $p = 0.40$ ). All studies including thalidomide maintenance reported improved PFS, although a longer follow-up was needed to detect an OS benefit. These findings support the concept that thalidomide maintenance should be administered at the minimal effective dose associated with the lowest toxicity (50 to 100 mg/day) to avoid early discontinuation.

### Bortezomib

Bortezomib is another possible option as maintenance therapy. In one study, bortezomib plus either thalidomide (VT) or prednisone (VP) was administered after induction with either VMP or bortezomib-thalidomide-prednisone [42]. Median PFS tended to be longer with VT (32 months) than with VP (24 months) ( $p = 0.1$ ). In another study, bortezomib-melphalan-prednisone-thalidomide (VMPT) induction followed by VT maintenance (VMPT-VT) was compared with VMP followed by no maintenance [43,44]. VT consisted of 1.3 mg/m<sup>2</sup> bortezomib every 15 days and 50 mg/day thalidomide for 2 years or until progression or relapse. Median PFS was significantly longer with VMPT-VT (35.3 months) than with VMP (24.8 months,  $p < 0.001$ ). The 5-year OS was greater with VMPT-VT (61%) than that with VMP (51%,  $p = 0.01$ ). Another study assessed the role of bortezomib alone as maintenance therapy (1.6 mg/m<sup>2</sup>, days 1, 8, 15, and 22 for five 35-day cycles) after induction with VD, VTD, or VMP [45]. Median PFS was 14.7 months with

**Table 3. Maintenance therapy for patients ineligible for autologous stem cell transplantation**

Study	Type of trial	Treatment scheme	No. of patients	Median follow-up, mon	EFS or PFS, mon	OS
<b>Thalidomide-based</b>						
Palumbo et al. (2008) [39]	Phase III	MPT vs. MP	129 vs. 126	38.1	21.8 vs. 14.5	45 mon vs. 47.6 mon
Facon et al. (2007) [49]	Phase III	MPT vs. MP	191 vs. 124	51.5	27.5 vs. 17.8	51.6 mon vs. 33.2 mon
Hulin et al. (2009) [50]	Phase III	MPT vs. MP	113 vs. 116	47.5	24.1 vs. 18.5	44 mon vs. 29.1 mon
Waage et al. (2010) [41]	Phase III	MPT vs. MP	182 vs. 175	36	15 vs. 14	29 mon vs. 32 mon
Wijermans et al. (2010) [40]	Phase III	MPT vs. MP	165 vs. 168		EFS: 13 vs. 9 PFS: 15 vs. 11	40 mon vs. 31 mon
Beksac et al. (2011) [51]	Phase III	MPT vs. MP	62 vs. 60	23	DFS: 21 vs. 14	26 mon vs. 28 mon
<b>Bortezomib-based</b>						
Palumbo et al. (2014) [43], (2010) [44]	Phase III	VMPT vs. VMP → BT vs. No	511	54	35.3 vs. 24.8	5-yr OS: 61% vs. 51%
Mateos et al. (2010) [42]	Phase III	VMP vs. VTP → BT vs. BP	260	46	39 vs. 32	NR vs. 60 mon
Niesvizky et al. (2015) [45]	Phase IIIb	VD vs. VTD vs. VMP	502	42.7	14.7 vs. 15.4 vs. 17.3	49.8 mon vs. 51.5 mon vs. 53.1 mon
<b>Lenalidomide-based</b>						
Palumbo et al. (2012) [46]	Phase III	MPR-R vs. MPR vs. MP → Len	459	30	31 vs. 14 vs. 13	3-yr OS: 70% vs. 62% vs. 66%
Benboubker et al. (2014) [47]	Phase III	Ld cont vs. Ld 18 vs. MPT	535 vs. 541 vs. 547	37	25.5 vs. 20.7 vs. 21.2	4-yr OS: 59% vs. 56% vs. 51%
Zweegman et al. (2016) [48]	Phase III	MPT-T vs. MPR-R	688	36	20 vs. 23	4-yr OS: 52% vs. 56%

EFS, event-free survival; PFS, progression-free survival; OS, overall survival; MPT, melphalan, prednisone, and thalidomide; MP, melphalan and prednisone; DFS, disease-free survival; VMPT, bortezomib, melphalan, prednisone, and thalidomide; VMP, bortezomib, melphalan, and prednisone; BT, bortezomib and thalidomide; BP, bortezomib and prednisone; NR, not reached; VD, bortezomib and dexamethasone; VTD, bortezomib, thalidomide, plus dexamethasone; MPR-R, melphalan, prednisone, and lenalidomide and then lenalidomide maintenance; MPR, melphalan, prednisone, and lenalidomide; Len, lenalidomide; Ld cont, lenalidomide and dexamethasone continuous treatment; Ld18, lenalidomide and dexamethasone until 18 cycles; MPT-T, melphalan, prednisone, and thalidomide and then thalidomide maintenance.

VD, 15.4 months with VTD, and 17.3 months with VMP. The respective median OS rates were 49.8, 51.5, and 53.1 months, respectively.

### Lenalidomide

A phase 3 study evaluated the role of 10 mg of lenalidomide on days 1 to 21 of each 28-day cycle after melphalan-prednisone-lenalidomide (MPR-R) versus MPR versus MP [46]. In a landmark analysis from the start of lenalidomide maintenance, lenalidomide after MPR significantly prolonged median PFS from 7 to 26 months ( $p < 0.001$ ). However, 4-year OS was approximately 58% in the three treatment groups. A recent large phase 3 study compared lenalidomide plus low-dose dexamethasone (Rd) until relapse versus Rd for 18 cycles (72 weeks) versus

MPT for 12 cycles (72 weeks) [47]. After a median follow-up of 37 months, Rd significantly improved PFS compared with MPT ( $p = 0.00006$ ) and marginally improved OS ( $p = 0.01685$ ). These results suggest the need for continuous Rd because the outcomes after 18 cycles of therapy were similar between Rd and MPT. Finally, Zweegman et al. [48] randomly assigned 688 patients to a group with nine 4-week cycles of MPT followed by thalidomide maintenance until disease progression or unacceptable toxicity (MPT-T) or to a group with the same MP regimen but with thalidomide replaced with lenalidomide (MPR-R). After a median follow-up of 36 months, PFS was 20 months with MPT-T versus 23 months with MPR-R ( $p = 0.12$ ). OS rates at 2, 3, and 4 years in the MPT-T and MPR-R arms were 73% versus 84%, 64% versus 69%, and 52% versus 56%, respective-

ly ( $p = 0.13$ ). Based on these data, lenalidomide seems to be the most suitable choice for maintenance and may be preferable over thalidomide because of its higher efficacy.

## CONSIDERATIONS IN THE MAINTENANCE SETTING

### Toxicities

Toxicity considerations have an important role in any therapy, although application in long-term therapy is attractive from an efficacy point of view. In a meta-analysis of thalidomide maintenance trials conducted by Kagoya et al. [52], thalidomide resulted in more venous thrombosis and peripheral neuropathy (PN) compared with those of the control treatment. Bortezomib therapy can also lead to PN, although a number of strategies to improve tolerability can be followed. Specifically, bortezomib dosing can be reduced to once weekly or fortnightly, and the subcutaneous formulation can be used, which has demonstrated comparable efficacy to the intravenous formulation but with a substantially reduced frequency of PN [53].

### Second primary malignancy

Long-term administration of lenalidomide increases the risk of developing hematological second primary malignancy (SPM), which was demonstrated in an analysis of nine clinical trials involving 3,254 patients [54]. However, the PFS benefit associated with lenalidomide maintenance outweighs the increased risk of SPM. A recent meta-analysis of 3,218 patients reported that patients treated with lenalidomide have an increased risk of developing hematologic SPM (hazard ratio [HR], 1.55;  $p = 0.037$ ). Notably, risk increased when lenalidomide was paired with melphalan compared with melphalan alone (HR, 4.86;  $p < 0.0001$ ), whereas exposure to lenalidomide plus cyclophosphamide (HR, 1.26;  $p = 0.75$ ) or lenalidomide plus dexamethasone (HR, 0.86;  $p = 0.76$ ) did not increase hematologic SPM risk versus melphalan alone [54]. In the CALGB 100104 study [35], eight of 231 (3.5%) patients in the lenalidomide arm developed a hematologic malignancy or primarily myeloid malignancies (acute myeloid leukemia/myelodysplastic syndrome,  $n = 6$ ), whereas only one of 229 (0.4%) in the placebo arm developed such a malignancy (non-Hodgkin's lymphoma,

$n = 1$ ). When counting events of progression, death, and SPM, the median EFS was 43 months for the lenalidomide arm and 27 months for the placebo arm ( $p < 0.001$ ).

### Quality of life

When administering therapy for a prolonged period of time, QoL considerations become important. To date, only a few studies have analyzed the impact of consolidation or maintenance therapy on QoL. Stewart et al. [30] found that applying TP following ASCT had a substantial negative impact on QoL, with patients reporting worse QoL with respect to cognitive function, dyspnea, constipation, thirst, leg swelling, numbness, dry mouth, and balance problems. In contrast, Mellqvist et al. [21] reported that applying bortezomib consolidation did not reduce QoL. Toxicities, such as fatigue, nausea/vomiting, and PN, can be effectively managed with a reduction in dosing frequency or changing the route of administration. Nevertheless, more data are needed to elucidate the effect of long-term therapy on QoL.

### Minimal residual disease

Depth of response as manifested by the presence or absence of MRD is correlated with long-term disease control [20,55]. However, factors such as disease staging, cytogenetics, and gene expression profiling predict long-term outcome [56]. Thus, there have been attempts to incorporate cytogenetic risk factors and detection of MRD [57].

## CONCLUSIONS

To date, all available studies have demonstrated that novel agent-based consolidation therapy enhances the frequency and depth of response achieved during previous treatment phases, including either single or double ASCT. The enhanced rate and quality of responses offered by consolidation therapy contribute to the improved clinical outcomes including extending PFS. 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 are associated with a PFS advantage. Single agents, such as thalidomide, lenalidomide, or bortezomib maintenance, are well



tolerated, and each can be safely used as part of a sequential approach after induction and transplantation. Thalidomide maintenance is also a valuable option in elderly patients, although PN remains a serious problem. Lenalidomide is advantageous because it is not neurologically toxic and is a valuable option after lenalidomide-containing induction chemotherapy. Bortezomib maintenance also seems to improve treatment outcomes when used with a reduced schedule to decrease the frequency of PN. However, limitations, such as cost of drugs, toxicities, and QoL, should be considered in clinical practice compared with a clinical trial setting.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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