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REVIEW

Post-Transplant Maintenance Treatment Options in Multiple Myeloma

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ABSTRACT

Maintenance therapy post autologous stem cell transplant (ASCT) is commonly employed in myeloma patients to prolong remission, as relapse invariably occurs after ASCT. After initial diagnosis and risk stratification, patients receive initial therapy with a combination of drugs, typically a proteasome inhibitor and an immunomodulatory imide drug (IMiD), and in those considered eligible, high-dose chemotherapy followed by autologous stem cell transplant. The aim of our study was to review the literature and consolidate evidence regarding different maintenance therapies post stem cell transplant in myeloma patients. We reviewed major databases including PubMed, Cochrane Library and Evidence-Based Medicine Reviews (EBMR), along with American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) conference abstracts to include relevant literature. Ongoing clinical trials were also reviewed. Consolidation therapy is often employed to enhance the response to induction therapy and SCT and also to delay progression. Melphalan and thalidomide with or without steroids were initially used as maintenance therapy. More recently, lenalidomide-, bortezomib-, ixazomib-, or carfilzomib-based regimens have been employed as maintenance. Lenalidomide and bortezomib are the most commonly used drugs, with the latter being preferred in high-risk populations. Newer trials are utilizing tumor-specific antigen based vaccines along with adoptive T-cell therapies, and monoclonal antibodies as maintenance therapy. We conclude that maintenance therapy post SCT, with lenalidomide or bortezomib is the standard of care in myeloma patients. Patient tolerability, disease risk stratification and prior therapy received are major determinants of the choice of maintenance. Significant toxicity associated with maintenance therapies is a hindrance to long-term maintenance post stem cell transplant.

Keywords: Maintenance; Multiple myeloma; Stem cell transplant

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Key Summary Points

Autologous stem cell transplantation remains an integral part of myeloma therapy, most commonly used as part of initial treatment in patients eligible to undergo this procedure.

Multiple phase III trials have shown a benefit for post-transplant maintenance therapy with different agents. Lenalidomide is considered the standard post-transplant maintenance based on a meta-analysis of different phase III trials demonstrating an improvement in progression-free and overall survival.

In patients with high-risk multiple myeloma, maintenance therapy with a combination of a proteasome inhibitor and immunomodulatory drug appears to be the best choice based on available data.

The ideal duration of maintenance therapy remains unknown, and the current recommendation is to continue maintenance until disease progression, particularly in patients with high-risk disease.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13379480.

INTRODUCTION

Multiple myeloma (MM) is a disorder of plasma cells, and accounts for 17% of all hematologic malignancies, with an estimated incidence of 32,110 new cases in the United States in 2019. The disease has a high mortality rate; an estimated 12,960 deaths in 2019 were attributed to MM [1]. It is most common in adults aged 65 to 74 years, with a median age at diagnosis of 69 years [2]. The incidence varies based on ethnicity; prevalence is higher among African Americans, with a younger age of onset and comparable survival with appropriate access to treatment [3, 4]. MM typically presents with end-organ damage attributable to marrow plasma cell infiltration and monoclonal protein or cytokines secreted by the myeloma cells and may include anemia, hypercalcemia, bone destruction and renal insufficiency. Easy fatigability and weight loss are also common features accompanying the disease. Less common signs include hepatosplenomegaly, fever, peripheral neuropathy, radiculopathy and encephalopathy [5]. Very rarely, patients present with medical emergencies such as spinal cord compression [6].

Patients with symptomatic myeloma are treated with combinations of active agents, typically one that contains a proteasome inhibitor and an immunomodulatory imide drug (IMiD), following which eligible patients often proceed to high-dose chemotherapy in combination with autologous stem cell transplantation (ASCT). The latter has been shown to improve overall survival (OS) and increase the depth of response and durability of response [7, 8]. Primary therapy involves two- or three-drug regimens based on the patient's age, performance status, tolerability and eligibility for transplant. As disease relapse invariably occurs post-ASCT, different therapies have been employed post-transplant to improve progression-free survival (PFS) and OS. Post-ASCT therapies can be broadly classified as consolidation or maintenance therapy, though the distinction can sometimes be rather blurred. According to the International Myeloma Working Group (IMWG) 2012 consensus, the purpose of consolidation therapy is to further reduce the treatment burden after ASCT, thereby enhancing treatment response. Maintenance therapy is employed for a longer time to ensure continued disease suppression [9]. Different phase III trials have examined the relative role of these two approaches post-ASCT. With the development of two-drug maintenance regimens, the distinction between

consolidation and maintenance is becoming increasingly blurred. Lenalidomide [10–13] and bortezomib [14, 15] are commonly used maintenance therapies in patients post-transplant. Ongoing trials are examining the role of other agents in prolonging the response post-ASCT. There is a great need for alternative drugs as maintenance therapy, considering the significant side effects associated with the above treatments, such as neutropenia and increased risk of secondary malignancies, especially with the use of lenalidomide post-ASCT [16].

The objective of this review is to analyze the available literature on post-transplant maintenance therapies for myeloma patients and consolidate evidence to facilitate management. We aim to gather evidence on different maintenance options in terms of efficacy in disease prevention and safety profiles.

METHODS

An electronic search of the PubMed, Cochrane Library and Evidence-Based Medicine Reviews (EBMR) databases was conducted to include studies published between 2000 and 2019. The following article types were included: phase II, III and IV clinical trials, randomized control trials (RCTs), retrospective/prospective studies, conference abstracts and meta-analyses. All the studies were screened for relevance. The above databases were chosen for their large collection of peer-reviewed articles. Ongoing clinical trials evaluating different maintenance combinations were also reviewed and included in the study.

Our initial search of the database for English-language studies performed in adult humans with MM and employing maintenance therapy resulted in 110 reports. After an initial review, 55 abstracts/manuscripts were included for further analysis (Fig. 1). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Chemotherapy Drugs

Studies in the late 1970s employing chemotherapeutic agents as maintenance therapy did not lead to prolongation of survival [17]. In 1988, a randomized trial compared maintenance melphalan and prednisone to no maintenance therapy in patients with MM who responded to primary therapy. Though there was earlier relapse in the no maintenance group, the patients still had a response when melphalan/prednisone was restarted, thus not impacting OS [18]. Based on these results, along with the increased risk of toxicity with melphalan, trials employing maintenance melphalan-based regimens did not translate to clinical use.

Interferon Alfa

In 1990, Mandelli et al. published their findings on the use of interferon alfa-2b as a maintenance regimen in patients who had significant response to induction therapy. It was concluded that maintenance interferon alfa-2b enhanced the response and improved OS [19]. Palumbo et al. investigated "intensified maintenance therapy," adding glucocorticoids to interferon, which was associated with further prolonged duration of disease control [20]. Other prospective studies also suggested prolonged PFS with maintenance interferon [21], but the side effects, especially cytopenias, were significant. A small prospective study combined interferon alfa with granulocyte-macrophage colony-stimulating factor (GM-CSF) post-ASCT to combat cytopenia and found better tolerability [22]. However, two subsequent landmark meta-analyses concluded that the small survival benefit with interferon came with a huge toxicity profile, which significantly affected quality of life [23, 24]. Hence, the use of maintenance interferon was not recommended.

Thalidomide

Studies published in the late 2000s predominantly used thalidomide as a maintenance option. Two large RCTs were published in 2006

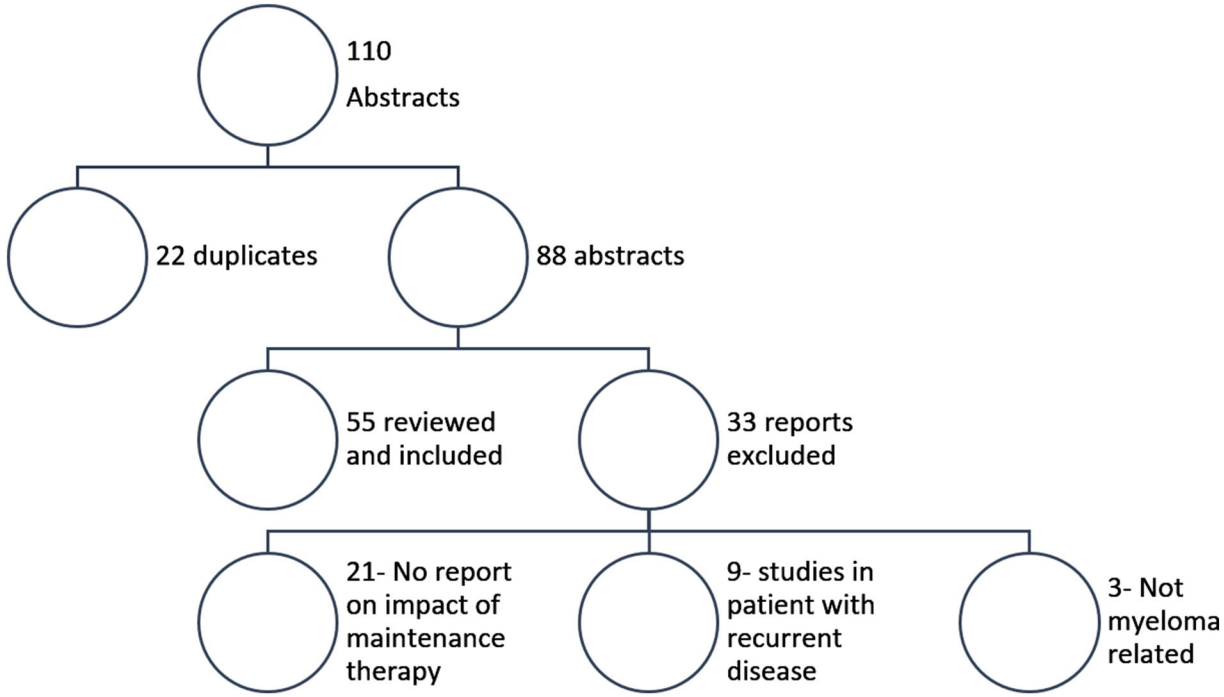

Fig. 1 Database search and results review

using thalidomide maintenance after induction therapy and ASCT. Both revealed improved event-free survival and better OS with maintenance thalidomide [25–27]. The HOVON-50 randomized phase III trial was a comparative study employing maintenance thalidomide or interferon-alfa following induction therapy. Patients received thalidomide, doxorubicin and dexamethasone or vincristine, doxorubicin and dexamethasone induction, followed by high-dose melphalan conditioning and stem cell transplant prior to receiving maintenance therapy. Thalidomide significantly prolonged PFS and improved OS compared with interferon [28]. The findings were reproduced in another trial, which confirmed improved PFS with thalidomide maintenance compared to interferon, but the OS rates were similar [29]. A few other clinical trials and meta-analyses confirmed improved PFS with thalidomide maintenance compared to no maintenance, but OS rates were not significantly different [17, 30–37] (Table 1). All the trials also demonstrated significant toxicity associated with thalidomide use, especially peripheral neuropathy [25, 27–37]. Long-term follow-up results of HOVON-50 reproduced earlier findings of prolonged event-free survival with thalidomide maintenance compared to the control group but with significant toxicity. The authors concluded that thalidomide might still be an option as post-ASCT maintenance in developing countries where access to IMiDs and proteasome inhibitors is limited [37].

Lenalidomide

The next agent to be evaluated as maintenance therapy was the immunomodulatory drug lenalidomide. A phase III placebo-controlled trial performed by Attal et al. randomized 614 patients under the age of 65 to receive lenalidomide or placebo after first bone marrow transplant. The study was conducted in 77 centers across Europe, with recruitment between 2006 and 2008. The study revealed significantly longer PFS in patients who were in the treatment arm, but there was also higher incidence of second primary cancers. At the 4-year follow-up, there was no difference in OS between the two groups [10]. Another randomized clinical trial, conducted by Palumbo

Table 1 Major studies utilizing thalidomide as maintenance therapy

Author [Refs.]	Median age, years No of patients	Induction therapy	Maintenance	Type of study	Follow-up duration (median)	PFS/event-free survival	OS/median survival	Toxicity reported
Attal et al. [25]	59, 597	High-dose therapy(vincristine, doxorubicin, dexamethasone)	1—No maintenance 2—Pamidronate 3—Pamidronate + thalidomide	RCT	39-40 months	1–36% 2–37% 3–52% ($P < 0.009$)	1–1–77% 2–74% 3–3–87% ($P < 0.04$)	NA
Barlogi et al. [26, 27]	57, 668	Melphalan-based chemotherapy	1—Thalidomide 2—No maintenance	RCT	42 months	1–56% 2–44% ($P = 0.01$)	1–1.1 years 2–2.7 years ($P = 0.90$)	Severe peripheral neuropathy, DVT
Lokhorst et al. [28]	56, 536	1—VAD 2—Thalidomide, doxorubicin, dexamethasone	1—Alpha IFN 2—Thalidomide	RCT	52 months	1–25 months 2–34 months ($P < 0.001$)	1–60 months 2–73 m ($P = 0.77$)	Peripheral neuropathy, DVT
Ludwig et al. [29]	71, 128	1—TD 2—MP	1—Thalidomide + IFN 2—IFN	RCT	35 months	1–27.7 months 2–13.2 months ($P = 0.0068$)	1–52.6 months 2–51.4 months ($P = 0.81$)	Neuropathy, constipation, skin toxicity, elevated creatinine

Table 1 continued

Author [Refs.]	Median age, yearsNo of patients	Induction therapy	Maintenance	Type of study	Follow-up duration (median)	PFS/event-free survival	OS/median survival	Toxicity reported
Morgan et al. (Myeloma IX results and meta-analysis) [34]	59/73, 820	Intensive group—CTD/CVAD, followed by HDM Non-intensive group—MP/attenuated CTD	1—Thalidomide 2—No maintenance	RCT	32 months	Intensive group: 1–30 months 2–23 months ($P = 0.003$) Non-intensive group: 1–11 months 2–9 months $P = 0.014$	Intensive group: OS not reached, 3-year survival: 1–75% 2–80% ($P = 0.26$) Non-intensive group, median OS: 1–38 months 2–39 months $P = 0.995$	Paresthesia, drowsiness, constipation, eczema/rash, hematologic events, infection, thrombosis, tremor
Spencer et al. [35]	57, 243	VAD or similar regimen	1—Thalidomide + prednisone 2—Prednisolone	RCT	36 months	1–42% 2–23% ($P < 0.001$) TTP, 931 days vs. 560 days	1–86% 2–75% ($P = 0.004$)	Neurotoxicity

Table 1 continued

Author [Refs.]	Median age, yearsNo of patients	Induction therapy	Maintenance	Type of study	Follow-up duration (median)	PFS/event-free survival	OS/median survival	Toxicity reported
Stewart et al (Myeloma.10-MY.10 trial) [36]	58, 332	Any induction, excluding thalidomide and lenalidomide	1—Thalidomide + prednisolone 2—Observation	RCT	48 months	1–32% 2–14% ($P < 0.0001$)	1–68% 2–60% ($P = 0.18$)	DVT, second malignancy

VAD vincristine, doxorubicin and dexamethasone, *TD* thalidomide and dexamethasone, *MP* melphalan and prednisolone, *CTD* cyclophosphamide, thalidomide and dexamethasone, *CVAD* cyclophosphamide, vincristine, doxorubicin and dexamethasone, *HDM* high-dose melphalan, *RCT* randomized controlled trial, *PFS* progression-free survival, *OS* overall survival, *DVT* deep vein thrombosis

et al., included 251 patients younger than age 65 who were randomized to lenalidomide maintenance versus no maintenance therapy. Lenalidomide maintenance was shown to improve PFS [13]. The Cancer and Leukemia Group B (CALGB) evaluated time to progression (TTP) with lenalidomide maintenance compared to placebo and found a statistically significant difference between the two groups, with patients on lenalidomide having delayed time to progression and improved OS [7]. This double-blinded RCT included patients with symptomatic disease who received induction therapy followed by ASCT, and had stable or improved disease at day 100. Patients were then randomly assigned to lenalidomide maintenance (10 mg first 3 months, then 15 mg) or placebo treatment arms. After the initial 18-month follow-up, 67% (128 of 460) of those without progressive disease crossed over to the lenalidomide arm because of significantly improved time to progression. Long-term follow-up subsequently confirmed the prolonged time to progression with lenalidomide maintenance [11]. A meta-analysis of these three trials confirmed the improvement in PFS and OS with the use of lenalidomide post-ASCT.

The major RCTs showing positive response with lenalidomide maintenance led to Food and Drug Administration (FDA) approval of the drug in February 2017 as maintenance therapy for MM patients after ASCT[38]

(Table 2). A health care cost analysis was performed post-approval and did not find a major impact on total plan costs, but this may have been due to the widespread use of maintenance lenalidomide even prior to approval [39]. Hematological adverse events such as cytopenias were common side effects with lenalidomide maintenance [7, 10, 11, 13].

The BMT CTN 0702 trial compared patients who received single ASCT to double ASCT (tandem transplant), lenalidomide, bortezomib and dexamethasone consolidation (VRD) or no further intervention before all three groups were started on maintenance lenalidomide. The trial found no difference in PFS or OS between treatment arms. Based on these results, single ASCT with lenalidomide maintenance is suggested as the standard of care for patients receiving VRD induction therapy [40]. The Myeloma XI trial enrolled patients who were 18 years or older and had received any induction, followed by ASCT or other treatment, who were randomized to receive lenalidomide (10 mg days 1–21 of a 28-day cycle) or observation. Patients on lenalidomide maintenance demonstrated a statistically significant improvement in PFS. Subgroup analysis was performed in patients who received transplantation, which showed PFS of 57 months compared to 30 months in the observation group (HR 0.48 [95% CI 0.40–0.58]; $P < 0.0001$), but the OS benefit was not statistically significant [41].

The impact of lenalidomide maintenance after ASCT in improving PFS was also observed in the Connect MM study, an observational study analyzing data from Connect MM Registry, which is the largest US-based database for newly diagnosed myeloma patients. The median OS was improved in the maintenance group but the 3-year mark was not reached [42].

A small prospective study performed by Solovev et al. aimed to evaluate the efficacy of maintenance lenalidomide in patients who achieved complete or stringent complete response following ASCT. Seventy patients with MM underwent ASCT/tandem ASCT after induction with bortezomib and immunomodulatory drugs. Bone marrow exam with flow cytometry was performed on day 100 to assess minimal residual disease (MRD) status. Patients were then randomized to receive maintenance lenalidomide (15 mg/day on days 1–21 of a 28-day course). Two-year PFS was prolonged in patients with MRD-positive status with maintenance therapy, but the difference was not observed in MRD-negative patients. This small prospective study suggests a possible relationship between MRD status and selection of candidates for maintenance therapy [43].

A retrospective chart review of 245 patients with MM treated at the Princess Margaret Cancer Centre confirmed prolonged PFS in patients who were on maintenance therapy after ASCT [44]. Another retrospective study evaluated the optimal duration of lenalidomide maintenance and revealed prolonged PFS with longer maintenance duration up to 3 years or more. The

Table 2 Major studies utilizing lenalidomide as maintenance therapy

Author [Refs.]	Median age (years) No. of patients	Induction therapy	Maintenance	Type of study	Follow-up duration (median)	PFS/TTP	OS	Toxicity reported
McCarthy et al. [7]	59, $N = 460$	Any	1—Lenalidomide 2—Placebo	RCT	34 months	Time to progression: 1–46 months 2–27 months ($P < 0.001$)	1–88% 2–80%	Hematologic events, second primary cancers
Attal et al. [10]	55, $N = 614$	VAD or VD or Other	1—Lenalidomide 2—placebo	RCT	30 months	1–41 months 2–23 months ($P < 0.001$)	1–80% 2–84% ($P = 0.29$)	Peripheral neuropathy, second primary cancers
Palumbo et al. [13]	71, $N = 459$	Lenalidomide, dexamethasone with MPR or melphalan consolidation	1—Lenalidomide 2—Placebo	RCT	30 months	1–42 months 2–22 months ($P < 0.001$)	1–88% 2–79%	Hematologic abnormality, infection, dermatologic events, second primary cancer

MPR melphalan, prednisone and lenalidomide, *VAD* vincristine, doxorubicin and dexamethasone, *VD* bortezomib and dexamethasone, *RCT* randomized controlled trial, *PFS* progression-free survival, *TTP* time to progression, *OS* overall survival

incidence of second primary malignancies was also low at 3%. That study concluded that longer duration of maintenance lenalidomide was associated with longer survival [45].

The Japan Study Group for Cell Therapy and Transplantation JSCT-MM12 trial included 64 patients with symptomatic myeloma. Patients received bortezomib, cyclophosphamide and dexamethasone induction, followed by bortezomib-melphalan conditioning and ASCT; they then received two cycles of bortezomib, thalidomide and dexamethasone consolidation, followed by lenalidomide maintenance for 1 year. Overall tolerability and response were very good [46]. Lenalidomide is now an established option for maintenance therapy post-ASCT.

Bortezomib

Bortezomib, a proteasome inhibitor, has also been used as maintenance therapy post-ASCT. The HOVON-65/GMMG-HD4 trial using bortezomib before and after SCT as maintenance therapy showed significantly prolonged PFS and OS with bortezomib use. Patients in the HOVON trial were randomly assigned to VAD (vincristine, doxorubicin, dexamethasone) as induction therapy, followed by ASCT and thalidomide maintenance or PAD (bortezomib, doxorubicin, dexamethasone) induction, followed by ASCT and bortezomib maintenance. Prolonged PFS and OS was observed in patients receiving bortezomib; the benefit was also established in patients with high-risk disease (those with chromosome 17p13 deletion and those with kidney disease with creatinine over 2 mg/dl) [15]. The long-term results of the trial (at 96 months) also confirmed prolonged PFS in the bortezomib or PAD arm, but OS and incidence of secondary malignancies were similar between the groups (PAD vs. VAD) [47].

GEM05MENOS65 was a phase III trial performed in myeloma patients to evaluate efficacy of different maintenance therapy. A total of 390 patients received different induction therapy followed by ASCT, and then 271 were randomly assigned to thalidomide-bortezomib or thalidomide or alfa2 interferon maintenance for 3 years. Complete response improved by 21% with the combination therapy, compared to 11% with thalidomide and 17% with interferon alone. The study concluded that the combination was associated with longer PFS, but the OS did not differ between the treatment arms [48].

Hence, bortezomib is a potential alternative maintenance therapy option post-ASCT to prolong PFS, especially in high-risk patients. Table 3 summarizes the major studies using bortezomib as maintenance therapy.

Ixazomib

Ixazomib, another proteasome inhibitor, has also been utilized as maintenance therapy in high-risk myeloma patients with bortezomib resistance. The drug is preferred for its ease of administration, as it can be given orally and once a week. Phase I trials suggested a clinically meaningful response in relapsed/refractory myeloma patients, without intolerable toxicity [49]. The TOURMALINE-MM3 phase III trial compared ixazomib maintenance versus placebo maintenance after ASCT in patients with newly diagnosed myeloma. Induction therapy included an immunomodulator or proteasome-based regimen. Patients had to have achieved at least a partial response to induction to be eligible for participation in this trial. Overall, 656 patients were randomized; the median age was 57, with a median follow-up of 31 months. Landmark analysis was performed from ASCT and revealed significantly prolonged PFS in the ixazomib arm, 30.7 months versus 24.9 in the placebo arm. Ixazomib was well tolerated with few grade 3 adverse events (infections, neutropenia, thrombocytopenia, peripheral neuropathy). Rates of secondary malignancies were similar across treatment arms. Considering the good tolerability, ease of administration, lower rates of second malignancies, and enhanced response with significantly improved PFS, the authors concluded that ixazomib is a valuable post-ASCT maintenance option [50]. Further trials are ongoing to confirm the role of ixazomib as post-ASCT maintenance in high-risk myeloma patients (Table 4).

Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor which has demonstrated excellent

Table 3 Major studies utilizing bortezomib as maintenance therapy

Author [Refs.]	Median age (years) No. of patients	Induction therapy	Maintenance	Type of study	Follow-up duration (median)	PFS	OS	Toxicity reported
Sonneveld et al. (HOVON-65/ GMMG-HD4-initial report) [15]	57, $N = 827$	1-VAD	1—Thalidomide	RCT	41 months	1–28 months	1–55%	Peripheral neuropathy, higher with PAD and thalidomide maintenance
		2-PAD* Followed by single or double ASCT or ASCT/allogeneic SCT	2—Bortezomib			2–35 months ($P = 0.002$)	2–61% ($P = 0.11$)	
Goldschmidt et al. (HOVON-65/ GMMG-HD4) [47]	57, $N = 827$	1-VAD	1—Thalidomide	RCT	96 months	1–28 months	1–82 months	
		2-PAD* Followed by single or double ASCT or ASCT/allogeneic SCT	2—Bortezomib			2–34 m ($P = 0.003$)	2–91 months ($P = 0.24$)	
Rosinol et al. (PETHEMA/ GEM)(48)	59, $N = 390$	VBMCP/VBAD/B**	1—Thalidomide, bortezomib	RCT	59 months	1–50.6 months	1–78%	Peripheral neuropathy, hematologic toxicity
			2—Thalidomide			2–40.3 months	2–72%	
			3—Alfa2 interferon			3–32.5 months ($P = 0.03$)	3–70% ($P = 0.3$)	

**PAD* bortezomib, doxorubicin, dexamethasone, **VBMCP/VBAD/B thalidomide/dexamethasone, bortezomib/thalidomide/dexamethasone and vincristine, *BCNU* melphalan, cyclophosphamide, prednisone/vincristine, *BCNU* doxorubicin, dexamethasone bortezomib, *RCT* randomized controlled trial, *PFS* progression-free survival, *OS* overall survival

Table 4 Actively recruiting trials for post-ASCT maintenance in myeloma

Clinical trial identifier	Phase	No.	Target group	Induction therapy	Maintenance	Objective
NCT02334865	Phase I	18	Newly diagnosed myeloma patients on lenalidomide maintenance	Any induction	Lenalidomide maintenance with SVN53-67/M57-KLH vaccine in incomplete Freund's adjuvant	To determine toxicity of combination and therapeutic efficacy
NCT01864018	Phase I/II	51	Newly diagnosed untreated symptomatic myeloma	Ixazomib citrate, cyclophosphamide, dexamethasone	Ixazomib citrate	Maximum tolerated dose of ixazomib, rate of CR/VGPR, AE, PFS, survival time
NCT02891811	Phase II	146	Newly diagnosed myeloma	Carfilzomib, thalidomide, dexamethasone vs. carfilzomib, lenalidomide, dexamethasone	Carfilzomib	Response, feasibility, safety
NCT03733691	Phase II	52	Newly diagnosed myeloma	Any (bortezomib/lenalidomide-based)	Ixazomib vs. ixazomib/lenalidomide	PFS, OS, AE, enhanced response
NCT03669445	Phase II	45	Newly diagnosed SR myeloma	Lenalidomide, ixazomib, daratumumab, dexamethasone	Lenalidomide, ixazomib, daratumumab, dexamethasone	MRD negativity, PFS, OS, AE, RR
NCT03896737	Phase II	400	Newly diagnosed myeloma	Daratumumab, bortezomib, cyclophosphamide, dexamethasone vs. bortezomib, thalidomide, dexamethasone	Ixazomib vs. ixazomib, daratumumab	PFS, MRD negativity, ORR, OS
NCT03104842	Phase II	153	Newly diagnosed myeloma	Isatuximab, carfilzomib, lenalidomide, dexamethasone	Isatuximab, carfilzomib, lenalidomide, dexamethasone	MRD negativity

Table 4 continued

Clinical trial identifier	Phase	No.	Target group	Induction therapy	Maintenance	Objective
NCT03477539	Phase II	50	Transplant-eligible myeloma	Daratumumab	Daratumumab, lenalidomide	MRD negativity, PFS, ORR, AE, survival time
NCT03942224	Phase II	76	Newly diagnosed myeloma	Daratumumab, ixazomib, dexamethasone	Daratumumab, ixazomib, dexamethasone	VGPR rate, best response, objective response rate, MRD, PFS, time to response, DoR
NCT03490344	Phase II	25	MRD-positive myeloma patients after induction with/without high-dose therapy/ASCT	Any	Daratumumab to lenalidomide maintenance	MRD negativity at end of 6 months of daratumumab therapy
NCT03188172	Phase II	95	HR myeloma	Cyclophosphamide, bortezomib, lenalidomide, daratumumab	Lenalidomide, daratumumab	PFS, AE, OS, maximum response, ORR, QoL
NCT03411031	Phase II	60	Relapse/progressive disease on maintenance lenalidomide	Any	Addition of elotuzumab to lenalidomide maintenance	PFS, ORR, MRD status
NCT03756896	Phase II	34	HR myeloma	Any	Carfilzomib, pomalidomide, dexamethasone	CR, PFS, ORR, OS, MRD status, DoR, objective response rate
NCT03622775	Phase II	56	Relapsed myeloma after salvage ASCT	Any	Daratumumab	Complete remission rate, PFS
NCT03376672	Phase II	120	Newly diagnosed myeloma	Ixazomib, lenalidomide dexamethasone	Ixazomib, lenalidomide vs. lenalidomide	FC assessment, FC negativity
NCT03346135	Phase II	40	Myeloma	Any	Daratumumab	PFS, MRD status, AE, ORR, response duration, depth of response, OS

Table 4 continued

Clinical trial identifier	Phase	No.	Target group	Induction therapy	Maintenance	Objective
NCT03606577	Phase II	50	Newly diagnosed HR myeloma	Carfilzomib, lenalidomide, dexamethasone, daratumumab	Lenalidomide, daratumumab	MRD, number of response, patients requiring second ASCT, AE, TTP
NCT02389517	Phase II	86	Residual disease after transplant	Any	Lenalidomide, ixazomib citrate, dexamethasone vs. lenalidomide	MRD, ORR, DoR, PFS, OS, AE
NCT02659293	Phase III	180	Myeloma	Any	Lenalidomide carfilzomib, dexamethasone vs, lenalidomide	PFS, MRD, RR, AE
NCT03901963	Phase III	214	Newly diagnosed MM who are MRD-positive after ASCT	Any induction	Daratumumab with lenalidomide vs. lenalidomide	Percentage of MRD-negative, PFS
NCT03617731	Phase III	662	Newly diagnosed myeloma	Isatuximab to lenalidomide/ bortezomib/ dexamethasone induction	Lenalidomide	MRD negativity, PFS, OS, CR
NCT03562169	Phase III	406	Relapsed myeloma	Ixazomib thalidomide dexamethasone	Ixazomib-based or no maintenance	ORR, PFS, OS
NCT04071457	Phase III	1100	Newly diagnosed myeloma	Any	Lenalidomide with daratumumab/ rHUPh20 vs. lenalidomide	OS, PFS, response, MRD negativity
NCT03948035	Phase III	576	Newly diagnosed myeloma	Elotuzumab, carfilzomib, lenalidomide, dexamethasone vs. carfilzomib, lenalidomide dexamethasone	Elotuzumab lenalidomide vs. lenalidomide	Induction phase/maintenance phase, long-term efficacy
NCT03792620	Phase III	20	Stage I multiple myeloma	Cyclophosphamide, thalidomide, dexamethasone, daratumumab	Daratumumab	RR, AE, ORR, TTP, PFS

Table 4 continued

Clinical trial identifier	Phase	No.	Target group	Induction therapy	Maintenance	Objective
NCT04221178	NA	50	MRD-negative myeloma	Any	Any	PFS after cessation of maintenance

ASCT autologous stem cell transplantation, *SR* standard risk, *MRD* minimal residual disease, *HR* high risk, *CR* complete response, *VGPR* very good partial response, *DoR* duration of response, *PFS* progression-free survival, *OS* overall survival, *AE* adverse events, *RR* response rate, *ORR* overall response rate, *TTP* time to progression, *FC* flow cytometry, QoL quality of life

efficacy. A phase I/II study of the combination of carfilzomib, lenalidomide and low-dose dexamethasone (CRd) suggested good tolerance and prolonged PFS when employed as induction and maintenance therapy post-ASCT. The patients in this trial received eight cycles of CRd initially, with the option for SCT after the first four cycles. After SCT, patients then received maintenance CRd for a total of 24 cycles. Finally, patients were to receive maintenance lenalidomide off study protocol. CRd was well tolerated in the induction and maintenance phases, with rapid, sustained responses [51]. Another phase I/II trial using carfilzomib-melphalan conditioning followed by ASCT and carfilzomib maintenance in patients with relapsed myeloma demonstrated good PFS and OS. All patients had received a median of three therapies prior to receiving the study drug [52]. Ongoing trials utilizing carfilzomib are documented in Table 4.

Monoclonal Antibodies: Elotuzumab/ Daratumumab

Monoclonal antibodies targeting specific receptors in myeloma cells are being explored in relapsed/refractory myeloma and also as first-line management of new myeloma patients. The anti-SLAMF7 antibody elotuzumab and anti-CD38 antibody daratumumab were approved by the FDA in 2015 for the management of myeloma patients [53].

The role of drugs in post-ASCT maintenance was explored in a phase II trial evaluating the efficacy of elotuzumab-lenalidomide combination. Recently published updated results suggest promising results and good tolerability. A total of 84 patients received 16 cycles of elotuzumab in combination with lenalidomide and dexamethasone. More than 90% of patients who had complete remission with MRD at the point of trial entry tested negative by flow cytometry. Fifty-two percent of patients achieved complete response, within a median time of 2 months. Common side effects reported were neutropenia, thrombocytopenia and anemia, with common gastrointestinal side effects as well (diarrhea, nausea, vomiting) [54]. A few other phase I/II and phase III trials are recruiting patients comparing the elotuzumab-lenalidomide/bortezomib combination in different dosing and in comparison with lenalidomide alone (Table 4).

Phase I/II trials employing daratumumab, an anti-CD38 monoclonal antibody, revealed good efficacy and overall safety [55, 56]. An ongoing phase II trial is evaluating the addition of daratumumab to bortezomib, lenalidomide and dexamethasone as induction, followed by ASCT and daratumumab-lenalidomide versus lenalidomide maintenance. Preliminary reports reveal an overall good safety profile with manageable toxicity. Daratumumab utilized as front-line induction therapy demonstrated an improved response rate and depth of response without affecting the percentage of stem cell collection [57].

The recently published LYRA study evaluated the combination of daratumumab with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed myeloma patients. Eligible patients received the above combination induction therapy followed by ASCT and daratumumab maintenance. Eighty-seven newly diagnosed myeloma and 14 relapsed myeloma patients were enrolled in the study, with a median age of 64. At the time of the report, 28 of the newly diagnosed myeloma patients had undergone ASCT. Subgroup analysis was not reported, but overall 12-month PFS in transplant-eligible/ineligible patients was 87% [58]. The combination of daratumumab with melphalan, bortezomib and dexamethasone in transplant-ineligible patients improved PFS to 71.6%, compared to 50.2% in the control group (melphalan, bortezomib and dexamethasone). The rates of hematologic and infectious adverse events were higher in the treatment arm, but the benefits of decreased mortality and improved disease-free survival times were significant [59]. Daratumumab is thus being explored as a highly efficacious and well-tolerated therapeutic target in myeloma (Table 4).

Adoptive Cell Transfer and Idiotype Vaccine

Phase II trials employing vaccines against tumor-specific antigen are also being performed to achieve longer relapse-free periods in myeloma. Trials employing Ig idiotype (Id tumor-specific antigen) vaccine, conjugated with the carrier protein keyhole limpet hemocyanin (KLH), had their origin in the management of follicular lymphoma. A double-blind RCT confirmed prolonged PFS in lymphoma patients who received the patient-specific Id vaccine [60]. Phase I/II trials involving adoptive transfer of tumor antigen vaccine-primed co-stimulated T cells showed enhanced cellular and humoral immune response to the vaccine and also anti-tumor immunity in post-ASCT patients [61]. This led the authors of the phase II RCT to combine the Id vaccine with adoptive cell transfer as maintenance therapy in myeloma post-ASCT. Thirty-six patients were randomized to a control arm with KLH only (20) or treatment arm with Id-KLH (16) combination, followed by ASCT. All patients then received vaccine-primed co-stimulated T cells and two booster vaccine doses (KLH or Id-KLH, depending on prior randomization status). The authors reported no acute vaccine-related reactions. Gene expression analysis was performed to evaluate humoral and cellular immunity in response to the vaccines. Higher expression of immune regulatory CD4+ and CD8+ T cells was noted in the treatment arm, translating to an enhanced clinical response [62].

Actively recruiting trials investigating different novel agents as maintenance post-ASCT in myeloma are documented in Table 4.

Post-ASCT maintenance options for myeloma patients is summarized in Fig. 2.

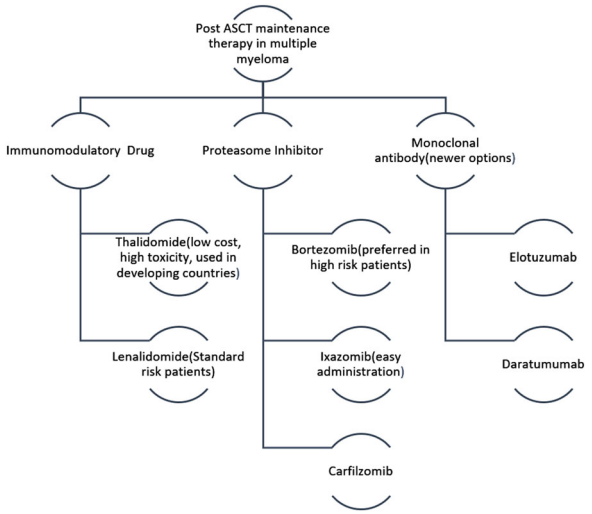

Fig. 2 Summary of post-ASCT maintenance therapy options

CONCLUSION

Post-ASCT maintenance therapy with lenalidomide or bortezomib is the standard of care for myeloma patients to prolong PFS and potentially OS. The type of maintenance therapy depends on multiple factors including prior therapy, presence of high-risk characteristics, patient tolerance and side effect profile. Longer

periods of maintenance translate to prolonged PFS and delayed disease relapse. Side effects need to be considered when using long-term maintenance therapy. Consolidation therapy can enhance post-ASCT response in some patients.

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