Int J Hematol (2013) 97:333–344
DOI 10.1007/s12185-013-1294-z

Current approaches for the treatment of multiple myeloma

Reiko Watanabe · Michihide Tokuhira · Masahiro Kizaki

Received: 28 January 2013 / Revised: 8 February 2013 / Accepted: 8 February 2013 / Published online: 10 March 2013

Abstract The development of novel therapeutic agents over the past decade, including the proteasome inhibitor, bortezomib, and the immunomodulatory drugs, lenalidomide and thalidomide, has resulted in improved outcomes for patients with multiple myeloma. However, there is still considerable controversy as to which regimen should be used as first-line therapy, which patients should be considered for autologous or allogeneic transplantation, and how consolidation or maintenance therapy is used in patients that have a good response to first-line therapy. The present paper will review clinical evidence from previous and ongoing studies to explore issues related to these questions.

Keywords Multiple myeloma · Bortezomib · Lenalidomide · Thalidomide · Stem cell transplantation

Introduction

The treatment of multiple myeloma (MM) has evolved tremendously over the past decade [1–4]. For example, the novel agents, bortezomib (BOR), lenalidomide (LEN) and thalidomide (THAL) are now widely used in the clinical treatment of MM. The wealth of data available from studies of different regimens, either alone or in combination, poses challenges in terms of determining the optimal composition and sequence of treatment regimens. In 2012, the Japanese Society for Myeloma (JSM) proposed revised guideline for MM therapy to incorporate data from recent studies (Fig. 1) [1]. Revised treatment guidelines from the National Comprehensive Cancer Network (NCCN) will also be published in 2013 [2] (Table 1). The high response rates associated with first-line therapy using novel agents may make the decision to utilize stem cell transplantation in young patients more difficult. By contrast, optimization of the use of novel agents is required to achieve a better quality of life in elderly patients.

R. Watanabe (✉) · M. Tokuhira · M. Kizaki
Division of Hematology, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan
e-mail: reikow@saitama-med.ac.jp

Induction therapy in patients eligible for autologous stem cell transplantation (ASCT)

High-dose therapy (HDT) and autologous stem cell transplantation (ASCT) is associated with good outcomes in patients younger than 65 years who do not have severe complications or cardiopulmonary failure. Therefore, the irreversible myelosuppressive agent melphalan, and other alkylating agents, should not be used as first-line therapy in patients who can potentially benefit from ASCT [1–4]. Before the development of BOR-, LEN- or THAL-containing regimens, a regimen of vincristine, doxorubicin and dexamethasone (VAD) was utilized as standard induction therapy for MM. It should be noted that LEN and THAL are not currently approved for use as frontline therapy under the Japanese medical insurance system. Data from phase III studies describing outcomes in response to regimens containing novel agents are summarized in Table 2 [5–13].

BOR is widely recognized as a basic agent in first-line therapy. BOR can be used in patients with renal failure, but its association with herpes zoster infection means that low-dose acyclovir should be used for prophylaxis in patients being treated with this agent.

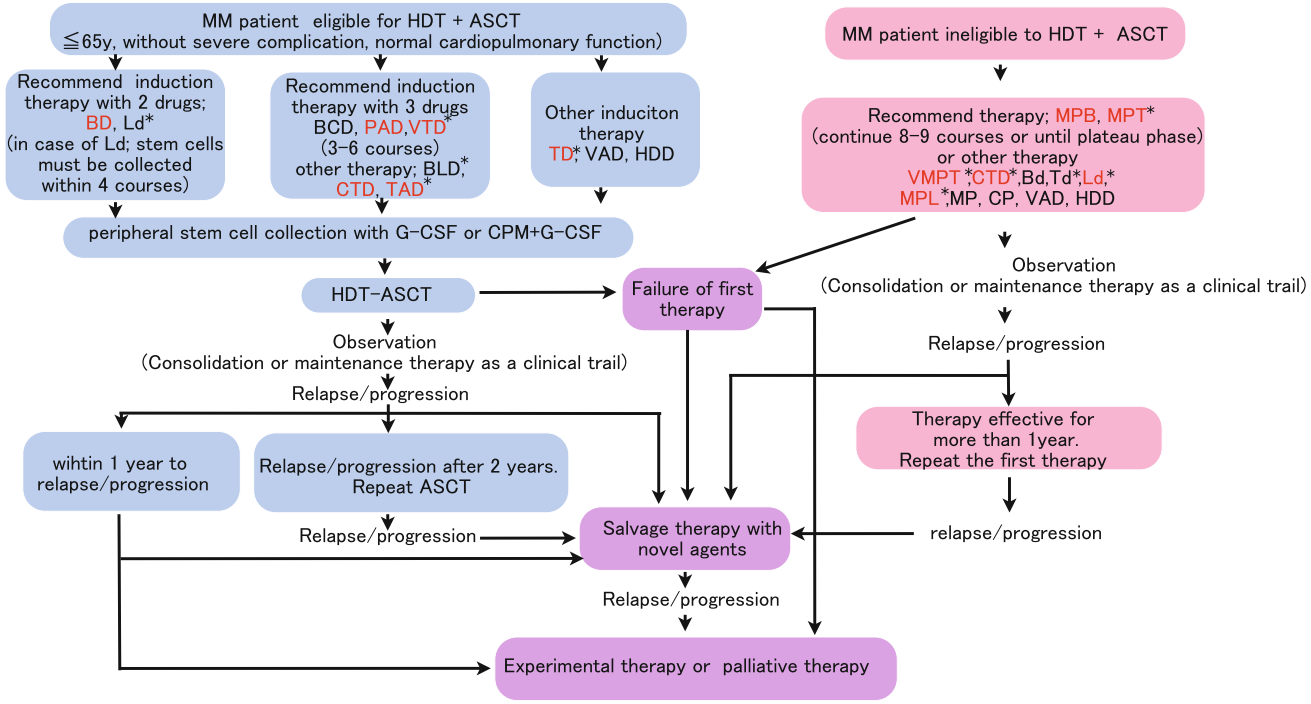

Fig. 1 Treatment algorithm for symptomatic multiple myeloma. *Asterisk* THAL and LEN are not permitted in Japanese insurance now. *Red characters* show existence of phase III trials. *HDT* high-dose chemotherapy, *ASCT* autologous stem cell transplantation, *PAD* bortezomib–doxorubicin–dexamethasone, *VTD* bortezomib–thalidomide–dexamethasone, *BCD* bortezomib–cyclophosphamide–dexamethasone, *BLD* bortezomib–lenalidomide–dexamethasone, *CTD* cyclophosphamide–thalidomide–dexamethasone, *TAD* thalidomide–doxorubicin–dexamethasone, *BD (Bd)* bortezomib–dexamethasone, *Ld* lenalidomide–dexamethasone, *TD (Td)* thalidomide–dexamethasone, *VAD* vincristine–doxorubicin–dexamethasone, *HDD* high-dose dexamethasone, *MPB* melphalan–prednisolone–bortezomib, *MPT* melphalan–prednisolone–thalidomide, *VMPT* bortezomib–melphalan–prednisolone–thalidomide, *MPL* melphalan–prednisolone–lenalidomide, *MP* melphalan–prednisolone, *CP* cyclophosphamide–prednisolone, *CPM* cyclophosphamide

BOR-based two- or three-drug combination regimens

In the phase III Intergroupe Franco du Myelome (IFM) 2005–2001 trial ($n = 482$) [5], BOR plus dexamethasone (BD) was compared with VAD. Overall response rates (ORR, 78.5 % in the BD arm vs. 62.8 % in the VAD arm), and rates of complete remission (CR), near CR (nCR), and very good partial response (VGPR) were significantly better in the BD arm when compared with standard chemotherapy. Of note, BD was effective in high-risk patients with International Staging System (ISS) III disease and cytogenetic abnormalities, such as 13-del. The BD arm was associated with lower hematological toxicity and higher incidences of >grade 2/3 peripheral neuropathy (PN) (29.7 % in BD vs. 13 % in VAD) when compared with the VAD arm. The HOVON/GMMG-HD4 trial [6] reported high ORR after induction therapy with BOR, doxorubicin and DEX (PAD) when compared with VAD. A significantly higher response rate was obtained in the PAD arm, and this advantage was maintained with superior ORR after ASCT. The incidence of grade 3/4 PN was higher with BOR than with VAD (16 vs. 7 %). A phase II study has demonstrated a rapid and profound response to cyclophosphamide (Cy), BOR, DEX (CyBorD) [14] in patients with newly diagnosed MM ($n = 33$). In response to this regimen, the ORR was 88 %, a response ≥VGPR occurred in 76 %, and CR/nCR occurred in 39 %. In the 23 patients that underwent ASCT and were evaluable at day 100, CR/nCR occurred in 70 %.

BOR + THAL regimen

The Italian Multiple Myeloma Network conducted the GIMEMA trial [7], which investigated the efficacy of BOR–THAL–DEX (VTD) versus THAL–DEX (TD). These conditioning regimens were followed by tandem ASCT and maintenance with the same regimen. ORR and progression-free survival (PFS) were significantly better in the VTD arm, although 3-year overall survival (OS) was similar when comparing the two arms. Grade 3/4 adverse events were more common with VTD than with TD (56 vs. 33 %). The incidence of PN was particularly high with VTD when compared with TD (10 vs. 2 %).

The Spanish Myeloma Group (PETHEMA/GEM) [8] compared VTD versus TD, versus alternating combination chemotherapy vincristine, carmustine (BCNU), melphalan, cyclophosphamide, prednisone (VBMCP)/vincristine, BCNU, doxorubicin, dexamethasone (VBAD) followed by bortezomib (VBMCP/VBAD/B). Pre- and post-ASCT CR

Table 1 NCCN guidelines version l. 2013 multiple myeloma

	Preferred regimens	Other regimens
Primary therapy for transplant candidates (assessed for response after 2 cycles)	BOR/DEX (category 1) BOR/Cy/DEX BOR/doxorubicin/DEX (category 1) BOR/LEN/DEX BOR/THAL/DEX (category 1) LEN/DEX (category 1)	DEX (category 2B) Liposomal doxorubicin/vincristine/DEX (DVD) (category 2B) THAL/DEX (category 2B)
Primary therapy for non-transplant candidates (assessed for response after 2 cycles)	BOR/DEX LEN/low-dose DEX (category 1) MEL/prednisone/BOR (MPB) (category 1) MEL/prednisone/LEN (MPL) (category 1) MEL/prednisone/THAL (MPT) (category 1)	DEX (category 2B) Liposomal doxorubicin/vincristine/DEX (DVD) (category 2B) MEL/prednisone (MP) THAL/DEX (category 2B) Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance therapy	BOR LEN (category 1) THAL (category 1)	Interferon (category 2B) Steroids (category 2B) THAL/prednisone (category 2B)
Salvage therapy	Repeat primary induction therapy (if relapse at $>$ 6 months) BOR (category 1) BOR/DEX (category 1) BOR/LEN/DEX BOR/liposomal doxorubicin (category 1) BOR/THAL/DEX Carfilzomib Cy/BOR/DEX Cy/LEN/DEX DEX/Cy/etoposide/cisplatin (DCEP) DEX/THAL/cisplatin/doxorubicin/Cy (DT-PACE) $\pm$ BOR (VTD-PACE) High-dose Cy LEN/DEX (category 1) THAL/DEX	Bendamustine BOR/vorinostat LEN/bendamustine/DEX

BOR bortezomib, *DEX* dexamethasone, *Cy* cyclophosphamide, *LEN* lenalidomide, *THAL* thalidomide

rates were significantly higher with VTD than with TD or with VBMCP/VBAD/B. The IFM [9] studied the efficacy of reduced-dose BOR–THAL–DEX (vtD) versus BD. After four cycles, the CR rate was the same in both groups (13 vs. 12 %). However, the VGPR plus CR rate was higher in the vtD arm when compared with the BD arm (49 vs. 36 %). Of note, the VGPR plus CR rate after ASCT was significantly higher in the vtD arm when compared with the BD arm (74 vs. 58 %), and the incidence of grade 3/4 PN was lower with vtD than with BD (14 vs. 34 %).

LEN-based regimen

LEN is a promising agent for use in induction therapy regimens and also in regimens for relapsed or refractory patients. The Southwest Oncology Group (SWOG) [10] S0232 study was conducted to compare LEN–DEX (LD) with high-dose DEX in patients with newly diagnosed MM. In this study, crossover to another arm was encouraged on progression. At interim analysis, many patients in the DEX arm ($n = 42$) crossed over to the LD arm. At the time, a preliminary report from the Eastern Cooperative Oncology Group (ECOG) phase III study (E4A03) [11] suggested that 1-year survival was significantly better in the LEN plus low-dose DEX (Ld) arm when compared with the LEN plus high-dose DEX (LD) arm, and this SWOG study closed early. The SWOG study [12] reported that PFS (78 vs. 52 %), ORR (78 vs. 48 %) and VGPR (63 vs. 16 %) were significantly better with LD than with DEX, but that 1-year OS was similar when comparing the two

Table 2 Phase III trials for patients eligible for autologous transplantation

Reference	Regimen	Patient (*N*)	≥VGPR (CR) after induction	≥VGPR (CR) after ASCT	PFS/TTP	OS
IFM 2005-01 Harousseau et al. [5]	BD (Dex or DCEP maintenance)	240	38 % (15 %)	54 % (35 %)	36 months	81 % at 3 years
	VAD (DCEP maintenance)	121	15 % (6 %) (+nCR)	37 % (18 %) (+nCR)	30 months	77 % at 3 years
HOVON-65/GMMG-HD4 Sonneveld et al. [6]	PAD (BOR maintenance)	413	42 % (11 %)	61 % (30 %)	46 % at 3 years	78 % at 3 years
	VAD (THAL maintenance)	414	15 % (5 %) (+nCR)	36 % (15 %) (+nCR)	42 % at 3 years	70 % at 3 years
GIMEMA MMY-3006 Cavo et al. [7]	VTD (VTD maintenance)	236	62 % (19 %)	82 % (42 %)	68 % at 3 years	86 % at 3 years
	TD (TD maintenance)	238	28 % (5 %)	64 % (30 %)	56 % at 3 years	84 % at 3 years
PETHEMA/GEM Rosiñol et al. [8]	VTD (LEN maintenance)	130	60 % (35 %)	(46 %)	56.2 months	74 % at 4 years
	TD	127	29 % (14 %)	(24 %)	28.2 months	65 % at 4 years
	VBMCP/VBAD/ BOR	129	36 % (21 %)	(38 %)	35.5 months	70 % at 4 years
IFM2007-02 Moreau et al. [9]	vtD	100	49 % (13 %)	74 % (31 %)	26 months	
	VD	99	36 % (12 %)	58 % (29 %)	30 months	
SWOG S0232 Zonder et al. [10]	LD	97	63 %			
	DEX	95	16 %			
ECOG E4A03 Rajkumar et al. [11]	LD	223	50 % (5 %)			
	Ld	222	40 % (4 %)			
HOVON50 Lokhorst et al. [12]	TAD (THAL maintenance)	268	37 % (3 %)	54 % (14 %)	34 months	73 months
	VAD (IFN maintenance)	268	18 % (2 %)	44 % (12 %)	25 months	60 months
MRC IX Morgan et al. [13]	CTD	548	43 % (13 %)	74 % (50 %)	27 months	NR
	CVAD	540	27 % (8 %)	62 % (50 %)	25 months	63 months

CR complete remission, *NA* not available, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *TTP* time to progression, *BOR* bortezomib, *LEN* lenalidomide, *THAL* thalidomide, *BD* bortezomib–dexamethasone, *VAD* vincristine–doxorubicin–dexamethasone, *PAD* bortezomib–doxorubicin–dexamethasone, *VTD* bortezomib–thalidomide–dexamethasone, *TD* thalidomide–dexamethasone, *VBMCP* vincristine–BCNU–melphalan–cyclophosphamide–prednisolone, *VBAD* vincristine–BCNU–doxorubicin–dexamethasone, *B* bortezomib, *vtD* reduced dose of boretzomib–thalidomide–dexamethasone, *VD* bortezomib–dexamethasone, *LD* lenalidomide–high-dose dexamethasone, *DEX* high-dose dexamethasone, *Ld* lenalidomide–reduced dose of dexamethasone, *CTD* cyclophosphamide–thalidomide–dexamethasone, *CVAD* cyclophosphamide–vincristine–doxorubicin–dexamethasone

arms. Toxicity ≥grade 3, including neutropenia (21 vs. 5 %) and deep vein thrombosis (DVT) (23.5 vs. 5 %), occurred more commonly in the LD arm than in the DEX arm.

The ECOG E4A03 study [11] was conducted to compare LD versus Ld. Of note, 79 % of the LD arm and 68 % of the Ld arm had CR or PR within four cycles. However, at interim analysis at 1 year, OS was 96 % in the Ld arm and 87 % in the LD arm ($p = 0.0002$). As a result, this clinical trial was discontinued, and patients in LD arm were crossed over to the Ld arm because of serious adverse effects in the LD arm. Toxic effects ≥grade 3 in during the first 4 months were more frequently observed in the LD arm than in the Ld arm, including DVT (26 vs. 12 %), infection (16 vs. 9 %), and general fatigue (15 vs. 9 %). Ld was also associated with better short-term OS and lower toxicity when compared with LD.

When using LEN in the early phase of MM treatment, clinicians should keep in mind that stem cells must be collected during the four courses of LEN, because a decrease in CD34-positive cells collected after prolonged LEN treatment has been reported [15].

BOR plus LEN regimen

The combination of BOR, LEN, and DEX (VRD) as primary therapy was evaluated in a phase 1/2 study [16]. This

regimen was associated with a high response rate (VGPR or better) of 74 %. Toxicities included sensory neuropathy (80 %) and fatigue (64 %), with ≥grade 3 neuropathy occurring in 2 % and ≥grade 3 fatigue occurring in 3 %. Thrombosis was rare (6 % overall). With a median follow-up of 21 months, the rate of 18-month PFS and 18-month OS was 75 and 97 %, respectively.

The randomized phase II EVOLUTION trial ($n = 140$) [17] evaluated the tolerability and efficacy of three- or four-drug regimens, including BOR, DEX, Cy, LEN (VDCR); BOR, DEX, LEN (VDR); BOR and DEX with Cy (VDC) or reduced Cy (VDC-mod). The ORR of the VDR arm after primary therapy followed by maintenance therapy with BOR was 85 %, with a CR occurring in 24 %. There was no substantial advantage with four-drug regimens when compared with three-drug regimens.

HDT + ASCT in the era of novel agents

Since the mid 1990s, HDT followed by ASCT has been considered the standard care for the frontline therapy in younger MM patients. Seven randomized trials investigated the efficacy of conventional chemotherapy (CCT) versus HDT + ASCT [18]. In all of them, the response rate was higher in the ASCT arm when compared with the CCT arm. In six of seven trials, event-free survival (EFS) was better for the ASCT arm when compared with the CCT arm. In three of seven trials, OS was better for the ASCT arm when compared with the CCT arm. One intent-to-treat trial compared early versus late ASCT [19] by randomizing 185 patients to receive ASCT (early ASCT) or a conventional dose chemotherapy regimen (late ASCT). In the latter group, ASCT was performed as rescue treatment. Although the estimated median survival was similar (64.6 months in early ASCT vs. 64 months in late ASCT), average time without symptoms, treatment, and treatment toxicity was 27.8 months in early ASCT versus 22.3 months in late ASCT. These data suggest that early ASCT is associated with better quality of life when compared with late ASCT.

Evaluation of the long-term prognostic significance of the response after ASCT was reported at a median follow-up of 153 months in 344 patients who underwent ASCT [20]. Achieving CR after ASCT is an important prognostic factor, and one landmark study showed a plateau phase in OS after 11 years; 35 % patients in the CR group and 11 % in the nCR + VGPR + PR group were alive at 17 years.

Over the past decade, the novel agents, BOR, LEN, and THAL, have been incorporated into frontline therapy for patients with MM. When compared with previously used chemotherapeutic agents, a higher CR rate and longer PFS has been achieved with novel agents containing frontline regimen. Therefore, the role of HDC + ASCT remains a matter of debate [21–24]: should all eligible patients with MM receive up front ASCT as a part of initial treatment or should ASCT be preserved as a salvage treatment for use at the time of progression of MM in patients initially treated with novel agents? Two large ongoing phase III studies are investigating the efficacy of up front HDC + ASCT. The first study is being conducted by the European Myeloma Network and is comparing VMP induction with high-dose melphalan and ASCT followed by VRD consolidation and LEN maintenance in patients with newly diagnosed MM. The second study is the Dana-Farber Cancer Institute (DFCI) 10-106 trial, which is a randomized trial of LEN, BOR, DEX versus HDT with SCT in patients younger than 65 years. Indications for ASCT may change based on the results of these studies.

Tandem ASCT refers to a planned second ASCT within 6 months after the first ASCT. According to the NCCN MM panel, a tandem transplant should be considered for all patients who are candidates for SCT and is an option for patients who do not achieve at least a VGPR after first ASCT [2]. The JSM also recommends peripheral stem cell collection in the early phase of treatment in case tandem ASCT is indicated [1].

Patients ineligible for HDT + ASCT

For patients ineligible for HDT + ASCT, melphalan plus prednisone (MP) has been considered as the standard therapy since the 1960s. However, PFS was approximately 18 months and OS was 2–3 years (at best) in the population treated with MP [1, 2]. The addition of novel agents to this standard therapy has resulted in a higher response rate and prolongation of survival in several trials (Table 3) [25–40]. However, clinicians should be aware that there is an increased risk of treatment-related adverse events in ASCT-ineligible patients when compared with ASCT-eligible patients in response to novel agent-containing regimens. Palumbo [3] proposed guidelines for dose reduction of novel agents and protocol modification in elderly patients with MM (Table 4).

BOR-based regimen

The combination of BOR and MP (VMP) versus MP was investigated in the large international phase III VISTA (BOR as initial standard therapy in MM) trial ($n = 682$) [25–27]. VMP was significantly superior to MP in terms of PR (71 vs. 35 %), CR (30 vs. 4 %), PFS (24 vs. 16 months) and OS. In fact, the 3-year OS rate was 68.5 % in the VMP arm when compared with 54.0 % in the MP arm, and time to progression and OS was unaffected by advanced age,

Table 3 Phase III trials for patients ineligible for autologous transplantation

Reference	Regimen	Patient (*N*)	≥PR (CR)	PFS/TTP (months)	OS
Bortezomib-based regimens VISTA San Miguel et al. [25–27]	VMP	344	71 % (30 %)	24	46 % at 5 years
	MP	338	35 % (4 %)	16.6	34.4 % at 5 years
Niesvizky et al. [28]	VD (BOR maintenance)	168	71 % (31 %)[a]	14[a]	NA
	VTD (BOR maintenance)	167	79 % (38 %)[a]	18	
	VMP (BOR maintenance)	168	73 % (34 %)[a]	17[b]	
Mateos et al. [29]	VMP (VT or VP maintenance)	130	81 % (20 %)	34	74 % at 3 years
	VTP (VT or VP maintenance)	130	79 % (27 %)	34	65 % at 3 years
Palumbo et al. [30]	MPB	257	42 % (2 %)	27	85 % at 3 years
	BMPT (VT maintenance)	254	37 % (2 %)	27	80 % at 3 years
Lenalidomide-based regimens Rajkumar et al. [31]	LD	223	81 % (5 %)	19	67 % at 2 years[c]
	Ld	222	70 % (4 %)	25	82 % at 2 years[c]
MM-015 Palumbo et al. [32]	MPR-R (LEN maintenance)	152	77 % (16 %)	31	45.2 months
	MPR	153	67 % (13 %)	14	NR
	MP	154	50 % (4 %)	13	NR
Thalidomide-based regimens GIMEMA Palumbo et al. [33]	MPT (THAL maintenance)	167	76 % (16 %)	21.8	45 months
	MP	164	48 % (4 %)	14.5	47.6 months
IFM 99-06 Facon et al. [34]	MPT	124	76 % (13 %)	27.5	51.5 months
	MP	193	35 % (2 %)	17.8	33.2 months
IFM 01/01 Hulin et al. [35]	MPT	113	62 % (7 %)	24.1	44 months
	MP	116	31 % (1 %)	18.5	29.1 months
HOVON49 Wijermans et al. [36]	MPT (THAL maintenance)	165	66 % (NA)	13	40 months
	MP	168	45 % (NA)	10	31 months
NMSG Waage et al. [37]	MPT (THAL maintenance)	182	57 % (13 %)	15	29 months
	MP	175	40 % (4 %)	14	32 months
TMSG Beksac et al. [38]	MPT	60	58 % (9 %)	21	26 months
	MP	62	38 % (9 %)	14	28 months
Ludwig et al. [39]	TD	144	42 % (2 %)	16.7	41.5 months
	MP	145	37 % (2 %)	20.7	49.4 months
MRC Myeloma IX Morgan et al. [40]	CTDa	426	64 % (13 %)	13.0	33.2 months
	MP	423	33 % (2 %)	12.4	30.6 months

CR complete remission, *MP* melphalan–prednisone, *NA* not available, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *TTP* time to progression, *BOR* bortezomib, *LEN* lenalidomide, *THAL* thalidomide, *VMP* bortezomib–melphalan–prednisolone, *VD* bortezomib–dexamethasone, *VTD* bortezomib–thalidomide–dexamethasone, *LD* lenalidomide–high-dose dexamethasone, *Ld* lenalidomide—low-dose dexamethasone, *MPR* melphalan–prednisolone–lenalidomide, *MPT* melphalan–prednisolone–thalidomide, *CTDa* cyclophosphamide–thalidomide–attenuated dose dexamethasone

[a] CR + nCR

[b] From the maintenance therapy

[c] OS in patients older than 65 years

renal impairment, and adverse cytogenetics [e.g., *t*(4;14), *t*(4;16), del(p17)] [26]. Updated results at a median follow-up of 60 months showed that the 5-year OS rate was 46 % in the VMP arm and 34.4 % in the MP arm [27]. Of note, patients with relapse after VMP were not resistant to salvage therapies [26]. The response rate after second-line therapy with BOR, THAL, and LEN in the VMP arm versus the MP arm was 50 %/58 %, 46 %/55 %, and 62 %/56 %, respectively [26]. They also compared VMP patients who received BOR salvage therapy with MP patients who received BOR salvage therapy. The median survival was significantly longer in the VMP arm (56.4 months) than in the MP arm (45.4 months), suggesting that BOR-based treatment should be used as first-line therapy rather than reserving it for salvage therapy.

In terms of adverse events, PN was the major cause of discontinuation of BOR in the VISTA study. Subsequently, the Italian Study [30] investigated the utility of four-drug induction therapy with THAL plus VMP followed by BOR plus THAL maintenance therapy (VMPT-VT) when

Table 4 Suggested age-adjusted dose reduction in patients with multiple myeloma

Drug	Age < 65 years	Age 65–75 years	Age > 75 years
Dexamethasone	Dose of 40 mg/day given orally on days 1–4, 15–18 every 4 weeks; or 40 mg/day given orally on days 1, 8, 15, 22 every 4 weeks	Dose of 40 mg/day given orally on days 1, 8, 15, 22 every 4 weeks	Dose of 20 mg/day given orally on days 1, 8, 15, 22 every 4 weeks
Melphalan	Dose of 0.25 mg/kg given orally on days 1–4 every 6 weeks	Dose of 0.25 mg/kg given orally on days 1–4 every 6 weeks; or 0.18 mg/kg given orally on days 1–4 every 4 weeks	Dose of 0.18 mg/kg given orally on days 1–4 every 6 weeks; or 0.13 mg/kg given orally on days 1–4 every 4 weeks
Cyclophosphamide	Dose of 300 mg/m^2 given orally on days 1, 8, 15, 22 every 4 weeks	Dose of 300 mg/m^2 given orally on days 1, 8, 15, 22 every 4 weeks, or 50 mg/day given orally on days 1–21 every 4 weeks	Dose of 50 mg/m^2 given orally on days 1–21 every 4 weeks; or 50 mg/day every other day given orally on days 1–21 every 4 weeks
Thalidomide	Dose of 200 mg/day given orally continuously	Dose of 100 or 200 mg/day given orally continuously	Dose of 50–100 mg/day given orally continuously
Lenalidomide	Dose of 25 mg/day given orally on days 1–21 every 4 weeks	Dose of 15–25 mg/day given orally on days 1–21 every 4 weeks	Dose of 10–25 mg/day given orally on days 1–21 every 4 weeks
Bortezomib	Dose of 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 weeks	Dose of 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 weeks; or 1.3 mg/m^2 given bolus intravenous infusion on days 1, 8, 15, 22 every 5 weeks	Dose of 1.0–1.3 mg/m^2 given as bolus intravenous infusion on days 1, 8, 15, 22 every 5 weeks

compared with MPB. Data from the interim analysis suggest that BOR dosing should be reduced from twice a week to once a week during the study period because of the toxicity of BOR. No difference was observed in the response rate, OS, and PFS when comparing the two BOR treatment schedules. Another study conducted by a Spanish group [29] compared MPB with BOR + THAL + prednisone (VTP) as induction therapy in elderly patients. BOR was administered twice a week (days 1, 4, 8, 11, 22, 25, 29, and 32) in the first cycle (6 weeks) only and was administered once a week during the next five cycles of induction therapy. After induction therapy, patients were randomized to BOR with THAL or BOR with prednisone maintenance therapy. Grade 3 or more PN occurred in 7 % in the MPB arm and in 9 % in the VTP arm during the induction phase and occurred in 2 % in the BOR with prednisone arm and in 7 % in the BOR with THAL arm during the maintenance phase.

We are currently conducting a phase II trial of MPB induction therapy, consisting of once weekly BOR induction therapy followed by a biweekly BOR maintenance regimen for elderly patients; endpoints in this study include QOL and PFS. Recent interim analysis has shown that adverse effects concerning PN rarely occurred with this BOR treatment schedule (Tokuhira M et al., personal communication).

The efficacy and safety of alternative routes of BOR administration has recently been described [41]. A large phase III trial demonstrated that subcutaneous (SC) administration was not inferior to intravenous (IV) administration of BOR in terms of ORR after four cycles or in terms of TTP and 1-year OS. BOR-induced PN of any grade (38 vs. 53 %) and more than or equal to grade 2 (24 vs. 41 %) or grade 3 (6 vs. 16 %) occurred less frequently with SC administration than with IV administration. Therefore, SC administration of BOR may be a better injection route than IV administration.

LEN-based regimen

LEN plus high-dose DEX (LD) versus LEN plus low-dose DEX (Ld) was examined in an ECOG study ($n = 445$) [31]. The PR rate after four cycles of therapy was 79 % in the LD arm versus 68 % in the Ld arm. However, interim analysis at 1 year showed an overall survival rate of 96 % in the Ld arm when compared with 87 % in the LD arm. Further, 12 of 222 patients in the LD arm and one of 220 patients in the Ld arm died within the first 4 months. Therefore, the trial was terminated, and patients in the LD arm were crossed over to the Ld arm. Grade 3 or worse toxicity was reported in 53 % in the LD arm and in 35 % of the Ld arm within the first 4 months. Common toxicities were DVT (LD/Ld: 26 %/12 %), infection (LD/Ld: 16 %/9 %), and fatigue (LD/Ld: 15 %/9 %). In elderly patients, toxicity was greater with LD than with Ld.

A phase III multicenter randomized double-blind controlled trial (MM-015) [32] compared melphalan–prednisone–lenalidomide (MPR) induction and LEN maintenance (MPR-R) ($n = 152$) versus MPR induction and placebo maintenance ($n = 153$) or MP and placebo maintenance

($n = 154$). The median follow-up period was 30 months. PFS was significantly longer with MPR-R (30 months) than with MPR (14 months) or MP (13 months). The response rates associated with MPR-R and MPR were superior to that associated with MP. However, PFS associated with MPR-R was age-dependent; MPR-R significantly prolonged PFS among patients 65–75 years of age but not in those older than 75 years of age. During induction therapy, the most frequent adverse events were hematologic events; grade 4 neutropenia was reported in 35 % in the MPR-R arm, 32 % in the MPR arm, and in 8 % in the MP arm. The 3-year rate of second primary malignancies (SPMs) was 7 % in the MRR-R arm, 7 % in the MRR arm, and 3 % in the MP arm.

Melphalan–prednisone–thalidomide (MPT)

Several phase III trials of patients with newly diagnosed MM have reported [33–39] significantly higher ORR with MPT (approximately 30 %) when compared with MP (approximately 5 %). But the OS advantage with addition of THAL was not clear. The IFM 01-01 study ($n = 232$) [35] compared the utility of MPT versus MP in elderly patients (age $\geq$ 75 years). At a median follow-up of 47.5 months, median OS was significantly prolonged in the MPT arm (44.0 months) when compared with the MP arm (29.1 months) ($p = 0.028$). Further, median PFS was 24.1 and 18.5 months in the MPT and MP arms, respectively ($p = 0.001$). The HOVON group study ($n = 333$) [36] also compared MPT with MP in elderly patients with newly diagnosed MM. ORR was significantly higher with MPT (66 %) than with MP (45 %), but 55 % of the MP group and 34 % of the MPT group developed progressive disease. EFS was 13 and 9 months and OS was 41 and 31 months in the MPT and MP arms, respectively.

A meta-analysis of six randomized trials ($n = 1680$) [42] compared MPT and MP. MPT was associated with better outcomes but also with increased non-hematologic toxicities. Serious non-hematologic toxicities, older age, poor performance status, and high creatinine level were predictors of poor survival.

Maintenance therapy

Optimization of maintenance therapy has been attempted in an effort to prolong the duration of response to initial treatment. Several randomized phase III studies have investigated THAL maintenance after ASCT [43–47]. There was improvement in the rate of PFS, but OS benefit was not always evident. Results from the IFM [35], HOVON [36], MRC [47] studies suggested that THAL has no benefit in patients with cytogenetic risk factors and may even be disadvantageous in patients with MRC del(17p). However, the TT2 study reported that THAL did indeed provide benefit in patients with cytogenetic risk groups according to the G-band method [46]. The HOVON49 trial was the only study to demonstrate a modest benefit for thalidomide maintenance after induction therapy in ASCT-ineligible elderly patients [36]. Because of its toxicity (e.g., PN) the average patient cannot tolerate THAL for more than 1 year. A dose of 50–100 mg/day is recommended [45].

LEN maintenance after ASCT was investigated in large trials conducted by the IFM ($n = 614$) [48] and CALGB ($n = 460$) [49]. In the IFM trial, results at 24 months revealed an increased incidence of SPMs, and discontinuation of LEN was recommended. Significant PFS prolongation was observed in both the IFM trial and in CALGB, but 4 years after randomization, there was no difference in OS when comparing LEN maintenance and placebo. In the CALGB study, improvement in TTP and OS was clearly present at the 34-month time point. Previous use of LEN or THAL in first-line therapy has no effect on the response to LEN. The optimal dose of LEN in this setting is 10–15 mg/day, and treatment duration must not be longer than 2 years in order to minimize the risk of developing SPMs.

The efficacy of LEN maintenance after induction therapy in ASCT-ineligible patients was described in the MM-015 study [32]. At a median observation period of 21 months, PFS was significantly longer in the MPR-R arm when compared with patients who did not receive maintenance therapy, but there was no difference in OS when comparing the two arms [32].

BOR as maintenance therapy is being investigated in phase III trials [28]. A preliminary report from the HOVON-65/GMMG-HD4 trial showed that BOR maintenance was associated with an increased response rate and PFS after ASCT when compared with another arm containing THAL maintenance. But the appropriate duration or dose of BOR has not yet been determined. There are no novel agents that have been approved for use in maintenance therapy, so further study is needed.

Therapy for relapse or refractory patients

Salvage therapy should be considered for patients with relapse after ASCT, for patients with primary progressive MM, and for patients ineligible for ASCT with relapse or progressive disease after frontline therapy. Appropriate therapy for a given situation depends on the aggressiveness of the disease (e.g., presence of extensive bone disease, plasma cell leukemia, extramedullary disease, cytogenetic abnormalities) and on patient-related factors (e.g., organ function, performance status, adverse effect of

prior therapy, and the availability of stem cell source) [50–52]. In these settings, the quality and duration of the response to previous therapy are thought to be the most important prognostic factors. In the case of MM relapse after a long response duration, repeat use of the previous effective therapy is generally recommended as salvage therapy [50–52]. In contrast, an aggressive disease that relapses within 6–12 months or that is refractory to frontline therapy warrants the use of an alternative regimen [3].

Recently, THAL, BOR and LEN have been incorporated into frontline treatment strategies. These changes raise new questions regarding the efficacy or feasibility of re-treatment with novel agents. As goals for treatment at relapse, several studies revealed that better quality of response as associated with better outcome for patients with relapsed or refractory MM, even beyond frontline therapy. For relapse more than 2 years after the first ASCT, patients should receive HDC + ASCT with the expectation of having long subsequent PFS. In the case of relapse within 1 year of ASCT, salvage treatment with novel agents (BOR, LEN, or THAL) should be conducted.

Considering the different novel drugs for treatment of MM, there are many different salvage therapy regimens. The phase III APEX trial reported that median TTP (6.22 vs. 3.49 months) and 1-year OS (80 vs. 66 %) was significantly better with BOR monotherapy than with high-dose DEX [53].

In an international phase III randomized study ($n = 647$), the combination of BOR with pegylated liposomal doxorubicin (PLD) [54] was compared with BOR monotherapy for relapsed/refractory MM patients. The median duration of response increased from 7.0 to 10.2 months with the addition of PLD. PLD therapy was associated with an increased incidence of grade 3/4 neutropenia, thrombocytopenia, asthenia, fatigue, diarrhea, and hand-foot syndrome when compared with BOR monotherapy.

A retrospective analysis of the efficacy of treatments at relapse was conducted in the phase III VISTA trial [56]. That study established the superiority of VMP over MP as initial treatment for elderly patients. Response rates to subsequent bortezomib-based therapy appeared similar after VMP or MP (47 vs. 59 %). The authors concluded that patients who relapsed after treatment with a BOR-based regimen were not intrinsically more resistant to subsequent therapies when compared with those who relapsed after MP. Further, these patients can be successfully treated with subsequent BOR- or LEN- or THAL-based regimens.

The efficacy of LD compared with high-dose DEX alone in the relapsed/refractory setting was confirmed in a large phase III study (MM-009, MM-010) [55, 56]. In the MM-009 study, previously treated MM patients ($n = 353$) had increased OS and median TTP in the LD arm when compared with the DEX arm. Similar observations were made in the MM-010 study ($n = 692$), in which thrombocytopenia and neutropenia were reported as frequent adverse events. Dose reduction of LEN is needed in patients with renal dysfunction. A recent retrospective analysis of SPMs associated with LEN [57] reported that the incidence rate (IR, event per 100 patients) of SRMs was 3.98 in the LD arm versus 1.38 in the DEX arm. Therefore, patients with a prior history of cancer should be carefully evaluated before and during LEN treatment using standard cancer screening.

THAL has efficacy in patients with relapsed/refractory MM. THAL monotherapy was associated with an ORR of 28.2 % and a CR of 1.6 % at a dose of 200–800 mg. Thromboembolism and discontinuation due to intolerance occurred in 2.7 and 14.9 %, respectively [58]. The use of THAL and DEX in patients with relapsed/refractory MM is associated with a higher response rate (approximately 50 % more than or equal to PR) when compared with thalidomide monotherapy [59]. The utility of THAL monotherapy may be limited, suggesting that other cytotoxic agent should be used to improve the response rate or PFS in patients with relapsed/refractory MM. PLD and other cytotoxic regimens are promising agents for this purpose. Of note, the adverse effects of THAL were potentiated when THAL was used in combination with other agents. Indeed, DVT occurs in up to 10 % of patients treated with THAL plus DEX and in 30 % of patients treated with other cytotoxic drugs [59, 60]. Thus, patients at risk for DVT should be treated with aspirin for prophylactic purposes.

For relapsed/refractory patient, many novel agents have been developed [61, 62], and clinical trials of carfilzomib and MLN9708 are now ongoing in Japan.

Conclusion

Treatment strategies for MM have changed over the last decade and now incorporate the early use of novel agents. For ASCT-eligible patients, induction therapy with novel agents and ASCT is recommended. For ASCT-ineligible patients, induction therapy with novel agents is recommended. The optimal regimen for use as maintenance therapy remains unclear. In patients with relapsed/refractory MM, novel therapy can prolong the response or survival. Adverse effects are common with novel agents for treatment of MM, and preventative measures and dose/schedule adjustment may be needed to minimize these events. The multitude of available agents means that the optimal regimen and sequence for treatment of MM remains unclear, and further clinical studies are needed to remedy this uncertainty.

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Japanese Society of Myeloma. Treatment guidelines of multiple myeloma. Version 3: Bunkodo 2012.
2. NCCN guidelines. Version 1. 2013 multiple myeloma.
3. Palumbo A, Anderson K. Multiple myeloma. New Engl J Med. 2011;364:1046–60.
4. Moreau P, Richardson PG, Cavo M, Orlowski RZ, San Miguel JF, Palumbo A, Harousseau JL. Proteasome inhibitor in multiple myeloma: 10 years later. Blood. 2012;120:947–59.
5. Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, Lenain P, Hulin C, Facon T, Casassus P, Michallet M, Maisonneuve H, Benboubker L, Maloisel F, Petillon MO, Webb I, Mathiot C, Moreau P. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005–01 phase III trial. J Clin Oncol. 2010;28:4621–9.
6. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, Zweegman S, Vellenga E, Broyl A, Blau IW, Weisel KC, Wittebol S, Bos GM, Stevens-Kroef M, Scheid C, Pfreundschuh M, Hose D, Jauch A, van der Velde H, Raymakers R, Schaafsma MR, Kersten MJ, van Marwijk-Kooy M, Duehrsen U, Lindemann W, Wijermans PW, Lokhorst HM, Goldschmidt HM. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol. 2012;30:2946–55.
7. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, Di Raimondo F, Crippa C, Zamagni E, Palumbo A, Offidani M, Corradini P, Narni F, Spadano A, Pescosta N, Deliliers GL, Ledda A, Cellini C, Caravita T, Tosi P, Baccarani M, GIMEMA Italian Myeloma Network. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous transplantation in newly diagnosed multiple myeloma: a radomised phase 3 study. Lancet. 2010;376:2075–85.
8. Rosiñol L, Oriol A, Teruel AI, Hernández D, López-Jiménez J, de la Rubia J, Granell M, Besalduch J, Palomera L, González Y, Etxebeste MA, Díaz-Mediavilla J, Hernández MT, de Arriba F, Gutiérrez NC, Martín-Ramos ML, Cibeira MT, Mateos MV, Martínez J, Alegre A, Lahuerta JJ, San Miguel J, Bladé J, Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma (PETHEMA/GEM) group. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2011;120:1589–96.
9. Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, Doyen C, Garderet L, Randriamalala E, Araujo C, Lepeu G, Marit G, Caillot D, Escoffre M, Lioure B, Benboubker L, Pégourié B, Kolb B, Stoppa AM, Fuzibet JG, Decaux O, Dib M, Berthou C, Chaleteix C, Sebban C, Traullé C, Fontan J, Wetterwald M, Lenain P, Mathiot C, Harousseau JL. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011;118:5752–8.
10. Zonder JA, Crowley J, Hussein MA, Bolejack V, Moore DF Sr, Whittenberger BF, Abidi MH, Durie BG, Barlogie B. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). Blood. 2010;116:5838–41.
11. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, Abonour R, Siegel DS, Katz M, Greipp PR, Eastern Cooperative Oncology Group. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomized controlled trial. Lancet Oncol. 2010;11:29–37.
12. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, von dem Borne P, Wijermans P, Schaafsma R, de Weerdt O, Wittebol S, Delforge M, Berenschot H, Bos GM, Jie KS, Sinnige H, van Marwijk-Kooy M, Joosten P, Minnema MC, van Ammerlaan R, Sonneveld P, Dutch-Belgian Hemato-Oncology Group (HOVON). A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood. 2010;115:1113–20.
13. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Navarro Coy N, Cook G, Feyler S, Johnson PR, Rudin C, Drayson MT, Owen RG, Ross FM, Russell NH, Jackson GH, Child JA, National Cancer Research Institute Haematological Oncology Clinical Studies Group. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematologica. 2012;97:442–50.
14. Reeder CB, Reece DE, Kukreti V. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood. 2010;115:3416–7.
15. Kumar S, Giralt S, Stadtmauer EA, Harousseau JL, Palumbo A, Bensinger W, Comenzo RL, Lentzsch S, Munshi N, Niesvizky R, San Miguel J, Ludwig H, Bergsagel L, Blade J, Lonial S, Anderson KC, Tosi P, Sonneveld P, Sezer O, Vesole D, Cavo M, Einsele H, Richardson PG, Durie BG, Rajkumar SV, International Myeloma Working Group. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. Blood. 2009;114:1729–35.
16. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, Avigan DE, Xie W, Ghobrial IM, Schlossman RL, Mazumder A, Munshi NC, Vesole DH, Joyce R, Kaufman JL, Doss D, Warren DL, Lunde LE, Kaster S, Delaney C, Hideshima T, Mitsiades CS, Knight R, Esseltine DL, Anderson KC. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116:678–86.
17. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, Stewart AK, Turturro F, Rifkin R, Wolf J, Estevam J, Mulligan G, Shi H, Webb IJ, Rajkumar SV. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119:4375–82.
18. Moreau P, Avet-Loiseau H, Harousseau JL, Attal M. Current trends in autologous stem cell transplantation for myeloma in the era of novel therapies. J Clin Oncol. 2011;29:1898–906.
19. Fermand JP, Ravaud P, Chevret S, Divine M, Leblond V, Belanger C, Macro M, Pertuiset E, Dreyfus F, Mariette X, Boccacio C, Brouet JC. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood. 1998;92:3131–6.
20. Martinez-Lopez J, Blade J, Mateos MV, Grande C, Alegre A, García-Laraña J, Sureda A, de la Rubia J, Conde E, Martinez R, de Arriba F, Viguria MC, Besalduch J, Cabrera R, Gonzalez-San

Miguel JD, Guzman-Zamudio JL, Gomez del Castillo MC, Moraleda JM, García-Ruiz JC, San Miguel J, Lahuerta JJ, Grupo Español de MM, Programa para el Estudio de la Terapé utica en Hemopatía Maligna. Long-term prognostic significance of response in myeloma after stem cell transplantation. Blood. 2011;118:529–34.
21. Moreau P, Rajukumar SV. Should all eligible patients with multiple myeloma receive autologous stem-cell transplant as part of initial treatment? Leuk Res. 2012;36:677–81.
22. Moreau P, Giralt S. Optimizing therapy for transplant-eligible patients with newly diagnosed multiple myeloma. Leuk Res. 2012;36(Suppl 1):S13–8.
23. Kapoor P, Rajukmar SV. Update on risk stratification and treatment of newly diagnosed multiple myeloma. Int J Hematol. 2011;94:310–20.
24. Johnson SK, Heuck CJ, Albino AP, Qu P, Zhang Q, Barlogie B, Shaughnessy JD Jr. The use of molecular-based risk stratification and pharmacogenomics for outcome prediction and personalized therapeutic management of multiple myeloma. Int J Hematol. 2011;94:321–33.
25. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, Dmoszynska A, Abdulkadyrov KM, Schots R, Jiang B, Mateos MV, Anderson KC, Esseltine DL, Liu K, Cakana A, van de Velde H, Richardson PG, VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359:906–17.
26. Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, Dmoszynska A, Abdulkadyrov KM, Schots R, Jiang B, Esseltine DL, Liu K, Cakana A, van de Velde H, San Miguel JF. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28:2259–66.
27. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, Dmoszynska A, Abdulkadyrov KM, Delforge M, Jiang B, Mateos MV, Anderson KC, Esseltine DL, Liu K, Deraedt W, Cakana A, van de Velde H, Richardson PG, Persistent overall survival benefit and no increased risk of second malignancies with bortezomib–melphalan–prednisone versus melphalan–prednisone in patients with previously untreated multiple myeloma. J Clin Oncol. 2012. (in press).
28. Niesvizky R, Flinn IW, Rifkin RM, Gabrail NY, Charu V, Clowney B, Essell J, Gaffar YA, Warr TA, Neuwirth R, Corzo D, and Reeves JA. Phase 3b UPFRONT Study: safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients. Blood 2010; 116:Abstract 619.
29. Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, de Paz R, García-Laraña J, Bengoechea E, Martín A, Mediavilla JD, Palomera L, de Arriba F, González Y, Hernández JM, Sureda A, Bello JL, Bargay J, Peñalver FJ, Ribera JM, Martín-Mateos ML, García-Sanz R, Cibeira MT, Ramos ML, Vidriales MB, Paiva B, Montalbán MA, Lahuerta JJ, Bladé J, Miguel JF. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol. 2010;11:931–41.
30. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, Offidani M, Patriarca F, Nozzoli C, Guglielmelli T, Benevolo G, Callea V, Baldini L, Morabito F, Grasso M, Leonardi G, Rizzo M, Falcone AP, Gottardi D, Montefusco V, Musto P, Petrucci MT, Ciccone G, Boccadoro M. Bortezomib–melphalan–prednisone–thalidomide followed by maintenance with bortezomib–thalidomide compared with bortezomib–melphalan–prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol. 2010;28:5101–9.
31. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, Abonour R, Siegel DS, Katz M, Greipp PR, Eastern Cooperative Oncology Group. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomized controlled trial. Lancet Oncol. 2010;11:29–37.
32. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, Gisslinger H, Wiktor-Jędrzejczak W, Zodelava M, Weisel K, Cascavilla N, Iosava G, Cavo M, Kloczko J, Bladé J, Beksac M, Spicka I, Plesner T, Radke J, Langer C, Ben Yehuda D, Corso A, Herbein L, Yu Z, Mei J, Jacques C, Dimopoulos MA, MM-015 Investigators. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. New Engl J Med. 2012;366:1759–69.
33. Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, Montanaro M, Ria R, Capaldi A, Zambello R, Benevolo G, Derudas D, Dore F, Cavallo F, Gay F, Falco P, Ciccone G, Musto P, Cavo M, Boccadoro M. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood. 2008;112:3107–14.
34. Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, Renaud M, Harousseau JL, Guillerm G, Chaleteix C, Dib M, Voillat L, Maisonneuve H, Troncy J, Dorvaux V, Monconduit M, Martin C, Casassus P, Jaubert J, Jardel H, Doyen C, Kolb B, Anglaret B, Grosbois B, Yakoub-Agha I, Mathiot C, Avet-Loiseau H, Intergroupe Francophone du Myélome. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007;370:1209–18.
35. Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, Dib M, Guillerm G, Salles B, Eschard JP, Lenain P, Casassus P, Azaïs I, Decaux O, Garderet L, Mathiot C, Fontan J, Lafon I, Virion JM, Moreau P. E Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol. 2009;27:3664–70.
36. Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H, Zweegman S, van Marwijk Kooy M, van der Griend R, Lokhorst H, Sonneveld P, Dutch-Belgium Cooperative Group HOVON. Phase III study of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 study. J Clin Oncol. 2010;28:3160–6.
37. Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Björkstrand B, Carlson K, Dahl IM, Forsberg K, Gulbrandsen N, Haukås E, Hjertner O, Hjorth M, Karlsson T, Knudsen LM, Nielsen JL, Linder O, Mellqvist UH, Nesthus I, Rolke J, Strandberg M, Sørbø JH, Wisløff F, Juliusson G, Turesson I, Nordic Myeloma Study Group. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood. 2010;116:1405–12.
38. Beksac M, Haznedar R, Firatli-Tuglular T, Ozdogu H, Aydogdu I, Konuk N, Sucak G, Kaygusuz I, Karakus S, Kaya E, Ali R, Gulbas Z, Ozet G, Goker H, Undar L, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol. 2011;86:16–22.

39. Ludwig H, Hajek R, Tóthová E, Drach J, Adam Z, Labar B, Egyed M, Spicka I, Gisslinger H, Greil R, Kuhn I, Zojer N, Hinke A. Thalidomide–dexamethasone compared with melphalan–prednisolone in elderly patients with multiple myeloma. Blood. 2009;113:3435–42.
40. Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ, Navarro Coy N, Cook G, Feyler S, Byrne JL, Roddie H, Rudin C, Drayson MT, Owen RG, Ross FM, Jackson GH, Child JA, NCRI Haematological Oncology Study Group. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood. 2011;118(5):1231–8.
41. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, Rekhtman G, Masliak Z, Robak T, Shubina A, Arnulf B, Kropff M, Cavet J, Esseltine DL, Feng H, Girgis S, van de Velde H, Deraedt W, Harousseau JL. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. Lancet Oncol. 2011;12(15):431–40.
42. Palumbo A, Waage A, Hulin C, Beksac M, Zweegman S, Gay F, Gimsing P, Leleu X, Wijermans P, Sucak G, Pezzatti S, Juliusson G, Pégourié B, Schaafsma M, Galli M, Turesson I, Kolb B, van der Holt B, Baldi I, Rolke J, Ciccone G, Wetterwald M, Lokhorst H, Boccadoro M, Rodon P, Sonneveld P. Safety of thalidomide in newly diagnosed elderly myeloma patients: a individual patient data meta-analysis of six randomized trials. Haematologica. 2013;91:87–94.
43. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, Fassas A, Zangari M, Hollmig K, Pineda-Roman M, Lee C, Talamo G, Thertulien R, Kiwan E, Krishna S, Fox M, Crowley J. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354:1021–30.
44. Ludwig H, Durie BG, McCarthy P, Palumbo A, San Miguel J, Barlogie B, Morgan G, Sonneveld P, Spencer A, Andersen KC, Facon T, Stewart KA, Einsele H, Mateos MV, Wijermans P, Waage A, Beksac M, Richardson PG, Hulin C, Niesvizky R, Lokhorst H, Landgren O, Bergsagel PL, Orlowski R, Hinke A, Cavo M, Attal M, International Myeloma Working Group. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012;119:3003–15.
45. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, Yakoub Agha I, Bourhis JH, Garderet L, Pegourie B, Dumontet C, Renaud M, Voillat L, Berthou C, Marit G, Monconduit M, Caillot D, Grobois B, Avet-Loiseau H, Moreau P, Facon T, Inter-Groupe Francophone du Myélome (IFM). Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108:3289–94.
46. Barlogie B, Attal M, Crowley J, van Rhee F, Szymonifka J, Moreau P, Durie BG, Harousseau JL. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the Intergroupe Francophone du Myelome, Southwest Oncology Group, and University of Arkansas for Medical sciences. J Clin Oncol. 2010;28:1209–14.
47. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, Coy NN, Cook G, Russell NH, Rudin C, Roddie H, Drayson MT, Owen RG, Ross FM, Jackson GH, Child JA, National Cancer Research Institute Haematological Oncology Clinical Studies Group. The role of maintenance therapy in multiple myeloma MRC myeloma IX results and meta-analysis. Blood. 2012;119:7–15.
48. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, Giralt S, Stadtmauer EA, Weisdorf DJ, Vij R, Moreb JS, Callander NS, Van Besien K, Gentile T, Isola L, Maziarz RT, Gabriel DA, Bashey A, Landau H, Martin T, Qazilbash MH, Levitan D, McClune B, Schlossman R, Hars V, Postiglione J, Jiang C, Bennett E, Barry S, Bressler L, Kelly M, Seiler M, Rosenbaum C, Hari P, Pasquini MC, Horowitz MM, Shea TC, Devine SM, Anderson KC, Linker C. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366:1770–81.
49. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, Stoppa AM, Hulin C, Benboubker L, Garderet L, Decaux O, Leyvraz S, Vekemans MC, Voillat L, Michallet M, Pegourie B, Dumontet C, Roussel M, Leleu X, Mathiot C, Payen C, Avet-Loiseau H, Harousseau JL, IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366:1782–91.
50. Jakubowiak A. Management strategies for relapsed/refractory multiple myeloma: current clinical perspectives. Semin Hematol. 2012;49:516–32.
51. Mohty B, El-Cheikh J, Yakoub-Agha I, Avet-Loiseau H, Moreau P, Mohty M. Treatment strategies in relapsed and refractory multiple myeloma: a focus on drug sequence and 'retreatment' approach in the era of novel agent. Leukemia. 2012;26:73–85.
52. Moreau P. The future of therapy for relapsed/refractory multiple myeloma emerging agents and novel treatment strategies. Semin Hematol. 2012;39:533–46.
53. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, San-Miguel JF, Bladé J, Boccadoro M, Cavenagh J, Dalton WS, Boral AL, Esseltine DL, Porter JB, Schenkein D, Anderson KC, Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;16:2487–9.
54. Orlowski RZ, Nagler A, Sonneveld P, Bladé J, Hajek R, Spencer A, San Miguel J, Robak T, Dmoszynska A, Horvath N, Spicka I, Sutherland HJ, Suvorov AN, Zhuang SH, Parekh T, Xiu L, Yuan Z, Rackoff W, Harousseau JL, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol. 2007;25:3892–901.
55. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, Siegel D, Borrello I, Rajkumar SV, Chanan-Khan AA, Lonial S, Yu Z, Patin J, Olesnyckyj M, Zeldis JB, Knight RD, Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357:2133–42.
56. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, San Miguel J, Hellmann A, Facon T, Foà R, Corso A, Masliak Z, Olesnyckyj M, Yu Z, Patin J, Zeldis JB, Knight RD, Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357:2123–32.
57. Dimopoulos MA, Richardson PG, Brandenburg N, Yu Z, Weber DM, Niesvizky R, Morgan GJ. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood. 2012;119:2764–7.
58. Prince HM, Schenkel B, Mileshkin L. An analysis of clinical trials assessing the efficacy and safety of single-agent thalidomide in patients with relapsed or refractory multiple myeloma. Leuk Lymphoma. 2007;48:46–55.
59. Anagnostopoulos A, Weber D, Rankin K, Delasalle K, Alexanian R. Thalidomide and dexamethasone for resistant multiple myeloma. Brit J Haematol. 2003;121:768–71.
60. Dimopoulos MA. Adverse effect of thalidomide administration in patients with neoplastic disease. Am J Med. 2004;117:508–13.
61. Abe M. Targeting the interplay between myeloma cells and the bone marrow microenvironment in myeloma. Int J Hematol. 2011;94:334–43.
62. Hideshima T, Anderson KC. Novel therapies in MM: from the aspect of preclinical studies. Int J Hematol. 2011;94:344–54.