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Chapter 7

Induction Therapy in Multiple Myeloma

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Additional information is available at the end of the chapter

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1. Introduction

Today, multiple myeloma (MM) can be defined as a heterogenous disease composed of different clinical conditions. The differences are a result of patient related factors (age, sex, comorbidity), disease related complications (renal failure, bone disease, neuropathy, thrombosis) and biological characteristics (cytogenetics, lactate dehydrogenase level, plasma cell labelling index, beta2-microglobulin, gene expression profiles). The widely used international scoring system is a powerful tool for determining survival. However, it cannot be used for treatment planning. The biological determinants of disease determined by flourescein in situ hybridization (FISH) and/or conventional cytogenetics are better tools to stratify myeloma subgroups with different survival profiles. Thus these are better tools for designing therapeutic approaches. A risk stratification of newly diagnosed MM according to FISH/Karyotyping has been recently reviewed by Rajkumar (Rajkumar, 2012).

High dose melphalan supported by autologous stem cell transplantation (ASCT) can increase response rates and prolong progression free and overal survival compared to conventional chemotherapies (Attal et al., 1996; Child et al., 2003; Fermand et al., 2005; Koreth et al., 2007). The initial induction regimen is chosen according to whether the patient is eligible or ineligible for a subsequent HDT-ASCT as well as the risk stratification of the patient. Advanced age or significant comorbidity are important limitations for ASCT. High dose therapy has been generally considered for patients ≤ 65 years. However, in medically fit patients, this can be extended up to age 70-75 years. Achievement of high quality responses (VGPR, CR/nCR) at the time of transplantation has been demostrated to be an early predictor of improved outcomes after ASCT (Harousseau et al., 2009; Chanan-Khan&Giralt, 2010). Elderly patients or patients ineligible for transplantation may also benefit from chemotherapy by achieving high quality responses preferably CR in terms of progression free survival (PFS) and overall survival (OS). As such, the choice of induction therapy is crucial for survival for most patients with MM. The emergence of novel agents (thalidomide, lenalidomide and bortezomib) and

incorporation of these agents in to the current induction protocols has increased the rate of CR and at least VGPR before ASCT and significantly improved the OS in MM (Kumar et al., 2008; Kastritis et al., 2009). This opened a new area of debate 'upfront' versus 'delayed' transplantation. However, current recommendations from experts is that high dose therapy supported by autologous stem cell transplantation (HDT-ASCT) should be the standard of care for eligible patients (Ludwig et al., 2011).

2. Induction therapy for patients eligible for HDT–ASCT

In patients for whom HDT-ASCT is planned, the goal of induction treatment before HDT-ASCT should be to achieve the deepest response preferably up to the level of ≥ VGPR as quickly as possible, to reverse disease related complications and ameliorate patient's symptoms. The protocol should not induce stem cell toxicity and impair stem cell collection. Hence, it is important to avoid melphalan prior to stem cell collection (Cavo et al., 2011; Ludwig et al., 2011).

Prior to novel agents, the standard of care for patients eligible for ASCT was based on high dose dexamethasone alone or VAD (Vincristine, adriamycin, high dose dexamethasone). Over the last few years, the emergence of novel agents (thalidomide, bortezomib and lenalidomide) has shifted the choice of induction regimen from conventional VAD or VAD-like regimens to novel-agent containing protocols. In the earlier studies, the combinations of novel agents with high dose dexamethasone were shown to be superior to VAD regimen before ASCT. The more recent trials have concentrated on upfront use of initially 2-drug and more recently 3-drug or even 4-drug combinations applied before ASCT.

2.1. Thalidomide–based regimens

Thalidomide is the first immunomodulatory drug used in the treatment of MM. Apart from the anti-angiogenic activity, this group of drugs also induce apoptosis in myeloma cells. Thalidomide induces responses in MM patients refractory to conventional and even high dose therapy suggesting that it can overcome drug resistance. It may alter the secretion and bioactivity of cytokines (e.g. TNF-α) secreted into bone marrow microenvironment by myeloma and bone marrow stromal cells that induce myeloma cell growth and survival. Thalidomide mediates its immunomodulatory action by induction of Th-1 T cell response with secretion of IFN-Y and IL-2 and regulation of adhesion molecule expression (Hideshima et al., 2000).

After the initial studies showing that single agent thalidomide could produce significant reponses and that combination of thalidomide with dexamethasone (TD) results in synergism in refractory/relapsed MM, thalidomide was introduced to the induction therapy for newly diagnosed MM (Singhal et al., 1999; Palumbo et al., 2001). The phase II studies demonstrated the efficacy of TD as front line therapy with 64%-66% response rates (Rajkumar et al., 2002; Cavo et al., 2004). In 2005, a retrospective matched case-control analysis provided the first demonstration of superior rate and depth of response by TD compared with VAD as induction

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(≥PR; 76% vs 52%, respectively, p<0.001) (Cavo et al., 2005). Based on the subsequent phase III studies which confirmed the superior response rates achieved with thalidomide containing regimens compared with the conventional induction therapies, TD regimen received an accelerated approval in patients with newly diagnosed MM (Rajkumar et al.,2006; Rajkumar et al., 2008). The summary of the phase II-III studies involving thalidomide-based induction regimens is shown in table-1.

Rajkumar et al. in a randomized double blind placebo-controlled study, provided the first data on significant prolongation of time to progression (TTP) and progression free survival (PFS) with TD compared with dexamethasone alone in patients with newly diagnosed MM (14.9 vs. 6.5 months; p<0.001). However, this study was not powered enough to compare the differences in OS (Rajkumar et al., 2008). Barlogie et al. randomized their patients to receive two cycles of high dose melphalan based chemotherapy each supported with ASCT (Total therapy-2) with or without thalidomide added from outset until disease progression and reported that addition of thalidomide improved the rate of CR and EFS but failed to prolong OS (Barlogie et al., 2006). In a retrospective pair-matched analysis, thalidomide incorporated to induction regimen and continued until the second ASCT revealed significantly improved clinical outcomes and a trend towards extended OS at 5 years (69% vs. 53%; p=0.07) (Cavo et al., 2009). The HOVON-50 trial incorporated doxorubicin to TD (TAD) and compared this regimen with conventional VAD as frontline therapy showing a better response before and after HDT-ASCT (Lokhorst et al., 2008). After long term follow-up, the TAD arm folowed by thalidomide maintenance after ASCT was able to induce longer event free survival compared to the VAD arm folloowed by interferon (34 vs. 22 months; p<0.001) but this did not translate into an improved OS (73 vs. 60 months; p=0.77). Which can be explained by a decreased survival from relapse while on thalidomide maintenance (Lokhorst et al., 2010). A recent MRC Myeloma IX randomized trial compared oral combination therapy CTD (cyclophosphamide, thalidomide, dexamethasone) with oral cyclophosphamide incorporated into conventional VAD (CVAD). Significantly superior response rates were attained with CTD compared with CVAD both after induction and after ASCT. CTD could not significantly prolong PFS or OS but longer followup suggests a trend towards a late OS advantage(Morgan et al., 2012).

Thalidomide does not compromise successful harvest of stem cells. However, it is associated with an increased risk of venous thromboembolism (VTE) and sensory peripheral neuropathy (PNP). Without thromboprophylaxis, the thrombosis risk is 15-17%, which is more frequent during the first 3 months of treatment and warrants prophylactic anticoagulation. Peripheral neuropathy improves within 3-4 months after dose reduction or cessation of the drug in most patients. However, thalidomide induced PNP may be irreversible if appropriate action is not taken when an emerging neuropathy is encountered. Thalidomide at low dose may be effective in the management of patients with renal failure, but close monitorization for complications is required in patients with serious renal and hepatic failure. Major thalidomide toxicities and the summary of the supportive care guidelines regarding the approach to PNP is given in tables 7 and 8, respectively (Beksac et al., 2008, Bird et al., 2011).

It is clearly understood that thalidomide-based regimens have produced better post-induction response rates (≥PR; 63-82.5%) and PFS than conventional high dose dexamethasone based

regimens. However, OS was not prolonged. Poorer response to salvage therapy and decreased survival have been observed in patients who relapsed while on thalidomide. This may be the result of emergence of resistant clones after thalidomide (Rajkumar et al., 2006; Barlogie et al., 2006;, Cavo et al., 2009; Lokhorst et al., 2010; Morgan et al., 2012). Thalidomide-dexamethasone is less active and more toxic than lenalidomide-based regimens and not recommended as first line therapy anymore. However, in countries where lenalidomide is not available as initial first line therapy and in patients with renal failure, thalidomide combinations may be preferred. On the other hand, thalidomide is still being investigated in combination with other drugs as induction and maintenance regimens for both transplant eligible and ineligible MM patients.

Regimen	N	After induction			After ASCT			PFS	OS	Reference
		≥PR %	≥VGPR %	CR %	≥PR %	≥VGPR %	CR %			
TD vs. D	103 104	63 41	nr nr	4 0	nr nr	nr nr	nr nr	nr nr	nr nr	Rajkumar 2006
TT2 with T vs. TT2 without T	323 345	nr nr	nr nr	nr nr	nr nr	nr nr	62 43	5-year 56% 44% P=0.01	5-year 65% 65% P=0.90	Barlogie 2006
TD vs. D	235 235	63 46	43.8 15.8	7.7 2.6	nr nr	nr nr	nr nr	14.9 mos 6.5 mos P<0.001	nr nr	Rajkumar 2008
Double ASCT + T vs. Double ASCT	135 135		30 15			68 49		4-year 51% 31% P=0.001	5-year 69% 53% P=0.07	Cavo 2009
TAD vs. VAD	268 268	71 57	37 18	3 2	84 76	54 44	14 12	Median 34 mos 22 mos P<0.001	Median 73 mos 60 mos P=0.77	Lokhorst 2010
CTD vs.CVAD	555 556	82.5 71	43 27.5	13 8	92 90	62[a] 74[a]	50[a] 37[a]	Median 27[a] mos 25[a] mos P=0.56	Median Not reach. 63[a] mos P=0.29	Morgan 2012

ASCT: autologous stem cell transplantation ; CTD: cyclophosphamide, thalidomide, dexamethasone; CVAD: cyclophosphamide added to VAD (vincristine, doxorubicin, dexamethasone); nr: not reported; TAD: thalidomide, doxorobicin, dexametahsone; TD: thalidomide, dexamethasone; T: thalidomide; TT2: Total therapy-2. [a] per-protocol analysis

Table 1. Phase II- III studies of thalidomide-based regimens as induction therapy before HDT-ASCT

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2.2. Bortezomib–based regimens

Bortezomib is an effective inhibitor of proteosome. The ubiquinitin-proteosome pathway plays an important role in intracellular protein homeostasis by regulating degradation of proteins, including mediators of cell cycle progression and apoptosis. Bortezomib also blocks TNF-α mediated upregulation of NF-KB resulting in decreased binding of myeloma cells to bone marrow stromal cells and results in myeloma cell apoptosis. This activity is observed even in cell lines resistant to conventional anti-myeloma therapies. Bortezomib also cleaves DNA repair enzymes increasing the susceptibility of myeloma cells to DNA damaging agents such as alkylating agents and anthracyclines (Hideshima et al., 2001; Cherry et al., 2012).

Bortezomib received FDA approval in 2003 after showing significant activity in relapsed-refractory MM (Jagannath et al., 2004; Richardson et al., 2005). The initial phase II study of single agent bortezomib in previously untreated MM revealed a response rate of 41% (Richardson et al., 2009). Other phase 2 studies incorporating bortezomib ± dexamethasone to induction regimens were consistent with superior responses ranging from 66% to 95% with 6% to 24% CR rates (Jagannath et al., 2005; Harousseau et al., 2006; Rosinol et al., 2007).

The IFM2005-01 Phase III trial compared VD with VAD as induction before ASCT and lenalidomide was given as post-ASCT maintenance in both arms in a randomized fashion. Post-induction at least VGPR (38% vs 15%) and CR/nCR (15% vs 6%) were superior with VD. This response difference was also maintained after ASCT. However, there was only slight improvement in PFS without an OS benefit. Responses with bortezomib were higher regardless of the disease stage or high-risk cytogenetics (Harousseau et al., 2010).

Popat et al. added doxorubicin at escalating doses (0, 4.5 and 9 mg/m^2) to standard dose bortezomib-dexamethasone (PAD) and demonstrated 95% post-induction response rate with 62% high quality responses (≥ VGPR) (Popat et al., 2008). Addition of pegylated-liposomal doxorubicin to bortezomib-dexamethasone revealed similar responses (≥ PR 85% and ≥ VGPR 57.5%) which was further enhanced in patients who underwent ASCT (≥ VGPR 76.6%) (Jakubowiak et al., 2009). A very recent HOVON-65/GMMG-HD4 trial compared pre-transplant PAD (Bortezomib, Adriamycin, Dexamethasone) induction and bortezomib maintenance after ASCT with pre-transplant VAD induction and thalidomide maintenance after ASCT and demonstrated that bortezomib during induction and maintenance significantly improved response rates, quality of response. Similar to other bortezomib containing 3-drug combinations, PFS was significantly improved. Additionally, unlike the other studies, OS was also prolonged in this study (61% vs 55%). Subgroup analysis also indicated that superior outcome with bortezomib was predominantly accomplished in high risk patients presenting with renal failure and del17p (≥ VGPR; 72% vs 43%) (Sonneveld et al., 2012).

Reeder et al. incorporated cyclophosphamide to bortezomib-dexamethasone (CyBorD/VCD) and reported 71% ≥VGPR after 4 cycles and 74% ≥VGPR after ASCT (Reeder et al., 2009). The German Myeloma Study Group reported 84% response rate (≥PR) with 10% CR after 3 cycles of VCD. Over 60% of their patients had high-risk cyctogenetics. The response rate in cytogenetically high-risk patients were 83.7% (del13q) and 90% t(4;14). However, del17p group had lower response rate at 69.2% (Einsele et al., 2009).

These studies demonstrate that bortezomib-based induction studies produce high response rates (≥ PR; 78%-93% and CR 7%-35%) without any adverse effect on stem cell mobilization (Harousseau et al., 2010; Cavo et al.,2010; Rosinol et al., 2012; Sonneveld et al.,2012; Moreau et al., 2010). However, neurotoxicity is a major concern especially when bortezomib is combined with thalidomide. Neurotoxicity can be reduced by reducing bortezomib dose once weekly without affecting the efficacy or by using subcutenous bortezomib (Mateos et al., 2010). Moreover, Moreau et al. used reduced doses of bortezomib (1 mg/m2) and thalidomide (100 mg/d) in vtD regimen and found that this regimen provided higher VGPR rates compared with VD and the dose reduction of both drugs could resulted in reduced incidence of polyneuropathy (Moreau et al., 2011). Major bortezomib toxicities and the summary of the supportive care guidelines regarding the approach to emerging PNP is given in tables 7 and 8, respectively (Bird et al.,2011).

Regimen	N	After induction			After ASCT			PFS	OS	Reference
		≥PR %	≥VGPR %	CR %	≥PR %	≥VGPR %	CR %			
VD vs. VAD	223 218	78.5 63	38 15	15 6	80 77	54 37	35 18	Median 36 mos 30 mos P=0.06	3-year 81% 77% P=0.5	Harousseau 2010 IFM 2005-02
VTD vs. TD	236 238	93 79	62 28	31 11	93 84	82 64	55 41	3-year 68% 56% P=0.005	3-year 86% 84% P=0.03	Cavo 2010 GIMEMA-MMY 3006
VBMCP/VBAD+V vs. VTD vs. TD	129 130 127	75 85 62	36 60 29	21 35 14	73 77 58	51 65 40	38 46 24	Median 38 mos 27 mos Not reach. P=0.006	Nr Nr Nr	Rosinol 2012 PETHEMA/ GEM
PAD vs. VAD	413 414	78 54	42 14	7 2	88 75	62 36	21 9	Median 35 mos 28 mos P=0.002	5-year 61% 55%	Sonneveld 2012 HOVON65/ GMMG HD4
VD vs. vtD	99 100	81 88	36 49	31 29	86 89	58 74	22 31	Median 30 mos 26 mos P=0.22	Nr nr	Moreau 2011 IFM2007-02

VD: Bortezomib, dexamethasone; VAD: Vincristine, doxorubicin, dexamethasone; VTD: Bortezomib, thalidomide, dexamethasone; TD: Thalidomide,dexamethasone; VBMCP/VBAD+V: Vincristine, carmustine, melphalan,cyclophosphamide, prednisone/ vincristine, carmustine, doxorubicin, dexamethasone + bortezomib; PAD: Bortezomib, doxorubicin, dexamethasone; vtD: Reduced dose bortezomib, reduced dose thalidomide, dexamethasone; mos: months

Table 2. Phase III studies of bortezomib-based regimens in preparation for HDT-ASCT

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Bortezomib has become an important component of therapy for patients with high risk MM associated with del13q and t(4;14) (Richardson et al., 2005; Jagannath et al., 2007). Bortezomib has also proven effective in management of MM patients with renal dysfunction. It has been suggested that in patients with acute renal failure secondary to light chain cast nephropathy VTD can be first choice due to lack of nephrotoxicity. The Mayo Clinic recommends plasma exchange until serum free light chain (FLC)<50 mg/dl and repeated as needed until VTD is fully effective (Rajkumar et al., 2011). Bortezomib is also beneficial for individuals with significant disease related bone-disease due to its inhibitory effect on osteoclastogenesis and stimulatory effect on osteoblast differentiation and proliferation (Zavrski et al., 2005).

Regimen	Progression free survival				Reference
	Overall		del13q	t(4;14)	del(17p)
VD + R ± R vs.	36 mos (median)	nr	28mos (median)	14mos (median)	Avet-Loiseau 2010
VAD + R ± R	30 mos (median)	nr	16mos (median)	nr	
PAD + Bort vs.	48% (at 3-yr)	40% (at 3-yr)	28% (at 3-yr)	22% (at 3-yr)	Sonneveld 2010
VAD + T	40% (at 3-yr)	29% (at 3-yr)	20% (at 3-yr)	16% (at 3-yr)	
VTD + VTD vs.	68% (at 3-yr)	62% (at 3-yr)	69% (at 3-yr)	nr	Cavo 2010
TD + TD	56% (at 3-yr)	46% (at 3-yr)	37% (at 3-yr)	nr	

Table 3. Impact of bortezomib incorporated into ASCT on PFS according to cytogenetic abnormalities (Cavo 2012)

2.3. Lenalidomide–based regimens

Lenalidomide is another IMID and has more potent in vitro activity; inhibition of angiogenesis, cytokine modulation and T-cell costimulation than thalidomide (Hideshima et al., 2000 ; Haslett et al., 2003). Lenalidomide primarily triggers the caspase-8 mediated apoptotic pathway and also down-regulates NF-KB activity via a mechanism distinct from bortezomib (Mitsiades et al., 2002). Lenalidomide alone (R) or with dexamethasone (RD) has shown significant activity in relapsed/refractory MM. Responses were observed even in patients in whom thalidomide therapy has previously failed (Richardson et al., 2002). Several phase II studies of lenalidomide and dexamethasone +/- chemotherapy have demonstrated response rates ranging 76-91% (Table-4). In a randomized controlled trial lenalidomide plus high dose dexamethasone (RD) (480 mg/28d cycle) was compared with lenalidomide plus low dose dexamethasone (Rd) (160 mg/28d cycle). Patient enrollment to study was not restricted with age or eligibility for ASCT. In each group lenalidomide was administered as 25 mg/d on 1-21 days. In accordance with others, this study demonstrated that lenalidomide in combination with dexamethasone is an efficient initial therapy for MM. Although RD produced higher response rates, this did not result in superior TTP, PFS or OS compared with Rd. The cause of inferior OS with high dose dexamethasone seems to be related to increased deaths due to toxicity, particularly in first 4 months and in eldely patients. The major grade 3 or higher toxicities including thromboembolic events and infections were significantly higher in the high dose dexamethasone group (Rajkumar et al., 2010). The multicenter, placebo controlled SWOG

trial has confirmed the superiority of lenalidomide in combination with dexamethasone over dexamethasone alone as initial therapy of MM in terms of response rate and PFS but not in OS. This study received early closure and open-label lenalidomide and dexamethasone was made available to all patients (Zonder et al., 2010). In a retrospective case-control study, RD produced better responses than TD including superior PFS and OS. However, this study was not a randomized trial and the choice of post-induction therapy was not standardized (Gay et al., 2010a). Claritromycin is an antibiotic that has shown efficacy in association with steroids and both thalidomide and lenalidomide. The same investigators added clarithromycin (Bioxin) to Rd(BiRd) and compared with Rd in a case-match study. The have reported significantly better responses with BiRd and the PFS was significantly longer. However, 3- year OS was not statistically different between the two study arms (Gay et al., 2010).

Lenalidomide can cause myelosuppression and concerns have been raised that its use may negatively impact the ability to mobilize stem cells in patients who received lenalidomide as part of their induction therapies (Kumar et al., 2007; Mazumder et al., 2008; Paripati et al., 2008; Popat et al., 2009). It is suggested that stem cells should be collected within 6 months of initiation of lenalidomide therapy and the IMWG recommends that patients >65 years or patients who have received ≥ 4 cycles Rd must undergo stem cell mobilization with cyclophosphamide + G-CSF or G-CSF + plerixafor (Kumar 2007; Kumar 2009). Dose reduction is required in presence of renal impairment. Patients may require thromboprophylaxis due to higher incidence of thromboembolic events. Major lenalidomide toxicities are summarized in table-10 (Bird et al., 2011).

2.4. Novel agent triplet combinations

To enhance response rates and prolong PFS combination of Bortezomib with an IMID has been attempted. Bortezomib-thalidomide-dexamethasone (VTD) resulted better response rates and PFS compared to TD or VD in initial randomized trials (Wang et al., 2005; Cavo et al., 2009). In a Phase III study of VTD compared with TD as induction before and consolidation after double ASCT, VTD was superior to TD in all response categories (CR/n CR; 31% vs 11% ; ≥VGPR; 62% vs 28%) as well as the 3 year estimated PFS (68% vs 56%). Progression free survival was also superior with VTD compared to TD in poor prognostic groups including del13q, increased LDH, age>60 years, t(4;14) ± del17p, increased bone marrow plasma cell ratio and ISS-II and III (Cavo et al., 2010). The results of the PETHEMA/GEM study also provided a strong support to VTD as a highly effective induction regimen compared with a combination chemotherapy containing bortezomib and with TD. Additionally, VTD resulted in a higher post-transplantation CR rate and a significantly longer PFS. However, this did not result in a significant prolongation of OS and could not overcome poor prognosis of high-risk cytogenetics (Rosinol et al., 2012).

Synergy has been demonstrated between bortezomib and lenalidomide. Moreover, both bortezomib and immunomodulatory drugs enhance the activity of dexamethasone. In a phase I study combining these three agents (RVD) in patients with newly diagnosed MM, the maximum tolerated dose was set as lenalidomide 25mg/day, bortezomib 1.3mg/m^2, dexamethasone 20mg/day and in phase II portion of the same study, 100% response rate (≥PR) could

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be obtained with ≥VGPR and CR rates 74% and 37%, respectively. This was the first study to result in 100% response rate. The 18-month PFS and OS were 75% and 97%, respectively (Richardson et al., 2010).

In phase II trials the most promising combinations were either lenalidomide or cyclophosphamide with bortezomib and dexamethasone. A phase II study of four-drug combination VDCR, VDR, VDC and VDC-mod (modification of the cyclophosphamide dose) was performed to evaluate the feasibility and activity of these combinations. The response seen with VDCR appear to be similar to those seen with VDR or VDC-mod arms (Table-5). However, the toxicities with VDCR appear to be more than the other arms, especially hematological toxicity. This study does not support an advantage of four drug combination (Kumar et al.,2012).

In another phase I/II study RVD was combined with pegylated-doxorubicin (RVDD) and this regimen was highly active and well-tolerated with response rates ≥PR 96% and 95%, ≥VGPR 57% and 65% after 4 and 8 cycles, respectively (Table-6). After a median 15.5 months follow-up, PFS and OS were not reached. The estimated 18-month PFS and OS were 80.8% and 98.6%, respectively. Among patients who proceeded to ASCT and were evaluable for posttransplant response, response rate further improved reaching 85% of patients ≥VGPR and 61% of those with CR/n CR at 3 months after ASCT. In patients who continued RVDD beyond 4 cycles, depth of response further improved reaching 65% ≥VGPR and 35% CR/n CR at the completion of 8 cycles (Jakuboviak et al., 2011).

Regimen	N	After induction			PFS	OS	Reference
		≥PR %	≥VGPR %	CR %			
RD	34	91	38	6			Rajkumar 2005
					Median		
RD vs.					19 mos	2-yr	Rajkumar 2010
Rd	223	79	42		25 mos	75%	
	222	68	24		P=0.026	87%	
						3-yr	
RD vs.					3-yr	79%	Zonder 2010
D	97	78			52%	73%	
	95	48			32%	P=0.28	
					Median	Median	
RD vs.					26.7mos	Notreach	Gay 2010
TD	228	80	37.8	13.6	17.1 mos	57.2 mos	
	183	61	15	3.3	P=0.036	P=0.018	
					Median	Median	
BiRd vs.					48.3 mos	89.7%	Gay 2010
Rd	72		73.6	45.8	27.5 mos	73%	
	72		33	13.9	P=0.044	P=0.170	

Table 4. Results of phase II-III Studies of induction with lenalidomide and dexamethasone

	VDCR N=39	VDR N=36	VDC N=31	VDC-mod N=16
After 4 cycles				
CR	5%	7%	3%	12%
≥VGPR	33%	32%	13%	41%
≥PR	80%	73%	63%	82%
Best response across all cycles (median=6 cycles)				
CR	25%	24%	22%	47%
≥VGPR	58%	51%	41%	53%
≥PR	88%	85%	75%	100%
1-yr PFS	86%	83%	93%	100%
After censoring patients going to ASCT				
1-yr PFS	83%	68%	97%	100%
1-yr OS	92%	100%	100%	100%
Patients who undergo ASCT				
1-yr PFS	100%	100%	88%	100%
1-yr OS	100%	100%	100%	100%

Table 5. Results of EVOLUTION Study comparing bortezomib-based multi-drug combinations

	N	Best response after induction (%)			Reference
		≥PR	≥ VGPR	CR	
RVD	66	100	67	39	Richardson 2010
VDCR vs.	39	88	58	25	Kumar 2012
VDR vs.	36	85	51	24	
VDC vs.	31	75	41	22	
VDC-mod	16	100	53	47	
RVDD					
After 4 cycles		96	57	29	Jakubowiak 2011
After 8 cycles	74	95	65	35	

Table 6. Phase II Trials of triplet or quadruplet lenalidomide-based induction

Thalidomide	Lenalidomide	Bortezomib
Venous thromboembolism	Cytopenias	Peripheral neuropathy
Sensory peripheral neuropathy	Venous thromboembolism	Gastrointestinal toxicity
Constipation	Constipation	Postural hypotension and pre-syncope secondary to autonomic neuropathy

Thalidomide	Lenalidomide	Bortezomib
Hematological toxicity	Fatigue	Thrombocytopenia
Somnolence	Neuropathy	Fatigue
Rashes	Skin rash	Increased incidence of varicella zoster infections
Arrhythmias	Muscle cramps	
Thyroid dysfunction	Thyroid dysfunction	
Congenital malformations due to fetal exposure	Diarrhea	

Table 7. Major toxicities of novel agents

Grade of neuropathy	Bortezomib	Thalidomide
Grade 1 Paresthesia, weakness and/or loss of reflexes without painor loss of function	No action	No action
Grade 1 with pain or grade 2 interfering with function but not with daily activities	Reduce bortezomib dose to 1mg/m^2	Reduce thalidomide dose to 50% or suspend thalidomide until disappearence of toxicity, then reinitiate at 50% dose
Grade 2 with pain or grade 3	Suspend bortezomib until disappearence of toxicity then re-initiate at 0.7 mg/m^2 and administer once weekly	Suspend thalidomide until disappearence of toxicity, then reinitiate at low dose if PNP grade 1
Grade 4	Discontinue	Discontinue

Table 8. Guidelines for the management of bortezomib and thalidomide induced PNP

2.5. Conclusions

High dose melphalan supported by autologous stem cell transplantation after novel agent-based induction regimen is the standard of care for patients younger than 65. The quality of response achieved with induction regimens before ASCT affect PFS and potentially the OS. In this regard, the availability of novel anti-myeloma drugs, thalidomide, bortezomib and lenalidomide has improved the pre-transplantation responses. Recent data suggest that 3-drug induction regimens, containing at least one novel agent result in better responses than 2-drug combinations. The results of studies with combinations of VD with either doxorubicin (PAD), cyclophosphamide (CyBorRd), thalidomide (VTD) or lenalidomide (VRD) have demonstrated that the responses can be further enhanced and PFS ± OS can be improved. Within the 3-drug combinations, bortezomib-dexamethasone combined with thalidomide or cyclophosphamide(VTD or VCD) appear to be the most active regimens. So, 3-6 cycles of a triplet bortezomib

based regimen should be considered the standard induction for patients eligible for ASCT. The objective of treatment should be the achievement of a sustained CR with a good quality of life. Current studies concentrate on best approach to combine available drugs to affect long-term disease control as well as consolidation and maintenance after ASCT and minimize the long-term toxicities, especially neurotoxicity. Bortezomib is effective not only in patients with standard risk disease but also in the presence of high risk cytogenetic abnormalities especially in presence of t(4;14). Current question under evaluation is whether to apply or delay ASCT when a CR is achieved with a novel agent induction treatment.

3. Induction therapy for patients ineligible for HDT–ASCT

Melphalan was the first alkylating agent used for treatment of MM and melphalan –prednisone (MP) has been the standard therapy for over 30 years although it yielded only PR in 40-60% of patients with CR <5% and PFS about 18 months and OS 2-3 years. Trials comparing MP with high dose dexamethasone-based combinations revealed no survival advantage (Mateos et al., 2012). During the last decade, with the emergence of novel agents and the studies revealing the importance of achieving VGPR/CR on survival of myeloma patients, the historical goals of induction have changed to achieving a high quality response in elderly patients as well.

3.1. Bendamustine

Bendamustine is a novel bifunctional drug which has similarities to both alkylating agents and purine analogs. It has promising activity in low grade lymphoid malignancies. The East German Study Group conducted a phase III trial comparing bendamustine and prednisone (BP) with standard MP in previously untreated patients with MM who are ineligible for transplantation. Bendamustine –prednisone was superior to MP with respect to CR rate (32% vs 13%, p=0.007) and TTF (14 mos vs 10 mos, p=0.02). There was no significant difference with regard to OS between the two treatment groups and the toxicity profile was comparable (Pönisch et al., 2006). Mainly based on the results of this study, bendamustine is currently approved for treatment of newly diagnosed MM patients who are not candidates for HDT-ASCT and who can not receive thalidomide or bortezomib due to peripheral neuropathy. The same investigators in a recent study demonstrated that bendamustine in combination with bortezomib and prednisone (BPV) is also effective in patients with newly diagnosed MM and renal failure. Eighty-three percent of the patients treated with this protocol responded to therapy and 72% had their renal function improved after treatment (Pönisch et al., 2012).

3.2. Thalidomide–based regimens

Thalidomide incorporated in to the MP regimen (MPT) has been compared with the standard MP regimen in six randomized phase III studies. Each protocol had some minor differences in their schedules which is shown in table-9. The overall response rate (57%-76%) with MPT was significantly higher than MP (31%-48%).The CR rates with MPT ranged between 7%-13%, one study reported ≥ VGPR rate as 27%. In the IFM-I/II studies and in HOVON study, the prolon-

gation in the PFS with MPT was also translated in to OS advantage (Facon et al., 2007; Hulin et al., 2009; Wijermans et al., 2010). Despite in the other three studies the PFS advantage was not translated into OS advantage (Palumbo et al., 2008; Waage et al., 2010; Beksac et al., 2011), a metaanalysis of the pooled data of 1682 patients from these six trials showed that the addition of thalidomide to MP improves OS and PFS in previously untreated elderly patients with multiple myeloma, extending the median survival time by on average 20%. In this metaanalysis, median PFS was prolonged by 5.4 months (HR 0.67 (0.55-0.80) p<0.0001) and the median OS was prolonged 6.6 months (HR 0.82 (0.66-1.02) p=0.004) (Fayers et al., 2011). This improvement was less pronounced in patients aged ≥ 75 years and no favorable effect of thalidomide on OS in this population could be demonstrated. The most frequent grade 3-4 adverse events with MPT protocol were polyneuropathy (6-23%) and VTE (3-12%), infections (10-13%), cardiac complications (2-7%), gastrointestinal events (5%). The discontinuation rate ranged 16-45% (Hulin et al., 2009; Wijermans et al., 2010; Fayers et al., 2011). Based on these results, MPT became one of the new standard therapies for elderly patients with newly diagnosed MM.

Thalidomide-dexamethasone (TD) combination was also compared with MP in 289 elderly patients with MM. Patients achieving stable disease or better were randomly assigned to maintenance therapy with either thalidomide 100 mg daily or interferon alpha-2b. Thalidomide-dexamethasone resulted in a higher proportion of ≥VGPR (26% vs 13%; P=.006) and ORR (68% vs 50%; P=.002) compared with MP. However, PFS was similar (16.7 vs 20.7 months; P=.1) and OS was significantly shorter in the TD group (41.5 vs 49.4 months; P=.024). Decreased survival was more evident in patients older than 75 years due to increased non-disease related deaths during the first year (Ludwig et al., 2009). Combinations with high dose dexamethasone is not recommended for elderly patients especially those ≥ 75 years due to increased toxicity. In a randomized MRC Myeloma IX trial, cyclophosphamide, thalidomide and dexamethasone (CTDa) in which dexamethasone dose was reduced, produced higher response rates than MP but was not associated with improved PFS and OS. Additionally, CTDa was associated with higher rates of adverse events compared to MP (Morgan et al., 2011).

3.3. Bortezomib–based regimens

After showing significant efficacy in relapsed-refractory myeloma, bortezomib was also incorporated into trials for initial therapy of MM in transplant ineligible patients. The clinical value of adding bortezomib to the standard MP regimen (VMP) was explored in Velcade as Initial Standard Therapy (VISTA) Study (San Miguel et al., 2008). In this phase III study, 682 newly diagnosed myeloma patients were randomly assigned to receive nine 6-week cycles of melphalan (9 mg/m2) and prednisone (60 mg/m2) on days 1 to 4, either alone or with bortezomib (1.3 mg/m2) on days 1, 4, 8, 11, 22, 25, 29 and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9. Addition of bortezomib to MP significantly improved all responses, PFS as well as the OS (Table-10). The main adverse events associated with VMP were neutropenia (40%), thrombocytopenia (37%), peripheral neuropathy (14%), infection (10%) and gastrointestinal events (7%). A recent update of the VISTA study and a subsequent study showed that grade 3-4 hematological and non-hematological adverse events in partic-

Regimen	N	Schedule	ORR%	CR%	TTP (months)	OS (median)	Reference
MPT+T(until PD) MP	129 126	M: 4mg/m2, d1-7 P: 40mg/m2, d1-7 T: 100mg/d 6 cycles every 4 wks until relapse	76 48	16 2.4	22 15 p=0.004	45 47.6 p=0.79	GIMEMA Palumbo 2008
MPT MP No maintenance	125 196	M:0.25mg/kg, d1-4 P: 2mg/kg, d1-4 T:100-400mg/d 12 cycles every 6 wks	76 35	13 2	28 18	52 33 P=0.0006	IFM-I Facon 2007
MPT MP No maintenance	113 116	M:0.20mg/kg, d1-4 P: 2mg/kg, d1-4 T:100mg/d 12 cycles every 6 wks	62 31	7 1	24 19 P=0.001	44 29 P=0.028	IFM-II Hulin 2009
MPT+T(until PD) MP	148 179	M:0.25mg/kg, d1-4 P: 100mg/d, d1-4 T:200-400mg/d Until plateau every 6 wks Maintenance T 200mg	57 40	13 4	15 14 ns	29 32 ns	NMSG Waage 2010
MPT+T(until PD) MP	165 168	M:0.25mg/kg, d1-5 P: 1mg/kg, d1-5 T:200mg/d 8 cycles every 4 wks Maintenance T 50mg	66 45	27 10 ≥VGPR	13 9 P<0.001 PFS	40 31 P=0.05	HOVON Wijermans 2010
MPT MP No maintenance	62 60	M: 9mg/m2, d1-4 P: 60mg/m2, d1-4 T: 100mg/d 8 cycles every 6 wks	58 38	9 9	21 14 P=0.34 DFS	26 28 P=0.65	TMSG Beksac 2011

M:Melphalan; P:Prednisone; T:Thalidomide; PD:Progressive disease; PFS:Progression free survival; DFS: Disease free survival; GIMEMA: Italian Myeloma Network IFM: Intergroupe Francophone du Mye´lome; NMSG: Nordic Myeloma Study Group; HOVON: Dutch-Belgium Hemato-Oncology Cooperative Group; TMSG:Turkish Myeloma Study Group

Table 9. Phase III Studies comparing MPT versus MP for newly diagnosed MM ineligible for HDT-ASCT

ular PNP as well as discontinuation of the drug was significantly reduced without affecting the efficacy when once weekly bortezomib schedule was used (Mateos et al., 2010a; Brignhen et al., 2010). In the VISTA trial, patients with high risk cytogenetic profile had similar response rate and OS with the patients with standard risk profile suggesting that addition of bortezomib may overcome the poor prognosis confered to high risk cytogenetics. Another important point of this study was that first-line bortezomib use did not induce more resistant relapse unlike

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that is seen in thalidomide relapses. The survival data of the VISTA trial was updated at 3 years and 5 years and the survival benefit of VMP protocol remained significant (Mateos et al., 2010a; San Miguel et al., 2011). A part of the VISTA trial investigated the efficacy of VMP protocol in renal impairment excluding patients with Cr >2mg/dl. Response rates with VMP and TTP in both arms did not appear significantly different between patients with GFR ≤ 50 or > 50 mL/min. Moreover, VMP resulted in 44% renal impairment reversal suggesting that this protocol is also an active and well-tolerated treatment option for patients with moderate renal impairment (Dimopoulos et al., 2009).

	VMP N=344	**MP N=338**	**p**	**References**
ORR (≥PR)	71%	35%	<0.001	San Miguel 2008
CR	30%	4%	<0.001	
TTP	24 mos	16.6 mos	<0.001	
OS Median follow-up 16.3 mos			0.008 HR[a]=0.61	
OS Median follow-up 36.7 mos	Not reached	43 mos	<0.001 HR[a]=0.653	Mateos 2010
OS Median follow-up 60 mos	56.4 mos	43.1 mos	0.0004 HR[a]=0.695	San Miguel 2011
3-yr OS	68.5%	54%		

a Hazard Ratio

Table 10. Results of the VISTA trial and the long-tem follow-up

In the PETHEMA trial Mateos et al. have demonstrated that reduced intensity induction with a bortezomib based regimen followed by maintenance is a safe and effective treatment. The investigators compared VMP with VTP (bortezomib, thalidomide, prednisone) as initial therapy in newly diagnosed patients with MM ineligible for transplantation. In both protocols, a reduced intensity bortezomib schedule consisting of one cycle of bortezomib twice per week for 6 weeks followed by five cycles of bortezomib once per week for 5 weeks was used. Patients who completed the six induction cycles were randomly assigned to maintenance therapy with bortezomib plus prednisone (VP) or bortezomib plus thalidomide (VT). The response rates were higher with VTP compared to VMP (CR 28% vs 20% ; ORR 81% vs 80%). Maintenance with VT significantly improved time to progression compared with that for patients who received VP. The support to better response rates with VTP also came from the initial results of UPFRONT study which compared VD, VTD and VMP and revealed better response rates

with VTD (Table-11). On the other hand, in both studies patients treated with VTP had more frequent serious adverse events especially PNP and thrombosis (Mateos et al., 2010b; Nievizsky et al., 2011). Combining four drugs (bortezomib, melphalan, prednisone, thalidomide) followed by maintenance with bortezomib-thalidomide (VMPT-VT) was superior to VMP alone in patients with MM who are ineligible for autologous stem-cell transplantation. The 3-years PFS was also improved with VMPT-VT. However, no significant difference in 3-year OS was observed. Additionally, grade 3 to 4 neutropenia, cardiologic events and thromboembolic events were more frequent among patients assigned to the VMPT-VT group than among those assigned to the VMP group (Palumbo et al., 2010). Due to significantly increased adverse events with 4-drug regimen, VMP or MPT are better alternatives for induction of elderly myeloma patients.

	N	ORR % CR % After induction		PFS	OS	Reference
VMP VTP maintenance VP or VT	130 130	80 81	20 28	37 mos 32 mos	60mos median 5-yr 53%	Mateos 2010
VMPT + VT VMP + no maintenance	254 257	89 81	38 24 P<0.001	3-year 56% 41% p=0.008	3-year 89% 87% p=0.77	Palumbo 2010
VD VTD VMP	168 167 167	73 80 69	24 36 31	NA	NA	Nievizsky 2011

VD:Bortezomib dexamethasone; VTD: Bortezimib, thalidomide, dexamethasone; VMP: Bortezomib, melphalan, prednisone; VT: Bortezomib, thalidomide; mos: months; NA: Not available

Table 11. Phase III Studies comparing bortezomib containing regimens

3.4. Lenalidomide–based regimens

In a randomized controlled trial lenalidomide (25 mg/d on d 1-21) plus high dose dexamethasone (480 mg/28d cycle) (RD) produced higher response rates compared with lenalidomide (25 mg/d on d 1-21) plus low dose dexamethasone (Rd) (160 mg/28d cycle). However, this did not translate into superior PFS (Median 19.1 months vs 25.3 months). Moreover, Rd was associated with significantly improved 1-year OS than with RD (96% vs 87%, p=0.0002) and treatment related toxicity was significantly reduced. The cause of inferior OS with high dose dexamethasone seems to be related to increased deaths due to toxicity particularly in first 4 months and in elderly patients. Hence, the advantages of Rd over RD were more pronounced in patients aged > 70 years (Rajkumar et al.,2010; Zonder et al., 2010). A recent double-blind, multicenter, randomized study compared melphalan-prednisone-lenalidomide induction followed by lenalidomide maintenance (MPR-R) with melphalan-prednisone-lenalidomide

(MPR) or melphalan-prednisone (MP) followed by placebo. Response rates were superior with MPR-R compared with MPR or MP (ORR, 77% vs 68% vs 50%; CR, 18% vs 13% vs 5%; respectively). MPR-R significantly prolonged PFS in patients with newly diagnosed multiple myeloma who were ineligible for transplantation, with the greatest benefit observed in patients 65 to 75 years of age. This study also underlines the importance of lenalidomide maintenance after MPR induction as another treatment option for elderly myeloma patients The toxicity profile was excessive for frail patients, which negatively affected the efficacy. Main grade 3-4 adverse events of MPR were neutropenia (52-71%), thrombocytopenia (23-38%), infections (10%) and thromboembolism (5%)(Palumbo et al., 2012).

Various circumstances	Suggestions
Rapid reversal of spinal cord compression or renal impairment	Bortezomib
Pre-existing neuropathy	Lenalidomide (MPR, Rd) or bendamustin (BP)
History of venous thromboembolism	Bortezomib
In cases with renal failure	Thalidomide, bortezomib, bendamustin can be administered at full dose, Lenalidomide requires dose reduction according to creatinin clearence
Contraindications to use of alkyllating agents such as presence myelodysplasia or increased risk of myelosuppression	TD or VD can be used instead of MP
Frail patients	Prednisone is beter tolerated than dexamethasone

Table 12. Individualized treatment strategies for non-transplant candidate patients

It is clear that the novel agents have prolonged the survival of patients with MM. However, this benefit is more pronounced in younger patients. Age has been reported to be a negative prognostic factor. It is not because the elderly patients have biologically different disease but because they can not tolerate high intensity therapy protocols, have lower bone marrow reserves, increased tendency for infections and also difficulty in recovering from infections and have more frequent drug toxicities. A patient's overall physical condition, fraility, comorbidity and disability should be asessed before starting therapy in order to choose the appropriate treatment protocol and dosing. These terms are fully explained in a review by Palumbo et al (Palumbo A et al. 2011). Although the novel agents offer important survival for patients with MM, the incidence of grade 3-4 adverse events and drug discontinuations are significantly higher with combination regimens that are based on novel agents than with traditional chemotherapy regimens. It has been suggested that modifying drug doses at the start of therapy and management of adverse events during the therapy improves tolerability so that the patients can receive the drugs for a longer time to get survival benefit. Secondly, the tolerability of treatment can be further improved with full supportive therapy with bisphosphanates, antivirals, anticoagulants, growth factors and appropriate pain control.

3.5. Conclusions

At present, the induction regimen for patients ineligible for HDT/ASCT is either MP or high/lower dose of Dexamethasone combined with one of the three novel agents (thalidomide or bortezomib or lenalidomide). Selection between these combinations depends on the patients' presenting symptoms such as presence of neuropathy, renal impairment or the rapidity required to reverse the symptoms. In countries where lenalidomide is not yet allowed as first line therapy, induction can be started with thalidomide or bortezomib containing triple regimens and in case of unresponsiveness or intolerability, lenalidomide can be used as second line therapy. Fraility, comorbidity and disability of the elderly patients should be taken into account before choosing the induction protocol and appropriate dose reductions should be done. Thus, the treatment should be individualized. Melphalan-based regimens are used for a fixed duration (9-18 months) and then observed. However, the duration of treatment with revlimid (Rd) is unclear either continue until relapse or a fixed duration of 18 months has been tested in ongoing phase III trials. Evidence is now emerging that maintenance or continuous therapy with novel agents is improving PFS with a potential to improve OS. However, in elderly patients, it is particularly important to start treatment at a dose that can be tolerated over the long term. Specific recommendations yet can not be made regarding the impact of novel treatment regimens on prognosis of elderly patients with high-risk cytogenetics. Although the Italian study (Palumbo et al., 2010) suggested some PFS benefit in response to VMPT+VT over VMP regarding the high-risk cytogenetics, other studies did not confirm this.

Regimen	Usual dosing schedule	Reference
Melphalan-Prednisone (MP-7 day Schedule)	Melphalan 8-10 mg oral days 1-7 Prednisone 60mg/d oral days 1-7 Repeated every 6 weeks	Kyle et al., 2004
Thalidomide-Dexamethasone (Td)	Thalidomide 200 mg oral days 1-28 Dexamethasone 40 mg oral days 1,8,15,22 Repeated every 4 weeks	Rajkumar et al., 2006
Lenalidomide-Dexamethasone (Rd)	Lenalidomide 25 mg oral days 1-21 Dexamethasone 40 mg oral days 1,8,15,22 Repeated every 4 weeks	Rajkumar et al., 2010
Bortezomib –dexamethasone (Vd)	Bortezomib 1.3 mg/m^2 iv days 1,8,15,22 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1,8,15,22) Repeated every 4 weeks	Harousseau et al., 2006
Melphalan-Prednisone-Thalidomide (MPT)	Different MPT protocols are described in table…	

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Regimen	Usual dosing schedule	Reference
Bortezomib-Melphalan-Prednisone (VMP)	Bortezomib 1.3 mg/m^2 iv days 1,8,15,22 Melphalan 9 mg/ m^2 oral days 1-4 Prednisone 60 mg/ m^2 oral days 1-4 Repeated every 35 days	San Miguel et al., 2008
Bortezomib-Thalidomide-Dexamethasone (VTD)	Bortezomib 1.3 mg/m^2 iv days 1,8,15,22 Thalidomide 100-200 mg oral days 1-21 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1,8,15,22) Repeated every 4 weeks	Cavo et al., 2009
Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD)	Cyclophosphamide 300mg/ m^2 oral days 1,8,15,22 Bortezomib 1.3 mg/m^2 iv days 1,8,15,22 Dexamethasone 40 mg oral days 1,8,15,22 Repeated every 4 weeks	Reeder et al., 2009
Bortezomib-Cyclophosphamide-Dexamethasone (VCD)	Bortezomib 1.3 mg/m^2 iv days 1,4,8,11 Cyclophosphamide 900mg/ m^2 on day 1 every 3 weeks Dexamethasone 40 mg on day of and day after bortezomib	Einsele et al., 2009
Bortezomib-Lenalidomide-Dexamethasone (VRD)	Bortezomib 1.3 mg/m^2 iv days 1,8 and 15 Lenalidomide 25 mg oral days 1-14 Dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1,8,15,22) Repeated every 3 weeks	Richardson et al., 2010
Bortezomib-Melphalan-Prednisone-Thalidomide (VMPT)	Bortezomib 1.3 mg/m^2 iv days 1,8,15,22 every 35 days Melphalan 9 mg/ m^2 oral days 1-4 every 35 days Prednisone 60 mg/ m^2 oral days 1-4 every 35 days Thalidomide 50 mg/day	Palumbo et al., 2010
Melphalan-Prednisone-Lenalidomide (MPR-R)	Melphalan 0.18 mg/kg on days 1-4 every 4 weeks x 9 cycles Prednisone 2mg/kg on days 1-4 every 4 weeks x 9 cycles Lenalidomide 10 mg on days 1-21 then 10mg/d until relapse	Palumbo et al., 2012
Cyclophosphamide-Thalidomide-Dexamethasone (atenuated dose) (CTD a)	Cyclophosphamide 500mg/week Thalidomide 50 mg/day for 4 weeks, 50 mg increments every 4 weeks to a maximum 200mg/day Dexamethasone 20 mg/day on days 1- 4 and 15-18 every 4 weeks	Morgan et al., 2011
Bortezomib-Lenalidomide-Dexamethasone-Cyclophosphamide (VRDC)	Bortezomib 1.3 mg/m^2 iv days 1,4,8,11 Lenalidomide 15 mg oral days 1-14 Dexamethasone 40 mg days 1,8,15 Cyclophosphamide 500mg/ m^2 days 1,8	Kumar et al., 2010

Table 13. Main treatment protocols in Multiple Myeloma

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