Chapter 9

Proteasome Inhibition and Hematopoietic Stem Cell Transplantation in Multiple Myeloma

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Additional information is available at the end of the chapter

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1. Introduction

Multiple myeloma is a malignant plasma cell disorder in which the proliferation of the malignant plasma cells leads to anemia, infections, bone fractures, hypercalcemia and renal dysfunction [1]. Affecting approximately 32,000 people each year worldwide, with a median age of onset of approximately 68 years, it is the second most common hematological malignancy after non-Hodgkin's lymphoma (NHL). Two major advances have occurred in the treatment of multiple myeloma in the last two decades: the introduction of high-dose chemotherapy with autologous stem cell transplantation (ASCT), and the development of active drugs with a novel mechanism of action (proteasome inhibition and immunomodulation). Both advances have led to significant improvements in overall survival in this disease.

The superiority of ASCT over conventional chemotherapy treatment in younger subjects with newly diagnosed multiple myeloma was first established in a French IFM Phase 3 study in the 1990s [2]. The ASCT approach led to higher tumor response rates, better event-free survival (EFS) and overall survival (OS). This superiority of ASCT over conventional treatment was later confirmed in a British phase 3 study [3]. Both EFS and OS appear directly related to the depth of the tumor response to treatment [4]. Due to this correlation achieving complete response (CR) or at least very good partial response (VGPR) has become an important goal of the ASCT approach. ASCT can be complicated by severe myelosuppression and infections and has therefore been reserved for patients who are <65-70 years old without significant comorbidities [5].

ASCT is preceded by an *induction regimen* the primary objective of which is to debulk the tumor without causing damage to the hematopoietic progenitor cells. Until recently, the standard induction regimens in myeloma were vincristine, doxorubicin and dexamethasone (VAD), which has 5-7% CR rate post induction [6], or Thalidomide-Dexametha-

sone (Thal-Dex), which has a 4% CR rate post induction [7]. After induction therapy autologous CD34+ hematopoietic stem cells are harvested from peripheral blood, and less often collected as part of bone marrow cells, and reinfused after conditioning with high-dose chemotherapy regimen with high-dose melphalan (*conditioning regimen*). The conditioning and reinfusion of CD34+ stem cells can be done once or twice (single or double ASCT). The addition of a limited number of cycles of standard dose chemotherapy (*consolidation treatment*) or of a prolonged exposure to low dose therapy (*maintenance treatment*) after the ASCT is increasingly being used to further improve EFS and OS, although their value has not been fully established [5]

If the ASCT approach is not used in the treatment of a newly diagnosed patient with multiple myeloma, it can still be applied upon relapse. A randomized study by the French GMA group indicated that a second-line rescue with high dose therapy and ASCT resulted in similar overall survival as compared to initial treatment with this approach [8].

The value of allogeneic bone marrow transplantation (Allo-SCT) in multiple myeloma is controversial [9]. The high treatment related mortality associated with myeloablative conditioning in allo-SCT has led to the development of reduced-intensity conditioning (Allo-RIC). Convincing evidence is sofar lacking that Allo-RIC can improve the survival compared with autologous stem-cell transplantation. For this reason, allo-RIC in myeloma is currently only recommended in the context of clinical trials.

It is still unclear whether any of these treatment approaches can be curative, even in a subset of patients, although they have extended the median overall survival of patients with newly diagnosed multiple myeloma beyond 5-6 years [10]. Improvement of outcomes by incorporation of the proteasome inhibitor bortezomib into autologous stem cell transplantation approaches has been an area of intense clinical research over the last decade and is the topic of this review.

Bortezomib is a first-in-class proteasome inhibitor which was originally approved for the treatment of relapsed or refractory multiple myeloma by the US Food and Drug Administration (FDA) in 2003 and by the European Agency for the Evaluation of Medicinal Products (EMEA) in 2004 [11,12]. Bortezomib is a reversible inhibitor of the 26S proteasome which is a large protein complex that degrades ubiquitinated proteins. Regulatory proteins relevant to the initiation and progression of cancers including multiple myeloma are known to be degraded during the cell cycle by the ubiquitin-proteasome pathway [13]. Binding of bortezomib to the 20S β5 subunit of the proteasome results in a reversible inhibition of the chymotrypsin-like protease in the proteasome. In multiple myeloma cells, this results in inhibition of NF-kB activation, in attenuation of interleukin-6-mediated cell growth, and direct apoptotic and anti-angiogenic effects [14,15].

In relapsed multiple myeloma, single agent bortezomib was shown to improve time to progression, response rate and overall survival as compared to high-dose dexamethasone [16]. Median survival of patients treated with bortezomib was 29.9 months as compared to 23.7 months in the dexamethasone control group ($p=0.027$) [17]. In patients with newly diagnosed multiple myeloma who were not candidate for ASCT, the addition of bortezomib to

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standard chemotherapy with melphalan-prednisone also resulted in improvement in time to progression, response rate and complete rate, and overall survival. Complete response rate of patients treated with the bortezomib-melphalan-prednisone combination was 30% as compared to 4% in the melphalan-prednisone control group ($p<0.001$) [18]. Median survival of patients treated with the bortezomib-melphalan-prednisone combination was 56.4 months as compared to 43.1 months in the melphalan-prednisone control group ($p=0.0004$) [19]. Based on these significant improvements in outcomes in other settings in multiple myeloma, the introduction of bortezomib in autologous stem cell transplant approaches in myeloma has been an area of intense clinical study activity.

The approved single agent bortezomib dose and schedule in multiple myeloma is 1.3 mg/m^2, on days 1, 4, 8, and 11, followed by a 10-day rest period (21 day cycle). The most clinically significant side-effect is a cumulative dose-related peripheral neuropathy which is managed by treatment interruptions and dose modifications [20]. Other common adverse events include lower grade gastro-intestinal adverse events and thrombocytopenia [16]. In most clinical studies, including those reviewed in this chapter, bortezomib has been given intravenously. Recent data in relapsed multiple myeloma have indicated that the subcutaneous administration of bortezomib is as efficacious and results in less neurotoxicity [21]. However, data on subcutaneous administration of bortezomib as part of transplant regimens in myeloma are currently still lacking.

2. Methodology

We followed published guidelines for medical literature reviews [22,23,24]. The medical literature was searched in the OVID database (Medline; Derwent Drug File; Your journals @ Ovid; Biosis Previews; and Embase). The search was limited to the English language and articles published without a data range limit to August 1, 2012. The following search strategy was used with the following words being entered in the basic search section of OVID:

1. randomized AND phase AND 3 AND bortezomib OR velcade AND stem AND cell AND transplantation.
2. the second phase of searching showed the addition of 'myeloma AND proteosome inhibitor' with 'autologous'
3. the third phase of searching substituted 'bone AND marrow' for the words 'stem AND cell

Further selection of the identified studies included in this review was based on following criteria: (1) prospective study design; (2) publication in peer-reviewed journals; (3) randomized phase 3 or phase 2 design, or single arm phase 2 design with sample size >25 patients. These criteria were chosen to increase likelihood of scientific quality and interpretability of the selected studies. Twenty-nine studies were initially retained in the search and 16 studies were subsequently selected based on these criteria.

VELCADE (Bortezomib for Injection) is a small molecule proteasome inhibitor being codeveloped by Millennium Pharmaceuticals, Inc. (Millennium) and Janssen Research & Development. The selection of the identified was solely based on the criteria indicated above and no studies were de-selected due a conflict-of-interest.

3. Results

3.1. Bortezomib in induction therapy

The search of an optimal induction regimen prior to high-dose therapy and ASCT in multiple myeloma is still ongoing. An ideal induction regimen should, among others, have the following characteristics:

1. Able to give the optimum post induction tumor response, since better response is associated with better long-term outcomes;
2. Able to act quickly to debulk the tumor, as often the patients present with advanced disease and complicated presentations;
3. Able to work even in renal failure, since this is a common feature of multiple myeloma;
4. Allowing collection of an adequate of viable hematopoietic stem cells necessary for successful bone marrow rescue and engraftment.

All randomized studies published in peer reviewed journals and investigating the role of bortezomib in induction therapy have been analyzed in this section. Some of the randomized phase 2 and 3 studies compare a bortezomib containing regimen with a non-bortezomib containing regimen, while other studies investigate various combinations and doses with all treatment groups containing bortezomib. Further, all single arm phase 2 studies with more than 25 patients are also included in this review.

Early studies started soon after the introduction of bortezomib into the treatment of relapsed myeloma compared the role of a bortezomib-containing induction regimen against VAD, the standard regimen at that time.

A first phase 3 study by the French IFM group provided evidence that the combination of bortezomib plus dexamethasone was superior to VAD as induction regimen [25]. In this IFM2005-01 study 481 patients who were eligible for autologous stem cell transplantation (≤65 years) were randomized to receive VAD (n = 121); VAD plus DCEP (n=121); bortezomib plus dexamethasone (n = 121) or bortezomib plus dexamethasone plus DCEP (n = 119). DCEP (dexamethasone, cyclophosphamide, etoposide and cisplatin) were given as a consolidation course, soon after 4 induction cycles and before the high dose melphalan for conditioning. The study allowed a second high-dose therapy and stem cell transplant procedure for patients failing to attain at least a VGPR after first transplant. The primary endpoint was post induction CR/nCR rate. Patients in the VAD group were treated with four 4-week cycles of vincristine 0.4 mg/d and doxorubicin 9 mg/m^2/d by continuous infusion on days 1 to

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4, and dexamethasone 40 mg daily po on days 1 to 4 (all cycles) and days 9 to 12 and days 17 to 20 (cycles 1 and 2 only). Bortezomib plus dexamethasone comprised four 3 week cycles of bortezomib 1.3 mg/m^2 iv days 1, 4, 8 and 11 plus dexamethasone po 40 mg/d on days 1 to 4 (all cycles) and days 9 to 12 (cycles 1 and 2 only). DCEP comprised two 4-week cycles of dexamethasone 40 mg/daily on days 1 to 4; plus cyclophosphamide 400 mg/m^2, etoposide 40 mg/m^2 and cisplatin 15 mg/m^2 by continuous iv infusion day 1 to 4. Stem cells were collected after priming with granulocyte stimulating factor alone or cyclophosphamide for those who mobilize poorly. The CR/nCR rate was significantly higher (14.8%) for patients receiving bortezomib plus dexamethasone compared to patients receiving VAD (6.4%, p-value=0.004). ORR was 78.5% vs 62.8% (p=<0.001). Patients with del13, a negative prognostic cytogenetic abnormality in multiple myeloma, also reported higher response rates in the bortezomib containing arm : ORR was 78.2% vs 65.1% (p=0.037); and CR/nCR was 20.8% compared to 5.8%(p=0.002). The study showed that the addition of DCEP did not further improve the outcomes wither either regimen. The PFS for the bortezomib group was 36 months vs 29.7 months in the VAD arm after 32.2 months follow-up (p=0.064 unadjusted). Median OS was not yet reached but the 3 year OS rate was 81.4% compared to 77.4% in favor of the bortezomib-dexamethasone combination. Stem cell collection was adequate in both arms. The safety profile was similar between the groups for most adverse events except for all grade peripheral neuropathy (45.6% for bortezomib and dexamethasone and 28% for VAD) and grade 3/4 neuropathy (7.1% and 2.1%, respectively).

A second phase 3 study by the Dutch-German HOVON-GMMG groups randomized 827 patients to receive 3 cycles of either bortezomib combined with adriamycin and dexamethasone (PAD) or VAD during induction given every 28 days [26,26,27]. This HOVON-65/GMMG-HD4 study had a maintenance part post ASCT in which patients on VAD further received thalidomide 50 mg po daily for a further 2 years while those on PAD received bortezomib 1.3 mg/m^2 iv every two weeks for 2 years. The primary objective of the study was to compare PFS of the two arms. Response rates post induction were analyzed as secondary objectives. The CR/nCR rate post induction was 5% in patients who were randomized to VAD and 11% in patients who received PAD (P <.001). The post transplant response rate for nCR/CR was 15% (VAD) versus 31% (PAD), (P <.001). Overall nCR/CR rates were 34% versus 49%, (P <.001) for patients on VAD and PAD respectively. The median PFS was 28 months for the VAD arm and 35 months for the PAD arm (p=0.002). Median OS was not reached after 66 months of follow-up, with 5-year OS of 55% (VAD) versus 61% (PAD). In patients with del17p, the worst prognostic cytogenetic abnormality in multiple myeloma, both PFS (median PFS, 12 vs 22 months, p=0.01) and OS (median OS, 24 vs > 54 months, p=0.003) were significantly better in the PAD arm. In patients with del13, a negative impact on PFS was observed in both treatment arms. OS in patients with this deletion was similar to the OS in patients with no del13 in the PAD arm and significantly better than OS in the VAD arm (median OS for VAD 49 vs 59 months for the PAD arm, p=0.007). Stem cell collection was adequate in both treatment arms. In patients presenting with a baseline serum creatinine of more than 2 mg/dL, bortezomib significantly improved CR/nCR rates which were 27% (VAD) compared to 53% (PAD) (p=0.02). The PFS in the same population improved from a median of 13 months to 30 months (p= 0.004) and OS from a median of 21 months to

54 months (HR, 0.33; $p < 0.001$) respectively. There was more neuropathy in the PAD arm (40% grades 2 to 4) compared to the VAD arm (18%, $p<0.001$). The contribution of the maintenance regimens in this study is discussed later in this chapter.

The above two large studies showed significant improvement of bortezomib-containing regimens as compared to VAD in terms of post-induction response and PFS, with a positive trend on overall survival. Later studies focused on comparing bortezomib-containing regimens against non-bortezomib containing regimens other than VAD.

The bortezomib-thalidomide-dexamethasone (VTD) regimen was compared to the thalidomide-dexamethasone (TD) regimen in a Phase 3 study randomizing 480 patients over four 21-day cycles [28,29]. The patients received thalidomide 100 mg po daily for the first 14 days and 200 mg daily thereafter, plus dexamethasone (40 mg po daily on 8 of the first 12 days, but not consecutively; total of 320 mg per cycle), either alone or with bortezomib (1 3 mg/m^2 iv on days 1, 4, 8, and 11). Post double ASCT the patients received two 35-day cycles of their assigned drug regimen, VTD or TD, as consolidation therapy (see below). The primary endpoint was the CR/nCR rate to induction therapy. After induction therapy, complete or near complete response was achieved in 31% patients receiving VTD compared to 11% for those on TD ($p<0$ 0001). Rates of complete or near complete response continued to be significantly higher in the VTD group than in the TD group after the first and second autologous stem-cell transplantations (55% vs 41%, $p=0.0024$). Median time to best complete or near complete response was significantly shorter for patients receiving VTD (9 months) than in those on TD (14 months). The contribution of the consolidation therapy is discussed below. The estimated 3-year PFS was 60% in the VTD arm compared to 48% in the TD arm. Overall, PFS was significantly longer with VTD compared to TD (median not reached vs 32 months, $p=0.0061$). The estimated 3-year probability of progression or relapse was 29% in the VTD group versus 39% in the TD group ($p=0$ 0061 by Kaplan-Meier analysis with an HR of 0 61. In the VTD group, the PFS of subjects with or without high-risk cytogenetic abnormalities [del13q, or del17p or t(4;14)] were similar (59% with abnormalities and 60% without). This contrasted with the TD group in which a much lower PFS of 19% for patients with high-risk cytogenetics was observed as compared to the 48% attained by patients without high-risk cytogenetics in the same TD group. Stem cell collection was adequate in both arms. Grade 3 or 4 adverse events were more frequent on VTD (56%) than on TD (33%), with a higher occurrence of grade 3 or higher peripheral neuropathy in patients on VTD (10%) than on TD (2%).

A further phase 3 study (GEM05-MENOS65) performed by the Spanish GIMEMA group randomized 390 patients in a three arm study to receive VTD versus TD versus a regimen called VBMCP/VBAD with bortezomib [30]. Combination chemotherapy with VBMCP/VBAD and bortezomib consisted of a total of 4 cycles of alternating VBMCP (vincristine, BCNU, melphalan, cyclophosphamide, prednisone) and VBAD (vincristine, BCNU, doxorrubicine, dexamethasone) followed by 2 cycles of bortezomib (1.3 mg/m^2 iv on days 1, 4, 8 and 11 at 3 weeks intervals), TD consisted of thalidomide 200 mg po daily (escalating doses in the first cycle: 50 mg on days 1 to 14 and 100 mg on days 15 to 28) and dexamethasone 40 mg po on days 1-4 and 9-12 at 4-week intervals for 6 cycles and the VTD arm was identical

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to TD plus bortezomib 1.3 mg/m^2 iv on days 1, 4, 8 and 11 of each cycle. The duration of the induction therapy was 24 weeks in all arms. Three months after ASCT patients were randomized to receive maintenance therapy with interferon alfa-2b subcutaneously versus thalidomide 100 mg po daily versus thalidomide 100 mg/day po daily plus one cycle of bortezomib iv on days 1, 4, 8 and 11 every three months (see below). The CR rate after induction was significantly higher with VTD (35%) compared to TD (14%) and VBMCP/VBAD/B (21%) (p=0.0001 and p=0.01, respectively). Of significance in the VBMCP/VBAD/Bortezomib arm, the CR rate increased from 8% after the 4 cycles of VBMCP/VBAD to 21% after the completion of the 2 bortezomib courses. The progressive disease (PD) rate during induction was significantly lower with VTD than with TD (7% vs. 23%, p= 0.0004). In patients with extramedullary soft-tissue plasmacytomas the CR rate after induction was significantly higher with VTD as compared with TD (42% vs. 14%, p=0.02). In all the above analysis the VBMCP/VBAD/Bortezomib arm showed an intermediate efficacy between VTD and TD. In this study VTD also had superior CR rates in the subgroup of patients with high-risk cytogenetic abnormalities as compared to the two other regimens. After a median duration of follow-up of 35.2 months, the median PFS was significantly higher for VTD (56.2m) than with VBMCP/VBAD/Bortezomib (35.3m) or with TD (28.2 m, p=0.01). The difference in the four-year survival rates between VTD (74%), VPMCP/VVBAD/bortezomib (70%) and TD (65%) is not statistically significant at this point. There were two stem cell mobilization failures in the VBMCP/VBAD/Bortezomib group. Peripheral neuropathy grade ≥ 3 with VTD (14%) was significantly higher than with TD (5%) (p=0.01) but not significantly different from VBMCP/VBAD/B (9%). An additional 46% of patients in the VTD arm developed grade 2 peripheral neuropathy compared with 8% and 15% in the TD and VBMCP/VBAD/B arms, respectively (p<0.001). Grade 3 and 4 neutropenia was significantly higher with VBMCP/VBAD/B (22%) than with remaining two arms TD (14%) and VTD (10%). There were no significant difference in incidence of all grade ≥ 3 adverse events between the three treatment groups.

In conclusion, all currently published phase 3 studies indicate that induction regimens containing bortezomib lead to improvements in CR/nCR rates after induction which are maintained after ASCT, and also lead to improved PFS as compared to standard regimens. Where reported, the time to response appear shorter, and the regimens have important activity in poor prognosis situations such as high-risk cytogenetic disease and renal insufficiency. After a relatively short duration of follow-up, a trend towards improved overall survival with the bortezomib regimens has been noted in several studies. All phase 3 studies also provide evidence of good hematopoietic stem cell collection but indicate a higher incidence of neuropathy in patients treated with a bortezomib combination. This phase 3 evidence is further supported by a plethora of randomized and non-randomized phase 2 studies which have incorporated bortezomib in the induction regimens.

In a randomized phase 2 study by the French IFM (IFM2007-02) a lower dose of bortezomib was investigated in combination with thalidomide and dexamethasone in order to reduce the peripheral neuropathy risk. One hundred ninety-nine patients were randomized to receive VD or vTD over four 3 week cycles prior to ASCT [31]. vtD was composed of reduced bortezomib at 1 mg/m^2 iv on days 1, 4, 8, and 11, thalidomide 100 mg/day po, and dexame-

thasone while VD consisted of bortezomib 1.3 mg/m^2 iv on days 1, 4, 8, and 11 plus the same dexamethasone regimen. In case of less than partial response (PR) after cycle 2, the dose of bortezomib was increased to 1.3 mg/m^2 and the dose of thalidomide to 200 mg/day in the vTD arm. The primary endpoint of this study was post induction CR rate. The CR rate between the groups was the same after 4 cycles, 13% in the vTD arm and 12% in the VD arm. However, both the bortezomib and thalidomide dose had to be increased in 7 patients in the vTD arm. The ORR was 88% in the vTD arm versus 81% in the VD arm, the difference not reaching statistical significance. Further, there was no difference in CR rate post transplant (29% in vTD arm and 31% in VD arm). The target stem cell collection yield of 2 × 10^6 CD34$^+$ cells/kg was achieved in 93% and 80% of VD and vTD patients, respectively (P =.01). While the overall safety profile was similar between the two arms, there was less peripheral neuropathy in the vTD arm (53% all grade vs 70% on VD, 11% grade 3 or higher vs 11% on VD). Results of the VD control group were consistent with prior observations from the IFM group on this VD induction regimen, both in a single arm phase 2 study [32] and in the randomized phase 3 study (see above).

Efficacy of VD in induction was also assessed in another phase 2 study with 57 patients, given over 4 cycles followed by 2 cycles of DCEP consolidation [33]. The median CR34+ cells collected were 7.5 x 10^6/kg and in 86% of these patients the amount was more than twice the minimum required for transplantation. The ORR was 87% and CR 30%. Univariate analysis found no difference between response and cytogenetic abnormalities.

Efficacy of VTD was further confirmed in a single arm phase 2 study of 44 patients treated with bortezomib combined with thalidomide and dexamethasone, administered over eight 3-week cycles [34]. The patient enrolment included both frontline and recurrent disease as long as the patients were eligible for ASCT. Thirty four patients were frontline, 8 with recurrent disease in second line and a further 2 had a third line recurrence. The ORR was 91% with CR/sCR rate of 20%. Post transplant these response rates increased to ORR of 100% and CR/sCR rate of 53%. All 44 patients had successful stem cell collection. Fifty-five percent of the subjects developed neuropathy of all grades, though grade 3 neuropathy was reported in 9%. DVT occurred in 5% of the patients.

Other multidrug combination induction regimens including bortezomib were also investigated in phase 2:

- In a randomized phase 2 study, 140 patients were initially randomized to VDCR, VDR, or VDC to receive eight 3-week cycles of induction therapy followed by four 6-week cycles of bortezomib maintenance therapy [35]. The VDC arm was modified after an interim analysis to add a third dose of cyclophosphamide at 500 mg/m^2 on day 15 (VDC-mod). Bortezomib was given in standard doses. Patients could undergo stem cell mobilization any time after 2 cycles and undergo ASCT any time after 4 cycles. After 4 cycles of induction therapy, the confirmed ORR was 80%, 73%, 63%, and 82% of patients in the VDCR, VDR, VDC, and VDC-mod arms including VGPR or better in 33%, 32%, 13%, and 41%, respectively. After ASCT, the ORR was 88%, 85%, 75%, and 100% for the VDCR, VDR, VDC, and VDC-mod arms including VGPR or better in 58%, 51%, 41%, and 53%, respectively. The 1-year PFS was 100%, 100%, 88%, and 100% for the VDCR, VDR, VDC, and

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VDC-mod arms, respectively. The 1-year OS estimate was 100% for all 4 arms. In addition the 1-year PFS for the high-risk patients (n = 24) was 100% and 85% for the standard-risk patients, and was similar across the study arms. The median CD34+ cell yield was 6.8 x 10^6/kg (VDCR); 7.8 (VDR); 7.95 (VDC) and 7.75 (VDC modified). At least one grade ≥ 3 AE was seen in ~ 80% of patients in each arm. AEs leading to discontinuation were seen in 21%, 19%, 12%, and 6% in the VDCR, VDR, VDC, and VDC-mod arms, respectively. The most common adverse event of grade 3 or higher was neutropenia occurring in 44% (VDCR), 10% (VDR), 30% (VDC) and 24% (VDC modified). Neuropathy grade 3 or higher occurred in 13%, 17%, 9% and 18% respectively.

- In two single arm phase 2 studies, bortezomib was combined with cyclophosphamide and dexamethasone (CyBorD) [36,37]. In one study, 33 patients were treated with four 3 weekly cycles with cyclophosphamide 300 mg/m^2 given orally and once weekly, while bortezomib and dexamethasone were given in standard doses. ORR was 88%, and 39% were CR/nCR. Responses were rapid with a mean 80% decline in the monoclonal protein at the end of two cycles. All patients undergoing stem cell harvest had a successful collection. The most common grade 3-4 adverse events were hematological (anemia in 12%, neutropenia in 13%, thrombocytopenia in 25%) and hyperglycemia (13%). All grade peripheral neuropathy adverse events occurred in 66% of the patients while grade 3 occurred in 7%. In the second study, 30 patients were treated with different IV cyclophosphamide dose levels in combination with bortezomib and dexamethasone for 3 cycles [37]. The recommended dose of IV cyclophosphamide was 900 mg/m^2 on day 1. The CR rate after induction therapy was 10% and the overall response rate was 90% at the end of the induction therapy. Most frequent adverse events were again hematologic and neuropathy as well as gastro-intestinal.

- The most intense bortezomib-containing induction regimen of VTD-PACE is included in a high-dose therapy approach called Total Therapy 3 and has been investigated in a large cohort of 303 patients [38]. The regimen consists of two cycles of VTD-PACE (bortezomib, thalidomide, dexamethasone and 4-d continuous infusions of cis-platin, doxorubicin, cyclophosphamide, etoposide) during induction and then another two cycles during consolidation after the ASCT. The patients are then maintained for 3 years on monthly cycles of VTD in the first and TD in the remaining years. The response rates of this Total Therapy 3 approach are among the highest reported in multiple myeloma. The 2 year CR rate was 56% whilst the nCR rate was as high as 83%. Two year OS estimates were also high at 82.9% and EFS of 79.9%. Although no randomized comparison was performed, the investigators consider those results better than a similar approach (Total therapy 2) which did not include bortezomib. Stem cell collection was successful. Adverse events grade 3 or higher included thrombo-embolic events in 27% and peripheral neuropathy in 12% of the patients.

In conclusion, these studies have provided evidence of the important role of bortezomib in induction therapy pre-ASCT. Randomized phase 3 studies indicate that induction regimens containing bortezomib lead to improvements in CR/nCR rates after induction which are maintained after ASCT, and also lead to improved PFS as compared to standard non-borte-

zomib containing regimens. After a relatively short duration of follow-up, a trend towards improved overall survival with the bortezomib regimens has been noted. Particularly in patients with high-risk cytogenetic abnormalities, such as del17p and del13, the addition of bortezomib to induction therapy has improved outcomes. All phase 3 studies also provide evidence of good hematopoietic stem cell collection. While bortezomib can safely be combined with several induction regimens, a higher incidence of neuropathy in patients treated with a bortezomib combination is generally noted. Other toxicities of the induction regimens appear related to the combination partner (such as neutropenia for cyclophosphamide, thrombo-embolic events for thalidomide, hyperglycemia for high-dose dexamethasone) and the optimal combination regimen, as well as the optimal number of induction cycles has not been identified yet. One phase 2 study provided evidence of a lower incidence of neuropathy with a lower dose of bortezomib.

3.2. Bortezomib during conditioning

The high-dose chemotherapy regimen which immediately precedes the autologous stem cell transplantation is referred to as the 'conditioning regimen'. Melphalan is the most frequently used conditioning agent in multiple myeloma and is given at the high-dose of 200 mg/m^2 or at a reduced dose in case of renal function impairment [39].

Two single arm studies have investigated the addition of bortezomib to the high-dose melphalan conditioning regimen. The rationale to combine the two agents in this setting was based on (1) the synergy between bortezomib and melphalan reported both in vitro and in vivo [14,40], as well as on (2) the lack of overlapping toxicities between the two agents (mainly neurologic for bortezomib and hematologic for melphalan).

In a dose and schedule-finding phase ½ study, 39 patients with newly diagnosed multiple myeloma who achieved less than VGPR following induction therapy were randomized to receive a single escalating dose of bortezomib (1 mg, 1.3 mg or 1.6 mg/m^2) either 24 hours before or 24 hours after melphalan (given 100 mg/m^2/d for 2 days) [41]. Stem cells were reinfused 2 days after the last melphalan dose. Median time to neutrophil recovery and platelet recovery was 12 days and 16 days, respectively, for both schedules. Transplant-related toxicities (gastro-intestinal and mucositis) were also similar for the two schedules. No peripheral neuropathy was reported. In the treatment group receiving bortezomib prior to melphalan (n=19) 47% had at least VGPR and 11% had CR post-transplant, while in the treatment group receiving bortezomib after melphalan (n=20) 55% had at least VGPR and 30% had CR. The investigators that the combination was safe with data suggesting improved efficacy and recommend the administration of bortezomib after high-dose melphalan as the preferred schedule.

In a phase 2 study conducted by the French IFM group, 54 patients with newly diagnosed multiple myeloma received melphalan 200 mg/m^2 in combination with four administrations of bortezomib at a dose 1 mg/m^2 (1 and 4 days prior to melphalan, and 3 and 6 days after melphalan) [42]. The autologous peripheral blood stem cells were reinfused 2 days after melphalan administration. While 4% of patients had CR and 28% had PR at the end of the induction therapy, 32% had CR and 68% had at least VGPR 3

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months after this conditioning regimen. The median time to neutrophil and platelet recovery was 7 days and 3 days after stem cell reinfusion respectively. No engraftment failure or treatment-related death was reported. Three patients developed de novo neuropathy, while the severity of pre-existing neuropathy was not affected. In a matched control analysis, only 11% of CR post-conditioning were reported.

In a randomized phase 2 study, 60 patients not in CR after induction therapy were randomized to receive an unconventional conditioning regimen with melphalan 200 mg/m^2 in combination with arsenic trioxide and ascorbic acid either without (group 1) or with bortezomib at either 1mg/m^2 (group 2) or 1.3 mg/m^2 for 3 doses (group 3). Fifty-eight patients were randomized between the 3 treatment groups. Addition of bortezomib to this regimen was found safe with no apparent increase in time to neutrophil or platelet engraftment, in grade ¾ non-hematologic toxicity or in treatment-related mortality. However, there was no significant improvement in the CR rate, PFS and OS rates in the bortezomib groups. The reason for this lack of improvement was interpreted by the authors as related to the high proportion of patients with relapsed disease (25%) and by the concomitant administration of ascorbic acid [43].

In conclusion, these studies have provided evidence that the addition of bortezomib to the conditioning regimen is feasible with no negative impact on hematopoietic recovery or treatment-related mortality after ASCT. From the two phase 2 studies adding bortezomib to high-dose melphalan, high CR rates post-ASCT were noted which appeared superior to historic data. A small randomized phase 2 study was not able to confirm improved efficacy outcomes when bortezomib was added to a multi-drug conditioning evidence.

3.3. Bortezomib in consolidation treatment

At the moment of our search, the results of only one randomized study incorporating bortezomib in consolidation therapy has been published in a peer-reviewed paper.

In the GIMEMA phase 3 study investigating bortezomib-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (TD), the combination regimens were given both in induction therapy pre-ASCT and in consolidation therapy post-ASCT[29]. Patients initially randomized to VTD received 2 post-ASCT consolidation cycles of bortezomib 1.3 mg/m^2 iv on d1,8,15,22 every 5 weeks in combination with thalidomide 100 mg/d po and dexamethasone, patients initially randomized to TD received 2 post-ASCT consolidation cycles without bortezomib. Of the 236 patients initially randomized to VTD induction, 160 patients (68%) continued with VTD consolidation, while of the 238 patients initially randomized to TD induction, 161 patients (68%) continued with TD consolidation. VTD consolidation significantly improved the CR and CR/nCR rates post-ASCT, while the TD consolidation did not. After a median follow-up of 30.4 months from start of consolidation, 3-year PFS was significantly longer for the VTD group (60% vs 48%, p=0.042) but sofar no difference in overall survival from this landmark has been seen (3-year survival rates 90% for VTD and 88% for TD). Grade 2 or 3 peripheral neuropathy (8.1% vs 2.4%) was more frequent with VTD versus TD consolidation. The authors conclude that VTD consolidation therapy significantly contribut-

ed to the improved clinical outcomes observed for patients randomly assigned to the VTD arm of the study.

3.4. Bortezomib in maintenance treatment

There were no studies identified which in a randomized fashion have investigated the role of single agent bortezomib as prolonged maintenance therapy post-ASCT. However, a lot of information on single agent bortezomib maintenance therapy can be derived from the HOVON-65/GMMG-HD4 study, the largest phase 3 study ever conducted in ASCT in newly diagnosed multiple myeloma. In addition, preliminary data are available from a randomized phase 3 study investigating the bortezomib-thalidomide combination in maintenance therapy (GEM05-MENOS65) and from a phase 2 study investigating a bortezomib-thalidomide-dexamethasone combination in maintenance therapy post-ASCT [44].

In the HOVON-65/GMMG-HD4 study, as discussed above, patients randomized to the bortezomib-doxorubicin-dexamethasone (PAD) induction treatment group continued bortezomib maintenance 1.3 mg/m^2 iv every 2 weeks for 2 years post-ASCT, whereas the control treatment group of vincristine-doxorubicin-dexamethasone (VAD) induction continued to be treated with thalidomide 50 mg/d po for the same treatment duration [26]. In this study, 833 patients were randomized between the PAD and the VAD induction regimens. After ASCT, 229 patients from the PAD treatment group (55%) continued with bortezomib maintenance, while in the VAD treatment group 270 patients (65%) continued with thalidomide maintenance. Of the 229 patients starting bortezomib maintenance, 109 (48%) completed the 2-year maintenance, while 26 (11%) discontinued because of toxicity and 74 (32%) discontinued earlier because of progression. Of the 270 patients starting thalidomide maintenance, only 73 (27%) completed the 2-year maintenance, while more patients (82 or 30%) discontinued because of toxicity and a similar percentage (86 or 32%) discontinued because of progression. Because of the sequential study design a direct comparison between the two maintenance regimens should be interpreted with caution. However, the main study publication indicates a statistically significantly higher incidence of serious adverse events (34% vs 23%, $p<0.01$) during bortezomib maintenance, mainly related to infection, while on the other hand more peripheral neuropathy was reported during thalidomide maintenance (5% vs 8%, $p<0.001$). The sequential design also limits the interpretation of the efficacy data of the maintenance regimens. Although in the bortezomib maintenance all patients had already been exposed to bortezomib during induction therapy, a similar percentage of patients (23%) had an upgrade of their tumor response post-ASCT as compared to the thalidomide maintenance which introduced a new agent (24%). An analysis of progression-free survival calculated from the last ASCT indicates that bortezomib contributed more to improvement of progression-free survival than thalidomide (31 months vs 26 months). Also, a landmark analysis starting at month 12 shows an improvement in progression-free survival ($p=0.04$) and overall survival ($p=0.05$) in the bortezomib-containing arm.

In phase 3 study GEM05-MENOS65 performed by the Spanish PETHEMA/GEM group, patients initially randomized to answer the induction regimen question of bortezomib-thal-dex vs thal-dex vs VBMCP/VBAD/bortezomib (discussed above) were rerandomized after ASCT

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between different maintenance regimens: interferon alfa-2b versus thalidomide 100 mg/d vs thalidomide 100 mg/d plus bortezomib (1.3 mg/m^2 d1,4,8,11 q3 month) until progression and for a maximum of 3 years [30]. Three-hundred ninety patients were initially randomized between the three induction arms; the initial study publication does not report how many patients were rerandomized between the 3 maintenance arms nor does it address the toxicities observed. However, the publication states that after a median follow-up of 24 months from initiation of maintenance, the PFS is significantly longer with thalidomide/bortezomib compared with thalidomide alone and with alfa2-interferon (78% vs 63% vs 49% at 2 years, p=0.01). However, at this early analysis, the overall survival is not significantly different between the 3 maintenance groups.

In a small phase 2 study of 40 patients post-ASCT, a sequential maintenance therapy including bortezomib was investigated [44]. In this study, 6 4-week cycles of weekly bortezomib at a dose of 1.3 mg/m^2 was given in combination with dexamethasone, followed by 6 cycles of thalidomide and dexamethasone and then followed by thalidomide single agent until progression. Of the 40 patients, 32 (80%) completed the bortezomib therapy and in 9 patients the bortezomib-dexamethasone combination upgraded the response from less than CR to CR. The combination regimen was feasible, with peripheral neuropathy grade 1-2 being reported in 27 patients. The authors concluded that this bortezomib maintenance regimen was able to upgrade post-ASCT CR responses with no severe grade ¾ peripheral neuropathy.

In conclusion, currently available data suggest that maintenance therapy with bortezomib, either as single agent or in combination with thalidomide, improves the PFS over thalidomide alone. Prolonged maintenance therapy with bortezomib at lower dose intensity than in the induction setting (either one dose weekly or every 2 weeks, or four doses every 3 months) appears feasible and is able to further improve the CR rate post-ASCT. More follow-up is needed on the impact of these bortezomib maintenance regimens on overall survival.

3.5. Bortezomib during or after ASCT procedure for relapsed myeloma

There were no studies identified which specifically looked into the use of bortezomib as part of an ASCT procedure for relapsed multiple myeloma.

However, one large randomized phase 3 study by the EBMT group (European Group for Blood and Marrow Transplantation) investigated the use of a bortezomib containing regimen to rescue patients with multiple myeloma progressing or relapsing after ASCT [45]. In this study, 269 patients were randomly assigned to receive bortezomib or no bortezomib for one year, in combination with thalidomide (200mg/d) and dexamethasone. Almost half of the patients (47%) had two prior ASCTs. The triplet combination of VTD resulted in a significantly longer time to progression (19.5 m vs 13.8 m, p=0.001) and a significantly better CR/nCR rate (45% vs 25%, p=0.001) with a trend towards improved overall survival (71% vs 65% 24-month survival rate, p=0.093) as compared to the TD control group. On the other hand, the triplet combination had a higher incidence of grade 3 peripheral sensory neuropathy (29% vs 12%, p=0.001) and a higher incidence of grade >=3 thrombocytopenia (17% vs 7%, p=0.016) not associated with serious bleeding complications. The neurotoxicity was at-

tributed by the investigators as due to the combination of the two neurotoxic agents bortezomib and thalidomide given for a prolonged period of time (1 year) and at higher dose levels (200 mg/d thalidomide). The investigators concluded that the VTD combination may be considered as a standard of care for patients relapsing after ASCT, but that the risk for neurotoxicity should be decreased by using lower doses of thalidomide and appropriate dose reductions of bortezomib.

4. Conclusions and future directions

There is an increasing body of literature on the incorporation of bortezomib in the different treatment phases of the autologous stem cell transplantation approach in multiple myeloma. The highest level of evidence on the benefit of bortezomib-containing regimens is available from multiple phase 3 studies in the induction treatment phase. In other treatment phases, the current experimental clinical evidence is more limited. In the conditioning phase, only phase 2 data are available on the addition of bortezomib and comparisons with historic data should be made with caution. In consolidation, only limited phase 3 information is currently available but phase 3 studies comparing bortezomib consolidation versus no consolidation are ongoing or awaiting final publication [46]. In the maintenance phase, randomized phase 3 studies have been published but did not directly test the value of bortezomib maintenance over no maintenance. Despite these limitations some common themes on the incorporation of bortezomib can be observed across the different treatment phases:

- The addition of bortezomib increased the quality of the response (higher complete and near-complete response rates) as compared to control groups or to historic data
- The addition of bortezomb improved the progression-free survival post-ASCT as compared to control groups or to historic data
- Where analyzed, the addition of bortezomib improved the outcomes of patients with poor prognostic features, such as high-risk cytogenetics and renal function impairment
- The addition of bortezomib had no negative impact on hematopoietic stem cell collection or engraftment
- The addition of bortezomib resulted in a higher incidence of peripheral neuropathy

The effect of the addition of bortezomib on the overall survival post-ASCT were variable across studies. While several studies appear to report a favorable survival trend, only in the largest phase 3 study (HOVON-65/GMMG-HD4) the survival improvement reached statistical significance. Potentially contributing to this could be the short duration of follow-up in the initial study publications, the effect of subsequent therapy (and in particular of cross-over use of bortezomib in subsequent therapy lines) and the sample size limitation of the individual studies. An argument for the latter could be found in a recent meta-analysis indicating a survival benefit of bortezomib-containing induction therapy if the different phase 3 study results are combined [47].

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Which future research directions can be expected on this topic in the next decade?

First, given the high response rates and complete response rates observed with bortezomib containing regimens, the question will be asked whether in this younger population with newly diagnosed multiple myeloma a non-transplant approach incorporating bortezomib and immunomodulatory agents can delay or prevent the need for a high-dose therapy and autologous transplant approach. Several randomized phase 3 studies are currently underway to test this hypothesis.

Second, if the ultimate goal of the autologous transplant approach is disease eradication and cure, more rigorous definitions of complete response and more sensitive diagnostic techniques will be required to optimize individual therapy decisions. A stringent CR (sCR) category has already been defined by the IMWG criteria [48]. This stringent CR (sCR) category requires a normalization of the free κ/λ ratio in serum and an immunophenotypic normalization of the κ/λ ratio in the bone marrow, but sofar has not been routinely reported in high-dose therapy studies. By the most recent criteria, also an immunophenotypic CR category has been defined to exclude minimal residual disease based on a more extensive immunophenotypic analysis of the bone marrow [49]. Characterization of minimal residual disease by immunophenotyping has only been reported in selected studies [50]. Alternative techniques such as magnetic resonance imaging or positron emission tomography have also been reported but require further characterization before incorporation in routine ASCT procedures. [51,52].

Third, second-generation proteasome inhibitors, such as carfilzomib, marizomib and MLN-9708, are currently in development in multiple myeloma [53]. These agents are also potent inhibitors of proteasome activity in vitro but show differences in enzyme binding kinetics which might affect their pharmacology and result in different efficacy and safety profiles [54]. Most data with the second generation proteasome inhibitors have been generated in the relapsed or refractory myeloma setting. As there are no full publications in peer-reviewed journals available addressing the incorporation of such agents in autologous stem cell transplant approaches, these agents were not included in this review. However, data of early studies combining carfilzomib with either thalidomide-dexamethasone or lenalidomide-dexamethasone as induction treatment prior to ASCT have already been reported at international conferences [55,56]. Further research on the incorporation of second-generation proteasome inhibitors in autologous stem cell transplant approaches in myeloma can therefore definitely be expected.

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