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RESEARCH ARTICLE

RECENT ADVANCES IN THERAPY FOR MULTIPLE MYELOMA IN TRANSPLANT-ELIGIBLE PATIENTS: LITERATURE OF REVIEW

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ABSTRACT

Multiple myeloma (MM) is a clonal plasma cell malignancy, characterized by the proliferation of neoplastic plasma cells. Delineation of the mechanisms mediating plasma cell proliferation, survival and migration in the bone marrow microenvironment may enhance the understanding of pathogenesis, and a better understanding of the molecular pathogenesis is fundamental to developing more effective prognostic, therapeutic and preventive approaches. It is still an incurable disease but the introduction of novel therapies and stem cell transplantation have altered the natural course of the disease, transforming it into a chronic disease from a terminal illness.

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INTRODUCTION

Nowadays, high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is routinely incorporated as treatment strategy either early in the disease course or at the time of relapse in eligible patients. (Rajkumar, 2009) However, with the availability of novel agents like thalidomide, bortezomib, and lenalidomide; therapeutic options have expanded and current trials are focusing on incorporating these agents in the transplant paradigm. (Jagannath, 2009)

Initial therapy

The first critical step in initiating therapy for multiple myeloma is to determine whether a patient is eligible for stem cell transplant and is willing to undergo the procedure or not. (Kumar *et al*., 2009) The eligibility for transplant is mainly determined by age, performance status, and coexisting comorbidities. As a standard practice, patients are treated with induction therapy before stem cell harvest and ASCT. Transplant-eligible candidates who prefer to reserve ASCT for relapsed/refractory disease often resume induction therapy following stem cell collection until a plateau phase is reached, reserving ASCT for relapse.

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(Rajkumar, 2009) With a proliferation of regimens available for initial therapy, comorbidities, tumor burden and the perceived need for rapid cytoreduction are often major factors influencing choice of initial therapy. (Multiple Myeloma, 2005) Currently, the options for initial therapy include thalidomide and dexamethasone; lenalidomide and dexamethasone; bortezomib and dexamethasone; and bortezomib-based combination regimens. (Palumbo and Rajkumar, 2009) The primary induction therapy for transplant-eligible candidates, as recommended by the National Comprehensive Cancer Network (NCCN) is given in Table 1. (NCCN Clinical Practice Guidelines in Oncology)

Table 1.

NCCN Recommendations for Primary Induction Therapy for Multiple Myeloma in Transplant-Eligible Patients (Rajkumar *et al*., 2006)
Bortezomib/dexamethasone (Category 1)
Bortezomlb/doxorubicin/dexamethasone (Category 1)
Bortezomib/lenalidomide/dexamethasone (Category 2B)
Bortezomib/thalidomide/dexamethasone (Category 1)
Dexamethasone (Category 2B)
Liposomal doxorubicin/vincristine/dexamethasone (category 2B)
Lenalidomide/dexamethasone (Category 1)
Thalidomide/dexamethasone

Thalidomide and Dexamethasone

In the early part of the decade, the combination of thalidomide and dexamethasone emerged as one of the most commonly used induction regimens for the treatment of newly diagnosed myeloma patients. (Rajkumar, 2009) This combination yielded superior response rate compared with dexamethasone alone as induction therapy for newly diagnosed multiple myeloma. In a clinical trial coordinated by the Eastern Cooperative Oncology Group (ECOG), thalidomide (200 mg/day orally) plus dexamethasone (40 mg orally on days 1 through 4, 9 through 12, and 17 through 20 every month) was compared with dexamethasone alone as induction therapy in 207 previously untreated patients. (Rajkumar *et al*., 2006) The combination therapy resulted in a superior overall response rate (63% vs 41 %; p = 0.0017). However, the combination resulted in higher rates of deep vein thrombosis (17% vs 3%), rash, neuropathy and bradycardia.

Another multicenter, randomized, double-blind, placebo-controlled trial evaluating the combination of thalidomide and dexamethasone versus placebo plus dexamethasone in previously untreated symptomatic multiple myeloma patients demonstrated a significantly higher rate of overall response (63% vs 46%; p < 0.001) and longer time to progression of disease (22.6 vs 6.5 months; p < 0.001) in patients receiving combination therapy. (Rajkumar *et al*., 2008) Grade 4 adverse events were more frequent with thalidomide and dexamethasone than with placebo (30.3% vs 22.8%).

A retrospective study compared the combination of thalidomide and dexamethasone with vincristine, doxorubicin and dexamethasone (VAD) regimen as front-line therapy prior to autologous transplantation. Thalidomide and dexamethasone resulted in a significantly higher response rate (76% vs 52%; p < 0.001). (Cavo *et al*., 2005) Non-fatal deep vein thrombosis were more frequently observed with thalidomide and dexamethasone (15%) and granulocytopenia with VAD (12%). In each of the two treatment groups, 91% of patients proceeded to peripheral blood stemcell mobilization. The median number of CD34+ cells collected were 7.85 x 10^6/kg in the thalidomide and dexamethasone group and 10.5 x 106/kg in the control group.

In another randomized prospective trial, the combination of thalidomide and dexamethasone was compared to VAD as pre-transplant treatment in newly diagnosed patients with multiple myeloma. (Macro *et al*., 2006) In both the groups, 91% of patients proceeded to peripheral blood stem cell (PBSC) mobilizations, and 83% of patients received HDCT and autotransplant. Before HDCT, very good partial remission (VGPR) rate was 34.7% in the thalidomide and dexamethasone arm as compared to 12.6% in the VAD arm (p=0.002). However, six months post-transplant, thalidomide and dexamethasone did not show further benefit, with VGPR rates of 44.4% in the thalidomide and dexamethasone arm and 41.7% in the VAD arm (p = 0.87).

In another prospective phase III trial (HOVON-50/GMMG-HD3), patients randomized to a combination of thalidomide, doxorubicin and dexamethasone had a significantly higher response rate (partial response) after induction compared with patients randomized to VAD (72% vs 54%; p < 0.001). Complete remission (CR) and VGPR were also higher after thalidomide, doxorubicin and dexamethasone. (Lokhorst *et al*., 2008) After high-dose melphalan 200 mg/m^2, CR+VGPR remained significantly higher in the patients randomized to thalidomide arm (49% vs 32%, p < 0.001). Grade 3-4 adverse events were similar in both arms.

The Medical Research Council (MRC) Myeloma IX trial compared cyclo- phosphamide, thalidomide, and dexamethasone with cyclophosphamide-VAD as induction regimen before ASCT. (Morgan *et al*., 2007) A preliminary analysis showed that the CR rate was 20.3% in the thalidomide group and 11.7% in the cyclophosphamide-VAD arm. This difference was maintained at 100 days post-ASCT with a CR rate of 58.2% in the thalidomide arm and 41% in cyclophosphamide- VAD following ASCT.

A brief summary of thalidomide induction regimens from prospective randomized trials incorporating ASCT is summarized in Table 2.

Lenalidomide and Dexamethasone

Lenalidomide has FDA approval for the treatment of relapsed/refractory multiple myeloma in combination with dexamethasone. This combination has also been evaluated in patients with newly diagnosed myeloma. (NCCN Clinical Practice Guidelines in Oncology)

In a phase II trial, 34 newly diagnosed patients with myeloma were administered lenalidomide 25 mg daily PO on days 1-21 of a 28-day cycle. Dexamethasone was given 40 mg PO daily on days 1-4, 9-12, and 17-20 of each cycle. (Rajkumar *et al*., 2005) Thirty-one of thirty-our patients (91%) achieved an objective response; including two (6%) achieving CR and 11 (32%) meeting criteria for both VGPR and near-complete response (nCR). Of the three remaining patients not achieving an objective response, two had minor response and one had stable disease. Unlike thalidomide, side effects such as constipation and neuropathy were uncommon and sedation was not seen; no patient developed grade three or higher neuropathy. Although lenalidomide was shown to be associated with myelosuppression in earlier trials, this adverse effect was less pronounced in this trial, probably reflecting the better bone marrow reserve of patients with previously untreated disease.

Treatment beyond four cycles were permitted at the physicians' discretion. After four cycles of therapy with lenalidomide and dexamethasone, patients were allowed to discontinue treatment to pursue ASCT. (Lacy *et al*., 2007) With extended follow-up, the 2-year progression-free survival (PFS) rates for patients proceeding to ASCT and patients remaining on lenalidomide and dexamethasone were 83% and 59%,respectively; the overall survival (OS) rates were 92% and 90% at 2-years and 92% and 85% at 3 years, respectively. The 3-year OS rate for the whole cohort was 88%. A randomized trial conducted by the ECOG compared lenalidomide plus high-(standard) dose dexamethasone with lenalidomide and low-dose dexamethasone in newly diagnosed myeloma.

Table 2.

Thalidomide Induction Regimens in Transplant-Eligible Patients							
Induction regimen	n	Post-induction			Post-transplant/Post-HDCT		
		CR (%)	VGPR (%)	ORR (%)	CR (%)	VGPR (%)	ORR (%)
Thal Dexa vs VAD (Macro *et al*., 2006)	204	NR	34.7 vs 12.6 (p=0.002)	NR	NR	44.R vs 41.7 (p=0.87)	NR
Thal/Doxo/Dexa Vs VAD(3 HOVON-50/GMMG-HD3) (Macro *et al*., 2006)	402	4 vs 4 P<0.001	33 vs 15 P<0.001	72 vs 54 (p=0.001)	16 vs 11 (p= 0.19)	49 vs 32 (p<0.001)	76 vs 79 (p=0.55)
Cyclo/Thal/Dexa vs Cyclo/VAD (MRC Myeloma IX Trial) (Morgan *et al*., 2007)	900	203 vs 11.7 (p=NR)	NR	95.7 vs 83.4 (p=NR)	58.2 vs 41 (p=NR)	NR	98.7 vs 95.7 (p=NR)

Thal: Thalidomide, Dexa: Dexamethasone, VAD: Vincristine, doxorubicin and dexamethasone, Cyclo: Cyclophosphamide, CR: Complete remission, VGPR: Very good partial remission, ORR: Overall response rate, HDCT: High-dose chemotherapy, NR: Not reported

Table 3.

Bortezomib Induction Regimens in Transplant-Eligible Patients							
		Post-induction			Post-transplant/Post-HDCT		
Induction regimen	n	≥PR (%)	≥VGPR %)	≥nCR %)	≥Pr (%)	≥VG (%)	≥nCR(%)
Bort/Daxa Vs VAD (IFM 2005/01) (Harousseau *et al*., 2007)	480	89 vs 71 (p=NS)	50 vs 24 (p=0.0001)	22 vs 9 (p=0.00085)	87 vs 88 (p=NS)q	66 vs 50 (p=0.021)	38 vs 28 (p=0.127)
Bort/Thal/ Dexa vs Thal/ Deax (GIEMMA) (Cavo *et al*., 2008)	480	94 vs78 (p<0.001)	62vs 29 (p<0.01)	32 vs 12 (p<0.001)	NR NR	76 vs 58 (p<0.001)	55 vs 32 (p<0.001)
Borte/VBMCP/ VBAD vs Borte/Thal/ Deax vs. Thal/ Dexa (PETHEMA/ Gem) (Rosinol *et al*., 2008)	190	72 vs 80 VS 66 (P=ns)	NR	28 vs 41 VS 12 VS (P<0.01)	97 vs 97 VS 97 (P=ns)	NR	64 VS 53 (P=ns0
Bort/Doxo/deax Vs. VAD (HOVON 65 MM/GMMGHD4) (Sonneveld *et al*., 2009)	833	79 vs 57 (P=NR)	45 vs 17 (p=NR)	7 vs 2 (p=NR)	91 vs 79 (p=NR)	71 vs 44 (p= NR)	26 vs 14 (p=NR)

Borte: Bortezomib, Thai: Thalidomide, Dexa: Dexamethasone, VAD: Vincristine-Doxorubicin-Dexamethas0one, VBMCP/VBAD; Vincristine, Carmustine, Melphalan, Cyclophosphamide, Prednisone/Vincristine, Carmustine, Doxorubicin, and Dexamethasone, PR: Partial remission, VGPR: Very good partial remission, nCR: Near complete remission, NR: Not reported, NS: Not significant treatment in terms of prolonging remission or OS.

(Rajkumar *et al*., 2008) With early follow-up, the OS favoured the low-dose dexamethasone group (p =0.006); 1-year survival was 96% and 88%, respectively, and 2-year survival was 87% and 75%, respectively. A landmark analysis was conducted after four months of treatment on the trial. There was no difference in the percentage of patients who underwent ASCT, between the two arms, 29% (standard dose dexamethasone) and 31% (low-dose dexamethasone). In the landmark analysis, the 2-years OS rate was 91% among patients who received primary therapy with lenalidomide and low-dose dexamethasone, and 94% among patients who received HDCT followed by ASCT.

As a result of these observations, the lower dexamethasone dose (40 mg by mouth on days 1, 8, 15, and 22 of each 28-day cycle) is now commonly used for all newly diagnosed patients with myeloma who are receiving dexamethasone in combination with lenalidomide, except perhaps in select situations like myeloma-induced renal failure, where rapid cytoreduction is critical. Following the availability of results from the above ECOG study, a Southwest Oncology Group (SWOG) trial (SO232) comparing the standard dexamethasone with combined therapy of dexamethasone plus lenalidomide in newly diagnosed myeloma patients was halted and all participants were given the choice of switching to lenalidomide plus low-dose dexamethasone (Zonder *et al*., 2007).

A recent case-control study compared the efficacy and toxicity of lenalidomide plus dexamethasone with thalidomide plus dexamethasone. (Gay *et al*., 20l0) This study demonstrated that lenalidomide plus dexamethasone was well-tolerated and more effective than thalidomide plus dexamethasone as initial therapy for newly diagnosed myeloma. The partial response (PR) rates to lenalidomide plus dexamethasone and thalidomide plus dexamethasone were 80.3% and 61.2%, ($p < 0.001$) and VGPR rates were 34.2% and 12.0%, respectively, ($p < 0.001$). Patients receiving lenalidomide plus dexamethasone had longer time-to-progression (median 27.4 vs 17.2 months; p : 0.019), PFS (median 26.7 vs 17.1 months; $p = 0.036$) and OS (median not reached vs 57.2 months; $p = 0.018$). The major grade 3 or 4 toxicities of lenalidomide plus dexamethasone were hematologic, mainly neutropenia (14.6% vs 0.6%, $p < 0.001$); the most common toxicities in thalidomide plus dexamethasone were venous thromboembolism (15.3% vs 9.2%, $p = 0.058$) and peripheral neuropathy (10.4% vs 0.9%, $p < 0.001$).

A phase II trial was designed to determine the safety and efficacy of the combination regimen clarithromycin (Biaxin), lenalidomide (Revlimid), and dexamethasone (BiRD) as first-line therapy for multiple myeloma. (Niesviéky *et al*., 2008) An objective response rate of 90.3% and a stringent complete response (SCR) rate of 38.9% was achieved. Clarithromycin increases the area under the curve and the maximum concentration levels of certain corticosteroids and may also possess immunomodulatory properties and direct antineoplastic effects.

The relatively low toxicity of the lenalidomide and dexamethasone combination lends itself as a major contender for primary therapy of myeloma. Further, as this regimen is orally administered, it is less cumbersome than complex intravenous regimens. However, several reports have indicated that prolonged lenalidomide treatment may result in a decrease in the ability to subsequently mobilize CD34+ cells. (Mazumder *et al*., 2008) In a representative single institutional study among those mobilized with granulocyte-colony stimulating factor (G-CSF) alone, there was a significant decrease in total CD34+ cells collected ($p < 0.001$), average daily collection ($p < 0.001$), day one collection ($p < 0.001$) and increased number of aphaeresis (p : 0.004) in patients treated with lenalidomide compared to those receiving dexamethasone, thalidomide-dexamethasone or VAD. (Kumar *et al*., 2007) With increased duration of lenalidomide therapy and with increasing age, a decreased yield of PBSC was observed ($p = 0.002$). However, there was no effect on quality of PBSC collected based on similar engraftment across all groups. The NCCN recommends harvesting peripheral blood early in the course of induction with lenalidomide. (NCCN Clinical Practice Guidelines in Oncology)

Bortezomib- and Dexamethasone—Based Regimens

Phase II Studies

A phase II multicenter trial assessed the efficacy of single agent bortezomib in 64 patients with previously untreated symptomatic myeloma. (Richardson *et al*., 2009) The overall response rate was 40%, including 9% CR/nCR, which did not differ among different cytogenetic risk groups. The median duration of response was 8.4 months and median time to progression was 17.3 months. Half of the patients had a subsequent ASCT. Toxicities with bortezomib were generally mild and included sensory neuropathy (64%), constipation (53%), nausea (53%), and fatigue (44%). Baseline myeloma-associated neuropathy seemed more common than previously reported and bortezomib—associated neuropathy, although a common toxicity was reversible in most patients.

A Intergroupe Francophone du Myélome (IFM) phase II study further supported the use of bortezomib and dexamethasone in the induction treatment of newly diagnosed multiple myeloma patients prior to ASCT. (Harousseau *et al*., 2006) This phase II, open-label, trial of bortezomib (1.3 mg/m2, days 1, 4, 8, and 11) and dexamethasone (40 mg, days 1-4 and 9-12 for cycles 1-2, days 1-4 for cycles 3-4) administered for four cycles of 21-days, as induction therapy in chemotherapy-naive myeloma patients resulted in an over all response rate 66% including 21% CR rate and 10% VGPR rate. The most common side effects were gastrointestinal symptoms, peripheral neuropathy and fatigue, and were usually mild. CD34+ cells collection were adequate to perform ASCT.

Another phase II trial by the PETHEMA group studied alternating cycles of bortezomib and dexamethasone as an induction regimen before ASCT. (Rosinol *et al*., 2007) A partial response or greater was observed in 65% of cases with a minor response in 17.5%. Time to response was rapid, with an 82% serum M protein reduction achieved within the first two cycles. Toxicity was low, with no grade 3 to 4 peripheral neuropathy and no grade 2 to 4 thrombocytopenia. The response rate after ASCT was 88%, with 33% CR plus 22% VGPR.

A single-center, open-label, phase ll trial evaluated the bortezomib, pegylated liposomal doxorubicin, and dexamethasone combination regimen as initial treatment for patients with newly diagnosed multiple myeloma. (Jakubowiak *et al*., 2009) Following six cycles of therapy, the VGPR was 57.5%. Following ASCT, rates of VGPR increased to 76.6%. Overall, 1-year PFS and OS rates were 92.5% and 97.5%, respectively. Grade 3 or 4 hematologic toxicities occurred in S 10% of patients; grade 2 painful neuropathy occurred in 7.5%; and grade 3 palmar-plantar erythrodysesthesia occurred in 2.5%.

Based on the positive results seen with the bortezomib, cyclophosphamide, and dexamethasone combination in the relapsed/refractory myeloma patients, (Reece *et al*., 2008) the above combination was studied in the treatment of newly diagnosed multiple myeloma patients to assess response and toxicity. In a phase II single arm trial, the use of a modified version of this three drug regimen produced a rapid and profound response in patients with newly diagnosed multiple myeloma with manageable toxicity. (Reeder *et al*., 2009) The overall intent to treat response rate was 88% with 61% VGPR and 39% CR/nCR. An ongoing trial by the German Myeloma Group [Deutsche Studiengruppe Multiples Myelom (DSMM)] is evaluating this combination as an induction regimen. (Knop *et al*., 2009) Results of an interim analysis of the ongoing trial demonstrated positive results for the combination; with an objective response rate of 84% (CR of 12.5% and PR of 71.5%).

Comparative Trials

A recent retrospective analysis of patients with myeloma who received bortezomib- containing regimens or VAD before collection of peripheral blood stem cells and ASCT, demonstrated superiority of bortezomib therapy in terms of depth of response. (Eom *et al*., 2009) The VGPR rate in the bortezomib group was 66.7%, significantly higher compared with 34.2% for the VAD group ($p = 0.006$). Although not statistically significant, an objective response rate (at least a partial response) prior to ASCT was documented in 90% and 81.6% of patients with bortezomib-containing regimens and VAD, respectively. Recently, several phase III trials studying bortezomib-based regimen have been reported with early follow-up. A multicenter randomized phase III trial conducted

by the IFM cooperative group (IFM 2005/01 trial) compared a combination of bortezomib and dexamethasone to VAD as induction therapy prior to ASCT. (Harousseau *et al*., 2007) Better CR and VGPR rates were observed in the bortezomib and dexamethasone group (21% and 46.7%) as compared to the VAD group (8% and 18.6%) when assessed prior to transplant. In patients who underwent transplant, the CR rate was 41% with the bortezomib and dexamethasone regimen and 29% with the VAD regimen (p : 0.0089). Grade > 3 adverse events were similar (38.2% vs 40.6%); serious adverse event rates (25.2% vs 31.0%) and adverse events leading to death (0.8% vs 2.9%) were lower with bortezomib and dexamethasone. Neuropathy (all grades) was higher with bortezomib and dexamethasone (35.3% vs 22.6%). Stem cell collection was adequate (> 2 x 106 CD34+/kg) in both the bortezomib and dexamethasone (97%) and VAD (99%) arms. Early follow-up has shown that bortezomib and dexamethasone resulted in superior PFS.

An ongoing phase III HOVON 65 MM/GMMG—HD4 trial compares bortezomib, doxorubicin and dexamethasone induction therapy with VAD followed by either bortezomib or thalidomide maintenance treatment post-ASCT. (Sonneveld *et al*., 2009) In a preliminary analysis, the bortezomib based combination was found to be significantly superior to VAD in terms of the VGPR and PR rates.

Early results of total therapy III demonstrated that bortezomib could be safely combined with multiagent chemotherapy. (Barlogie *et al*., 2007) In this phase III trial, induction chemotherapy prior to and consolidation chemotherapy after transplants in the bortezomib arm consisted of two cycles of bortezomib, thalidomide, dexamethasone and four-day continuous infusions of cisplatin, doxorubicin, cyclophosphamide, etoposide; three-year maintenance comprised monthly cycles of bortezomib, thalidomide, dexamethasone in the first and thalidomide, dexamethasone in the remaining years. After two years, 83% had achieved nCR in the bortezomib arm, which was sustained in 88% at two years from its onset. With a median follow-up of 20 months, 2-year estimates of event-free survival (EES) and OS were 84% and 86%, respectively.

In summary bortezomib-based induction regimens have demonstrated no adverse impact on peripheral blood stem cell (PBSC) harvest numbers and on their quality as defined by time to engraftment. These regimens appear to be well tolerated and highly active as induction therapy; with high response rates and consistently high CR rates. (Oakervee *et al*., 2007) Bortezomib and dexamethasone-based regimens appear to overcome the need for intensification of chemotherapy before ASCT. (Corso *et al*., 2010)

Bortezomib- and Immunomodulatory Drug-Based Combination Therapies

Bortezomib and immunomodulatory drugs have demonstrated efficacy as single agents and in combination with dexamethasone. As these agents function through distinct mechanisms, there is potential for synergy and the ability to overcome resistance. Therefore, regimens that incorporate both bortezomib and immunomodulatory drugs are being investigated in early-phase clinical trials.

In a phase I/Il study, lenalidomide, bortezomib and dexamethasone has shown to be very active and well tolerated in newly diagnosed myeloma patients. (Richardson *et al*., 2007) This combination induced a partial remission (PR) rate of 98% including 52% VGPR. In view of the improved outcomes, this regimen has been included in the induction therapy for transplant-eligible patients under category 2B by the N CCN. (NCCN Clinical Practice Guidelines in Oncology)

In a single center, retrospective analysis, induction therapy with bortezomib, lenalidomide and dexamethasone resulted in CR, VGPR, and PR rates of 11%, 42%, and 47%, respectively, whereas bortezomib, thalidomide and dexamethasone yielded the above rates of 8%, 49%, and 47%, respectively. (Shah *et al*., 2009) In patients who achieved only a PR after induction therapy with either regimen, 40% experienced further improvement to a CR or VGPR after ASCT. An ongoing phase I/II study is currently assessing bortezomib, lenalidomide and dexamethasone plus pegylated liposomal doxorubicin in newly diagnosed myeloma patients. (Jakubowiak *et al*., 2009) The preliminary results show a PR in > 95%, VGPR in > 47%, and CR/nCR in > 26%.

The phase I/II EVOLUTION study is evaluating bortezomib, lenalidomide, and dexamethasone combined with the alkylating agent cyclophosphamide. (Kumar *et al*., 2008) This novel 4-drug combination regimen has achieved `PR in 100%, VGPR in 68%, CR/nCR in 32%, CR of 28% and stringent complete remission (SCR) of 20%. The Italian Myeloma Network (GIMEMA) cooperative group compared borte-zomib, thalidomide and dexamethasone to thalidomide and dexamethasone alone as induction therapy prior to ASCT. (Cavo *et al*., 2008) In this multicenter, randomized phase III trial, the bortezomib, thalidomide, and dexamethasone group showed a superior CR rate of 21% compared to 6% in the thalidomide and dexamethasone group ($p < 0.001$). Post-transplant, CR rate of 41% with the bortezomib, thalidomide, and dexamethasone regimen remained significantly superior to 20% in the thalidomide and dexamethasone group ($p < 0.001$).

The combination of bortezomib, thalidomide, and dexamethasone as induction therapy was also found to be superior in the terms of post-induction CR rate in a phase III trial (PETHEMA/GEM) investigating the combination in comparison with thalidomide and dexamethasone or VBMCP/VBAD (vincristine, carmustine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, and dexamethasone) plus two cycles of bortezomib. (Rosinol *et al*., 2008) The post-transplant CR rates were higher with bortezomib, thalidomide, and dexamethasone combination (50%) and with VBMCP/VBAD (39%) as compared to the thalidomide and dexamethasone arm (26%), although the difference did not reach statistical significance.

Summarizing the above evidence (Table 3), a number of bortezomib induction regimens are now available. The combination of bortezomib and dexamethasone appears to be superior to the traditional VAD regimen. The addition of

thalidomide may further improve response rates, especially CR and VGPR rates, and possibly the PFS interval. Only long-term follow-up studies will determine whether this translates into an OS advantage.

Conclusion

High-dose chemotherapy followed by ASCT has greatly improved outcomes in patients with multiple myeloma. As discussed in detail, the introduction of thalidomide, bortezomib, and lenalidomide have led to the introduction of novel induction regimens and, it has now become possible to achieve CR in 30-40% of newly diagnosed patients prior to HDCT. However, a number of questions regarding these novel induction regimens remain unanswered. Only long-term survival data will provide answers to the questions on the optimal induction treatment and whether aggressive multi-modality treatment up-front, using all or most of the new agents with ASCT can significantly extend survival.

Also, with any treatment strategy, the use of new cytogenetic and molecular information will be paramount to develop optimal risk-adapted care. Already with the realization that hematopoietic stem cell transplantation results in shorter PFS in patients with high-risk disease, several experts have suggested that ASCT be kept in reserve for these patients. It has been proposed that these patients can be initially treated with bortezomib containing regimens, as bortezomib seems to overcome the adverse prognostic impact of 13q deletion and t(4;14).66On the other hand, investigators have also suggested delaying ASCT in patients who have achieved CR to induction therapy, or till maximum cytoreduction is reached. Only randomized trials in the future may be able to establish whether these novel regimens may make HDCT ur1necessary in a subset of patients.

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Conflict of Interest : None

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