

REVIEW

Targeted treatments to improve stem cell outcome: old and new drugs

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Thalidomide, lenalidomide and bortezomib have been approved for the treatment of relapsed or refractory multiple myeloma in the recent years. These agents are now being increasingly integrated into therapeutic regimens for newly diagnosed patients. First data are available on the promising activity of these novel agents in induction therapy, as well as maintenance treatment to improve outcome after stem cell transplantation. Whether these early results will lead to prolonged overall survival and thereby ultimately redefine the role of stem cell transplantation in first-line treatment of multiple myeloma will be one of the most important questions to be answered in the coming years.

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Introduction

In recent years, significant advances have been made in standard dose chemotherapy and high-dose therapy (HDT) followed by autologous stem cell transplantation (auto-SCT), allowing improvements in both progression-free survival (PFS) and overall-survival (OS) of patients with multiple myeloma (MM). Yet, MM continues to be characterized by a relapsing and increasingly refractory disease course. While HDT seems to prolong PFS, controversial results have been reported for OS in trials comparing standard vs high-dose therapy. A recent systematic review and meta-analysis of currently available data from 10 randomized controlled trials comparing HDT to conventional combination therapy concluded that although single course HDT with auto-SCT offers PFS benefit in newly diagnosed MM, no OS advantage could be confirmed.¹ One attempt to improve outcome after HDT was dose intensification. The French trial IFM 99-04 was the first to show significantly improved 7-year event-free

survival (EFS) and OS for tandem transplants as compared to single courses of HDT followed by auto-SCT.² Recently, final data of the Italian Bologna 96 trial confirmed a prolonged relapse-free and a significantly extended EFS after double transplant. However, no significant benefit could be shown for OS.³ Several other groups have reported similar, though preliminary results. Another attempt to improve outcome after HDT was made possible by the emergence of novel agents such as the immunomodulatory drug lenalidomide (Revlimid, Rev) and the first-in-class proteasome inhibitor bortezomib (Velcade, Vel). Together with the re-emergence of thalidomide, these compounds have not only proven to be highly active in relapsed/refractory myeloma, but are now increasingly used in front-line therapy. Data are now becoming rapidly available about these novel agents in conventional combination therapy, as well as before and after transplantation in newly diagnosed patients.

Thalidomide

Thalidomide was initially introduced in 1956 as sedative and treatment for nausea and was mainly prescribed for morning sickness in pregnant women. Multiple birth defects, including phocomelia, led to the withdrawal of thalidomide from the market. In the late 1990s, the interest in thalidomide was renewed after its anti-angiogenic activity was first described.^{4,5}

On the basis of the known finding of increased angiogenesis in the bone marrow in multiple myeloma, a first clinical study was performed in relapsed and refractory myeloma patients. The overall response rate was 32% leading to increased interest in thalidomide as a potential treatment in multiple myeloma.⁶ Since then, thalidomide has been widely used as a single agent in heavily pretreated and relapsed or refractory multiple myeloma.^{7–17} *In vitro* studies revealed synergistic activity between dexamethasone (Dex) and thalidomide.¹⁸ Combining thalidomide and Dex in clinical trials clearly represented an advance in treatment options for relapsed MM with overall responses up to 55%.^{19,20} The combination of Thal/Dex with other conventional chemotherapeutic agents like cyclophosphamide further increased response to 60%.^{21,22} Moehler *et al.*²³ investigated the effect of the combination regimen thalidomide, cyclophosphamide, etoposide and dexamethasone (TCED) followed by HDT and auto-SCT in relapsed

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and refractory multiple myeloma. They revealed a remarkable total response rate of 86% and a PFS of 16 months.

In newly diagnosed non-transplant candidates, Palumbo *et al.*²⁴ compared melphalan and prednisone (MP) with MP plus Thal (MPT) as front-line therapy in a phase III clinical trial for older myeloma patients. Patients randomly received MP or MPT. Patients treated with MPT showed higher response rates compared with MP (CR/PR 76 vs 47.6%, respectively) and had longer 2-year EFS rates (54 vs 27%, respectively). Subsequently, the IFM 99-06 clinical phase III trial compared MP with MP-Thal, and with high dose therapy in 447 myeloma patients aged 65–75 years.²⁵ They demonstrated that the median OS for MP, MPT and transplant was 32, 54 and 39 months, respectively. The OS and PFS were significantly longer in the MPT arm compared with either MP or transplant.

Thalidomide and high-dose therapy

In newly diagnosed MM eligible for HDT, several phase II and III clinical trials have been performed with Thal/Dex as induction regimen. Weber *et al.*²⁶ used thalidomide doses of 400 mg day⁻¹ and achieved response rates of 72%, compared with the group of Rajkumar *et al.*²⁷ reporting response rates of 58–64% using a thalidomide dose of 200 mg day⁻¹. The most frequent toxicities of Thal/Dex treatment were venous thrombosis (10%), constipation (8%) and rash (6%).²⁸ A third pilot study by Cavo *et al.*²⁹ with 200 mg day⁻¹ of thalidomide resulted in 66% overall response with deep-vein thrombosis occurring in 16% of patients. The promising results with Thal/Dex as induction therapy in newly diagnosed MM led to several clinical phase III trials comparing the efficacy of thalidomide combination therapy with standard induction regimens in preparation for HDT and auto-SCT.

In a non-randomized, matched case-control study involving 200 newly diagnosed patients, significantly better response rates were seen in those who received Thal/Dex as an induction regimen as opposed to VAD.³⁰ They administered four cycles of 200 mg thalidomide in combination with dexamethasone before high dose chemotherapy and auto-SCT. While collected stem cell numbers were lower after thalidomide treatment, the amount was sufficient in all patients to proceed to HDT. In comparison with VAD, Thal/Dex achieved a significantly higher overall response rate of 76 vs 52% ($P=0.0004$). The major side effect was deep vein thrombosis (15%).

Breitkreutz *et al.*³¹ recently compared the induction regimens thalidomide, doxorubicin and dexamethasone (TAD) and VAD before PBSC collection and HDT with subsequent auto-SCT in 398 newly diagnosed MM patients. Patients in the thalidomide group harvested significantly fewer stem cells than patients after VAD induction. However, the yield was sufficient for at least two transplants in all cases. The interim analysis of response in this setting showed better response rates before transplant in TAD compared with VAD. The GMMG-HD3 and HOVON-50 study groups herein reported comparable response rates (GMMG-HD3: TAD: CR/PR 79%, VAD: CR/PR 58%; HOVON-50: TAD: CR/PR 81%, VAD: CR/PR 61%). After first transplant, the advantage of

thalidomide seemed to be maintained (CR + VGPR TAD 49% vs VAD 32%, $P<0.001$) (H Lokhorst, personal communication).

Recently, Barlogie *et al.*³² published the results of their phase III clinical study assessing whether the addition of thalidomide in a high dose therapy setting would further improve the survival of newly diagnosed myeloma patients. Six hundred and sixty-eight patients received two cycles of high-dose chemotherapy with melphalan and subsequent auto-SCT. A total of 323 patients were randomized to receive thalidomide, and 345 did not receive thalidomide. All patients who had not progressed after auto-SCT received maintenance therapy with interferon (3 million U m⁻²) three times a week and 4 days of pulse dexamethasone three times per month every 3 months for 1 year, and then, interferon alone. In addition, patients randomly received thalidomide 100 mg in the first year and 50 mg every other day after the first year until relapse or severe adverse events. The results after a median follow-up of 42 months showed a higher rate of CR in the thalidomide group compared with the control groups (62 vs 43%; $P<0.001$), and 5-year EFS rates of 56 and 44% ($P=0.01$). For all patients, the 5-year rate of OS was approximately 65% ($P=0.90$). However, there was no advantage in OS after relapse or progression in the thalidomide group. Thalidomide-treated patients showed a significantly lower OS after relapse compared with patients who had not received thalidomide (2.7 years; $P=0.0001$). Therefore, relapses experienced in the thalidomide arm seemed to be more drug-resistant than those of the control arm. Whether this might be due to a higher frequency of the chromosomal amplification 1q21 in the thalidomide arm, which has been shown to be an adverse prognostic factor that cannot be overcome by thalidomide, rather than a direct consequence of thalidomide treatment on the disease phenotype, remains to be determined.³³ They further observed that severe peripheral neuropathy (27%) and deep-vein thrombosis (30%) occurred more frequently in the thalidomide group than in the control group.

While thalidomide as a single agent does not appear to increase the incidence of thromboembolism, a large number of trials have found deep-vein thrombosis to be a major adverse event (up to 35% of patients) if combined with dexamethasone and/or chemotherapy, especially anthracyclins (extensively reviewed in Hussein³⁴). Therefore, strategies for prophylactic anticoagulation have been applied including warfarin, low-molecular-weight heparin, or low-dose aspirin. Several studies have shown effectiveness of either of these strategies to reduce significantly the incidence of deep-vein thrombosis and should strongly be considered for this patient group. However, there are no randomized trials yet to favor one anticoagulation agent over the other.³⁴

Given these results, final reports of the ongoing trials are awaited before thalidomide-containing regimens can safely be defined as a standard for induction treatment before HDT.

Thalidomide in maintenance therapy

High-dose chemotherapy has increased the response rate in multiple myeloma. However, effective maintenance

strategies are required to prolong the duration of response, EFS and OS. Many other groups have already focused on thalidomide as maintenance therapy. A multicenter, randomized phase II trial assessed the tolerability and efficacy of thalidomide 200 or 400 mg daily and prednisone (50 mg) as maintenance. Treatment was initiated 60–100 days after transplant. Stewart *et al.*³⁵ observed a median PFS of 32.3 months after transplant and an improved initial response rate. However, only the 200 mg dose of thalidomide was tolerated with 88% of all patients requiring a dose reduction of thalidomide. Prednisone was also dose-reduced in all patients within 2 years.

In the IFM 99-02 trial, Attal *et al.*³⁶ recently demonstrated that maintenance therapy with thalidomide plus pamidronate is superior to maintenance therapy without thalidomide after double auto-SCT in 597 myeloma patients younger than 65 years. Thal/pamidronate (arm C) reached CR/PR response rates of 67% compared to 55% in the no maintenance therapy arm (A) and 57% with pamidronate alone (arm B) ($P=0.03$). After 3 years, the EFS was 36% in patients with no maintenance, 37% in those receiving pamidronate, and 52% in patients on Thal/pamidronate ($P<0.009$). After 4 years, the OS was 77% in arm A, 74% in arm B and 87% in arm C ($P<0.04$). However, the benefit was significant only in patients who had not reached CR or VGPR after second auto-SCT and was therefore mainly caused by an increase of CR/VGPR, suggesting an additional effect as a post-transplant consolidation therapy. The rate of deep vein thrombosis was 2%. However, in 68% of thalidomide-treated patients, peripheral neuropathy was the main reason for dose reduction, with a median dose of thalidomide of 200 mg day⁻¹ for 15 months.

Brinker *et al.*³⁷ observed that the use of thalidomide as maintenance seems to improve the survival of myeloma patients. Independent of previous conditioning regimen, the median survival was 54 months after a median follow-up of 58 months. Patients who received thalidomide after transplantation had an improved median survival (65.5 months) compared with patients who did not receive thalidomide (44.5 months; $P=0.09$). The difference between these two studies raises the question of potential risks with long-term treatment with thalidomide.

In a multicenter prospective phase 2 study, Richardson *et al.*⁷ determined the PFS at 12 weeks and the toxic effects of thalidomide as maintenance therapy in patients with relapsed MM after high-dose chemotherapy and stem cell transplantation. The thalidomide dose was escalated from 200 to 600 mg day⁻¹ over 12 weeks, followed by a maintenance phase of 200 mg day⁻¹ for up to 1 year. The 12-week PFS rate was 67% (95% confidence interval, 48–86%). The observed response rate (PR/MR) was 43% with a median duration of 6 months. Dose escalation from 200 to 600 mg day⁻¹ was achieved in 50% of patients. Some patients had disease progression receiving a lower maintenance dose of 200 mg day⁻¹. They concluded that adverse effects can be dose limiting, and that the optimal thalidomide dose varies and should be predicated upon the achievement of response and tolerability in the individual patient. Currently, numerous phase III clinical

trials are still ongoing to evaluate the influence of Thal as maintenance therapy after high-dose chemotherapy in multiple myeloma.

Thalidomide and allogeneic transplantation

Nonmyeloablative conditioning for allografts can establish durable and stable disease control in MM. Donor lymphocyte infusion (DLI) is a valuable approach to induce graft-vs-myeloma (GvM) effect to treat relapsed or persistent disease post allograft. However, this is usually associated with GvHD, and durable responses are observed in only a minority of patients. Several studies have shown that thalidomide, lenalidomide and bortezomib have significant immunomodulatory properties, possibly allowing for dissociation of the cataclysmic bond between GvM and GvHD by enhancing one and inhibiting the other.^{38–41}

Hegenbart *et al.*⁴² analyzed a series of allo-SCT in patients who had relapsed after combination chemotherapy. Re-induction was performed with thalidomide, cyclophosphamide, etoposide and dexamethasone, consolidated by high-dose melphalan and auto-SCT in all 74 patients, followed by reduced intensity allo-SCT in 44 patients. No significant difference could be found in EFS (14 months, both groups) and OS (27 months, both groups) after a median follow-up of 24 and 21 months, respectively. More CR were found after allo-SCT due to graft vs myeloma effect, however, mortality rate was significantly higher (20 vs 1%, respectively; $P=0.007$).

DLI are often used for relapsed or persistent disease after allo-SCT; however, the GvM effect seems to be connected with GVHD in this strategy. Van de Donk *et al.*⁴³ reported that thalidomide led to a remarkable survival after DLI: 83.3% of the patients who did not respond or relapsed after allo-SCT were sensitive to thalidomide with six of nine patients achieved PR after thalidomide (100–300 mg day⁻¹). A retrospective study from the IFM evaluated the use of thalidomide (median dose 200 mg, range: 50–600 mg day⁻¹) as salvage therapy in 31 myeloma patients following allo-SCT. Six patients received PR and three VGPR and five patients developed GvHD.⁴⁴ Besides the goal of achieving good response rates and lowering TRM due to infections in relapsed and refractory myeloma patients after allo-SCT, the management of GvHD remains one of most challenging problems. Kroger *et al.*⁴⁵ investigated the effect of low-dose thalidomide (100 mg day⁻¹) in addition to DLI following relapse after allo-SCT in 18 myeloma patients. They found an overall response rate of 67%, including 22% CR, and observed mild acute GvHD of the skin and no grade II–IV GVHD. The 2-year estimated OS and PFS were 100 and 84%, respectively.

Kulkarni *et al.*⁴⁶ administered thalidomide to treat acute GVHD in 21 patients and chronic GVHD in 59 myeloma patients after failure to respond to cyclosporine and corticosteroids. They found that thalidomide particularly improved chronic GVHD and that OS was significantly longer in patients who responded to thalidomide. However, further clinical phase III studies are needed to ascertain the benefit of thalidomide in allo-SCT and the management of GVHD.

Lenalidomide

Lenalidomide (CC-5013, Revlimid) is a potent thalidomide analog with a different toxicity profile from the parent molecule. It induces apoptosis of myeloma cells, overcomes cytokine and bone marrow stromal cell-mediated drug resistance; has antiangiogenic effects, enhances dexamethasone cytotoxicity, and stimulates host antimyeloma T- and NK-cell immunity.^{18,47–50}

In a phase I dose-escalation study of lenalidomide, heavily pretreated patients with relapsed, refractory MM were treated at doses of 5–50 mg day⁻¹. The dose limiting toxicity in this study was myelosuppression, and a dose of 25 mg day⁻¹ was suggested for subsequent clinical trials. Compared to thalidomide, no significant somnolence, constipation or neuropathy was observed. Overall objective response was seen in 71% of the patients.⁵¹

Phase II trials confirmed these findings in 324 patients with additional improvement of response by the addition of Dex.⁵²

Recently, results of two randomized Phase III trials (MM-009, MM-010) comparing Rev/Dex with placebo/Dex in 700 patients revealed better response rates (PR + CR, MM-009: 61 vs 20.5%; MM-010: 59.1 vs 24%, $P < 0.001$) as well as superior time to progression (MM-009: 11.1 months vs 4.7; MM-010: 11.3 vs 4.7, $P < 0.001$) and OS (MM-009: 29.6 vs 20.5; MM-010: not reached vs 20.6, $P < 0.001$).^{53,54} In view of these data, lenalidomide has been recently approved by the FDA for the treatment of relapsed multiple myeloma.

In newly diagnosed patients, Rajkumar *et al.*⁵⁵ reported in a Phase II trial the combination of lenalidomide with Dex to be highly active with manageable side effects. This was recently updated including survival data. After a median follow-up of 21 months, an overall response rate of 91% was observed (34 patients enrolled) with CR + VGPR of 56%. Interestingly, 21 patients did not undergo HDT and achieved 67% VGPR/CR with 2-year PFS and OS rates of 74 and 91%, respectively.⁵⁶

In an Italian Phase I/II trial, Palumbo *et al.*⁵⁷ investigated the combination of lenalidomide with MP in 54 newly diagnosed patients older than 65 years of age, followed by a maintenance therapy with lenalidomide. Of the 21 patients treated at this dose level, all showed objective response with 85.6% achieving at least PR, including 52.3% at least VGPR and 23.8% CR. Grade 3–4 toxicities mainly consisted of neutropenia (66%) and thrombocytopenia (34%). Thromboembolic events occurred in three cases, mainly after discontinuation of aspirin.

A randomized Phase III study (E4A03) is currently being coordinated by ECOG to determine the dosing schedule of Dex (40 mg) in combination with lenalidomide (25 mg day⁻¹; days 1–21, every 28 days) in newly diagnosed patients. High-dose Dex was 40 mg on days 1–4, 9–12, 17–20 every 28 days, while low-dose Dex was 40 mg given on days 1, 8, 15 and 20 every 28 days. An interim analysis showed higher toxicity rates for high-dose Dex, especially thromboembolism (18.4 vs 5.4%), infectious complications (18.8 vs 9.0%) and hyperglycemia (5.8 vs 1.8%).⁵⁸ This study has recently been stopped due to a 10% overall

survival advantage in the lenalidomide/low Dex arm. A most recent update of this trial confirmed a 91% 1 year OS in this arm, with a survival advantage of 12% overall, 7 and 11% in patients < or > 65 years, respectively.⁵⁹

Lenalidomide and high-dose therapy

Given the convincing results of lenalidomide in the treatment of relapsed, refractory patients as well as in first reports of front-line therapy, several clinical trials are now recruiting patients to evaluate the potential of lenalidomide as part of induction therapy before HDT followed by auto-SCT. Two studies mentioned earlier, the ECOG E4A03 and the Phase II trial by Rajkumar *et al.*⁵⁵ (Rev/Dex) allowed patients to go off trial and proceed to HDT after four cycles of treatment.^{55,56,58} Importantly, Rajkumar *et al.*⁵⁹ show that the rate of serious adverse events was similar to those observed with dexamethasone alone in other trials. In addition, thalidomide side effects such as constipation and neuropathy were uncommon with lenalidomide treatment and sedation was not seen. No patient developed grade III or higher neuropathy. A sufficient amount of stem cells could be obtained for each patient. Given these results, the toxicity profile of lenalidomide before HDT appears to be favorable and high-dose corticosteroid therapy seems to contribute substantially to most of the non-hematologic adverse events. However, no final remission and survival data of these trials after HDT and transplant are yet available. An update at ASCO 2007 revealed 22 vs 6% occurrence of deep vein thrombosis, respectively in the high- vs low-dose Dex cohorts in spite of mandatory aspirin prophylaxis, suggesting that additional studies are necessary to define the optimal prophylactic strategy even with low dose Dex.

As already discussed for the use of thalidomide, prophylactic anticoagulation should always be considered for the use of lenalidomide in combination therapy.³⁴

Lenalidomide in maintenance therapy

As an orally available drug with a favorable single agent toxicity profile, lenalidomide appears to be an attractive agent for maintenance therapy. A number of trials are addressing this issue, either as part of a Phase II or III study for newly diagnosed patients^{57,58} or as separate protocols for patients having undergone HDT and auto-SCT (for example, ECOG-CALGB-100104; IFM 2005-02). To date, no data have yet been reported.

Taken together, lenalidomide already shows promising results in front-line therapy, but definitive data on PFS and OS in the context of HDT are not yet available. Moreover, the combination of lenalidomide with MP is highly active and is a promising alternative for non-transplant candidates.

Bortezomib

Bortezomib (PS-341, Millenium Pharmaceuticals Inc., Cambridge, MA, USA) is a proteasome inhibitor that has demonstrated significant *in vitro* and *in vivo* efficacy in preclinical studies (reviewed in Richardson and

colleagues⁶⁰). These findings enabled rapid translation to clinical trials, with bortezomib alone or in combination with Dex in relapsed/refractory patients with MM. As a single agent, bortezomib demonstrated an overall response rate of 35% in 202 patients (SUMMIT trial).⁶¹ In another Phase II trial, Jagannath *et al.*⁶² reported an increase in response to 50% by addition of Dex. This was pursued further by the APEX Phase III trial comparing bortezomib with high-dose Dex in patients with relapsed/refractory MM. A superior overall response for bortezomib (38%) in this heavily pretreated group of patients could be demonstrated compared to Dex (18%).⁶³ These studies led to the rapid approval of bortezomib by the FDA for relapsed/refractory MM.

Given the exciting efficacy in relapsed/refractory MM, Bortezomib is now moving forward to front-line therapy. The Spanish study group (Grupo Espanol de MM) explored tolerability, toxicity and efficacy of bortezomib combined with MP in 60 untreated, elderly patients not eligible for transplantation.⁶⁴ Response (overall 89%, CR 32%), EFS, (83%) and OS (90%) at 16 months were favorable, with manageable side effects, suggesting that this regimen is promising for non-transplant candidates. A Phase III trial (VISTA) is currently randomizing patients to bortezomib, MP vs MP. Numerous other trials of bortezomib in combination therapy for newly diagnosed non-transplant candidates are ongoing.

Bortezomib and high-dose therapy

Several Phase II trials have assessed the impact of bortezomib on the treatment of newly diagnosed patients before HDT/auto-SCT. Single agent bortezomib with added Dex dependent on response, showed a CR + PR rate of 88% with CR + VGPR of 25% in 32 patients. No effect on stem cell mobilization was observed in eight patients; neuropathy grade 2 and higher occurred in 10 patients, which was reversible in five cases.⁶⁵

Another Phase II trial by the IFM study group reported results for the combination bortezomib and Dex in 48 newly diagnosed patients undergoing transplantation. Overall response was 66%, with CR + VGPR 31%. Five patients progressed under treatment and grade 2–3 neuropathy was seen in 14% of the patients, but no DVT was detected. Sufficient PBSCs for at least one autograft were successfully collected in all cases.⁶⁶

Similar, but preliminary results have been recently reported for bortezomib (cycles 1, 3, 5) and Dex (cycles 2, 4, 6) administered on an alternating basis as induction regimen before ABSCT.⁶⁷ Interestingly, only mild neuropathy and no grade 4 toxicity was observed with this approach.

Since bortezomib has been shown to be synergistic with doxorubicin *in vitro*, Oakervee *et al.*⁶⁸ used this combination together with Dex ('PAD') in previously untreated patients. 21 patients were enrolled in this Phase II trial and PAD achieved at least PR in 95%, including CR in 24% patients. After HDT followed by auto-SCT, the intent-to-treat analysis revealed response rates with CR 43%, VGPR 38%, PR 14% and SD 5%. Collection of PBSCs was not compromised by PAD treatment.

Several study groups have therefore initiated randomized Phase III trials evaluating Bortezomib as part of induction therapy within the HDT + ABSCT setting. As part of the IFM 2005-01 protocol, the French study group presented preliminary data from an interim analysis 2006.⁶⁹ In this trial, Bortezomib + Dex is compared with VAD followed by a second comparison of consolidation with or without DCEP (Dex, cyclophosphamide, etoposide, cisplatin). In 161 evaluated patients having completed 4 cycles of induction therapy, the response rates for VAD were CR + PR 67% with CR + VGPR 26% and PD 2%, while bortezomib + Dex achieved CR + PR 82% with CR + VGPR 43% and PD 3%. Important, though preliminary, data from the subgroup of patients who had completed a first transplant indicates that 78% of patients treated with bortezomib + Dex did not require a second transplant, since they achieved a VGPR or better after their first transplant. DVT occurred in 2.7% (VAD) and 3.3% (bortezomib + Dex) of the patients. The rate of peripheral neuropathy was 1.3 and 3.3%, respectively.

Bortezomib in maintenance therapy

Although it is very appealing to use Bortezomib as maintenance therapy after transplant, only very limited data are yet available. However, numerous ongoing trials currently address this issue, and preliminary observations in dose finding studies suggest tolerable side-effects.^{70,71}

Bortezomib and allogeneic transplantation

As mentioned earlier, bortezomib was considered a valuable agent post allogeneic transplant due to its immunomodulatory as well as anti-MM effects.

Bortezomib alone and in combination with steroids was retrospectively evaluated by the Italian GITMO study group in 23 patients who had relapsed after allografting. Overall response (61% with CR 22%) was associated with significant peripheral neuropathy. The only risk-factor that could be identified was prolonged treatment with cyclosporine.^{72,73}

In another retrospective analysis of several European transplant centers, patients with relapsed or persistent disease after dose-reduced allografts and DLI were evaluated. Seven patients received bortezomib, and all responded, with two VGPR.⁴³

Kroger *et al.*⁷⁴ reported 18 patients who were intended to receive at least two cycles of bortezomib in an attempt to evaluate the role of bortezomib to enhance or maintain disease remission after nonmyeloablative SCT. While patients with measurable disease showed promising remission improvement (PR 50%, CR 30%), side effects including infectious complications, aggravation of GvHD, or hematological and neurotoxicity considerably hampered these positive results. Notably, neurotoxicity was again significantly more severe in patients treated concomitantly with cyclosporine.

Data available so far indicate that bortezomib is effective as treatment for relapsed or persistent disease after allogeneic transplantation. However, the increased risk of severe neurotoxicity associated with cyclosporine suggests

caution. Whether bortezomib can enhance the GvM-effect without inducing GvHD remains to be proven.

Future perspectives

More novel agents and more combinations

Future translational research in MM will focus on the development of molecularly based combination therapies to achieve a high frequency of durable responses in the majority of patients. Combination therapies have proven to be curative in childhood acute lymphoblastic leukemia, Hodgkin's disease and testicular cancer among others. Already cytogenetic abnormalities known to carry adverse prognostic import to conventional and high dose therapies do not apply to novel therapies (for example, bortezomib, lenalidomide), which will serve as platform drugs for future combined therapies.

As a result of advances in oncogenomics, on the one hand, and increased understanding of the role of the BM in the pathogenesis of MM on the other, a new treatment paradigm targeting the tumor cell and its BM microenvironment to overcome drug resistance and improve patient outcome has now been developed in MM. Thalidomide, lenalidomide and bortezomib are three agents which target the tumor cell in its microenvironment in both laboratory and animal models and which have rapidly translated from the bench to the bedside. These studies serve as a testament to the power of collaborations between academia, pharmaceuticals, Food and Drug Administration, National Cancer Institute and Advocacy groups to identify rapidly therapeutic targets in the MM cell and its BM microenvironment, use laboratory and animal models of human MM to validate novel agents directed at these targets, and then design clinical trials evaluating these agents which ultimately lead to their rapid FDA approval.

Ongoing and future efforts are identifying next-generation therapies in MM on the one hand, and using oncogenomics to inform the design of combination trials on the other. Examples of promising novel targeted therapies include agents targeting the tumor cell surface (CD40, CS-1, FGFR3), cytokines (VEGF, BAFF) and intracellular targets (MEK, PKC, NF- κ B, IKK, cyclin D, proteasomes). Having defined novel agents directed at these targets that can induce cytotoxicity against MM cells in the BM in both *in vitro* and *in vivo* models, we and others have gone on to define combination therapies to enhance cytotoxicity and overcome drug resistance.

Upfront vs salvage HDT: when to transplant

One major reason for the lack of differences between HDT and conventional combination therapy regarding OS, and in some studies even PFS, is the fact that a significant proportion of patients in the conventional therapy arm of these randomized trials actually underwent HDT as a salvage therapy for primary refractory disease or relapse. In this respect, the results of a randomized trial by Fermand *et al.*⁷⁵ have to be considered. In this study the relative merits of HDT, either upfront in the disease course or as salvage therapy for relapse after conventional front-line

therapy, have been investigated. While no differences were seen in OS, a time without symptoms, treatment and treatment toxicity analysis favored the early transplant cohort.

Given equivalent overall survivals whether HDT and auto-SCT is done early after induction therapy or late as a salvage therapy, it will be possible in the near future to carry out phase III clinical trials evaluating the role of transplant. Specifically, newly diagnosed patients can be treated with cocktails of novel agents, which achieve high frequency and extent of response and then, after collections of PBSCs, be randomized to receive early vs late HDT followed by auto-SCT. These studies will define durability of response, on the one hand, and the contribution of stem cell transplant on the other.

Conclusion

In recent years, thalidomide, lenalidomide and bortezomib have been approved by the FDA for treatment of relapsed or refractory multiple myeloma. These agents are now being successfully integrated into first-line therapy within the context of stem cell transplantation. Whether the remarkable response rates in newly diagnosed patients, reported to date, will translate to prolongation of patient survival will be one of the key questions in the years to come.

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