review

Novel agents in the frontline management of multiple myeloma

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Significant advances in our understanding of the biology of multiple myeloma have led to exciting new opportunities in treatment. The management of this disease is rapidly changing with a plethora of clinical trials initiated with novel agents, namely thalidomide, lenalidomide and bortezomib, either alone or in conjunction with established modalities such as conventional cytotoxic agents and stem-cell transplantation. The combination of these novel agents together with conventional regimens have led to higher response rates and survival, providing options for patients whose disease is otherwise resistant to conventional therapy. These pivotal trials that lead to the approval of these three novel agents in treatment naïve patients. The potential implications in the frontline treatment paradigm of multiple myeloma are discussed.

Despite advances in the management of multiple myeloma in the past few decades, it remains an incurable disease. Conventional treatments achieve a median survival of 3 to 5 years.[1,2] The disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. Recently, the management of patients with multiple myeloma has been transformed by the introduction of three novel agents: thalidomide, lenalidomide and bortezomib. These three agents represent a new generation of therapies for multiple myeloma that affect both specific intracellular signaling pathways within the tumor cell and also target the tumor microenvironment. This article describes the pivotal trials that have led to the incorporation of these novel agents in the frontline setting.

Traditionally, newly diagnosed myeloma patients have been classified as either transplant or non-transplant candidates. This classification has been based on a number of factors including age, performance status, co-morbid medical conditions, and patient preference. Induction therapy regimens are often decided by a patient's potential transplant status. Transplant candidates were typically treated with non-alkylating agents to prevent marrow damage. Non-transplant candidates often received alkylating-agent based therapy.

For those patients preselected for autologous stem cell transplantation (ASCT), the degree of clinical response was never as important as whether or not they actually proceeded to transplant. However, the achievement of complete response (CR) after induction therapy is now believed to be a strong predictor of long-term survival.[3] Unfortunately, traditional induction regimens only achieved a limited number of CR or near complete (nCR) treatment responses in the range of 3% to 7%.[4-8] In the interim analysis of the currently active multicenter Intergroupe Francophone du Myelome (IFM) 2005-01 study conducted in Europe, Harousseau et al reported a modest CR/nCR rate at 9% only in the control arm of vincristine, doxorubicin and dexamethasone (VAD).[8] There is clearly a need for improvement in induction therapy response. Emerging studies have shown that the incorporation of novel agents into traditional induction regimens can improve CR/nCR rates (Table 1).

Thalidomide

Thalidomide has been widely used in patients with relapsed or refractory multiple myeloma for a number of years. Following the initial report of single-agent activity in 1999,[9] thalidomide has since become one of the most widely used drugs to treat multiple myeloma in

Table 1. Summary of response rates using traditional induction regimens for patients with newly diagnosed multiple myeloma.

Study	N	Regimen	CR/nCR after induction	CR+PR after induction	Proceed with subsequent stem cell harvest
Rajkumar et al 2006[4]	100	Dexamethasone	0%	50%	Yes
Rifkin et al. 2006[6]	97	DVd	3%	43%	Yes
IFM90 1996[7]	100	VMCP	5%	52%	Yes/No
Palumbo et al 2006[5]	126	MP	7%	48%	No
Harousseau et al 2006[8]	82	VAD	9%	67%	Yes

CR: complete response, nCR: near complete response, PR: partial response. VAD: vincristine, doxorubicin, dexamethasone; DVd: liposomal doxorubicin, vincristine, dexamethasone; VMCP: vincristine, melphalan, cyclophosphamide, prednisolone, carmustine, and doxorubicin, MP: melphalan, prednisolone

the relapsed/refractory setting. The FDA has approved its use in combination with high-dose dexamethasone as treatment of newly diagnosed multiple myeloma.

Thalidomide combinations in the frontline setting

The approval of thalidomide plus dexamethasone in the frontline setting was based on the results of Eastern Cooperative Oncology Group (ECOG) trial E1A00.[4] This was a randomized, controlled phase III trial comparing thalidomide 200 mg daily PO plus high-dose dexamethasone at 40 mg daily on days 1-4, 9-12, 17-20 (Thal/Dex) repeated monthly for 4 cycles. The control arm received high dose-dexamethasone alone. In total, 207 patients were recruited into the trial. It is noteworthy that no specific thromboprophylaxis was mandated in this study.The response rate with thalidomide plus dexamethasone was significantly higher than with dexamethasone alone (63% v 41%, respectively; P=.0017). Complete responses occurred in 4% of patients within four cycles of therapy with Thal/Dex, and in 0% of patients in the dexamethasone-alone arm. Disease progression within four cycles of therapy was noted in 2% of patients with Thal/Dex and 5% of patients with dexamethasone alone. However, this regimen was associated with a significant incidence of deep venous thrombosis (DVT), requiring the use of anticoagulants like warfarin or low molecular weight heparin (LMWH). The incidence rates of grade 3 or higher DVT, rash, bradycardia, neuropathy, and any grade 4 to 5 toxicity in the first 4 months were significantly higher with thalidomide plus dexamethasone compared with dexamethasone alone (45% vs. 21%, respectively; P<.001). This study was also not powered to look at overall survival.

Based on a design similar to the ECOG E1A00, an extended study was performed by Rajkumar et al. Known as MM 003,[10] this phase III trial followed a similar design of 4 cycles of Thal-Dex vs. dexamethasone alone. Patients were then subsequently placed on maintenance dexamethasone 40 mg on days 1-4 every 28 days until progression. More than 400 patients have been recruited with specific end-points looking at time-to-progression (TTP), overall survival (OS), relative response (RR) and most importantly safety issues. Using intention-to-treat analysis, the median-TTP for Thal/Dex was 22.4 months compared with 6.5 months for dexamethasone alone (P<.0001). Median OS of the dexamethasone-alone arm was 32 months and the OS for the Thal/Dex group had not been reached yet as of the time of writing. Increased toxicities in the combination Thal/Dex arm in particular in the form of thrombotic events were reconfirmed (Table 2).

Thalidomide plus dexamethasone versus VAD as induction treatment

A randomized trial compared Thal/Dex with vincristine/doxorubicin/dexamethasone (VAD) as an induction regimen prior to ASCT in newly diagnosed multiple myeloma patients up to 65 years of age.[11] Since 2003, 204 patients were randomly assigned to receive a 4-month treatment with Thal/Dex (n=100) or a VAD-like regimen (n=104). All patients were intended to proceed to peripheral blood stem cell (PBSC) mobilization and to receive high-dose therapy with melphalan 200 mg/m^2 (MEL-200) and autologous PBSC support. The main characteristics of patients in each arm were similar. In both arms, 91% of patients proceeded to PBSC mobilization, PBSC harvests were similarly successful, and 83% of patients received high-dose therapy and ASCT. Very good partial response (VGPR, defined by serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 h) rates were significantly higher in the Thal/Dex arm before PBSC collection (25% vs. 6%, P=.0027) and before high-dose therapy and ASCT

Table 2. Summary of results and adverse events of phase III trials comparing thalidomide vs. thalidomide plus dexamethasone.

	MM-00310[10]		E1A004[4]	
	Thal/Dex (n=234)	Dex (n=232)	Thal/Dex (n=103)	Dex (n=104)
Time-to-progression (months)	22.4	6.5	Not determined	Not determined
Overall survival (months)	Not Reached	32	Not determined	Not determined
Adverse Events Grade ≥3				
Deep vein thrombosis	18%	3%	17%	3%
Pneumonia	11%	7%	NR	NR
Bradycardia	2%	0%	1%	0%
Peripheral Neuropathy	NR	NR	7%	4%
Any toxicities, grade ≥4	30%	23%	34%	18%

(35% vs. 12.5%, *P*=.002), but the benefit was not seen 6 months after transplant. Venous thromboembolism or pulmonary embolism was higher in the Thal/Dex arm versus the VAD arm (22.8% vs. 7.5%, *P*=.004). Toxicity profiles were otherwise similar. Before PBSC mobilization, the mean duration of hospitalization regardless of cause was significantly lower in the Thal/Dex arm (8.3 days vs. 20 days, *P*=.0001). This study confirms that Thal/Dex is an effective first-line treatment for multiple myeloma and supports its use as an induction regimen, which could be preferred to infusions of VAD in candidates for high-dose therapy.

Thalidomide and melphalan and prednisolone (MPT) in the elderly population

Although autologous stem-cell transplantation (auto-SCT) has been associated with longer progression-free survival, many patients diagnosed with myeloma are elderly with co-morbid conditions which may render them unfit for auto-SCT. For these patients, the standard treatment has been combination melphalan/prednisolone (MP) without stem cell transplantation.

Palumbo et al[5] looked at the addition of thalidomide to melphalan and prednisolone (MPT) in a phase III trial involving an elderly patient population older than 65 years of age. The rate of complete responders quadrupled from 7% with MP to 28% with MPT with an increase in the overall response rate from 48% to 76%. Median progression-free survival also increased from 14 months to 33 months and 2-year event free survival improved from 27% to 54% in favor of the triple-drug arm (Hazard ratio for MPT 0.51, 95% CI 0.35-0.75, *P*=.0006). There was also a trend towards improved overall survival rate at 3 years of 64% in the MP alone compared to 80% for the MPT arm.

In the three-arm phase III IFM 99-06 trial, Facon et al[12] compared MPT to MP and melphalan-based auto-SCT (MEL-100) in patients aged 65-75 years with newly diagnosed multiple myeloma. Initially planned for a recruitment of more than 480 patients, during the third interim analysis in 2005, results showed a clear superiority for the MPT arm and further enrollment was stopped. The PFS time was significantly longer in the MPT group than in the MP arm (RR=2.4, *P*<.0001), but no significant difference was noted between the MP and MEL100 groups (Relative risk=1.2, *P*=0.12). There was a clear advantage in favor of MPT vs. MEL 100 (Relative risk=2.0, *P*=.0001). The PFS advantage in favor of MPT translated to a significant benefit in terms of OS. The median OS time was 30.3 months and 38.6 months for MP and MEL-100 groups, respectively, while the median OS had not been reached yet at 56 months. Thus it was concluded that MPT should be, at the present time, the reference treatment for newly diagnosed multiple myeloma patients ineligible for autologous stem cell therapy (Table 3).

Thalidomide, thromboembolism and thromboprophylaxis

Although venous thromboembolism is a common complication in cancer patients, therapy with thalidomide combinations appears to substantially increase this risk.[4,13] Prophylaxis with therapeutic doses of warfarin or low-molecular weight heparin (LMWH) has been advised,[13,14] while aspirin may also reduce the risk of venous thromboembolic events. However, it has been suggested that this should only be reserved for patients unable or unwilling to take warfarin or LMWH. As these studies were performed in the West, whether the thromboembolic risk is equally as high in our predominantly non-Caucasian population has yet to be validated.

Table 3. Results of IFM 99-06 at the 3rd interim analysis in 2005.[12]

Treatment	Progressive-free survival (months)	*P*	Overall survival (months)	*P*
MP	17.2±1.5	<.0001	30.3±5.8	.0008
MPT	29.5±3.6	----------	> 56	----------
MEL100	19.0±1.3	.0001	38.6±3.0	.014

MP: melphalan and prednisolone; MPT: melphalan and prednisolone plus thalidomide, MEL100: (VAD×2 cycles, cyclophosphamide 3g/m^2+stem cell harvest, and 2 courses of melphalan 100 mg/m^2+stem cell reinfusion.

Other side effects of thalidomide

Aside from the potential of thromboembolism mentioned previously, the most common adverse events associated with thalidomide treatment are constipation, fatigue, somnolence and peripheral neuropathy.[9,15] Peripheral neuropathy is a common adverse event that often limits the dose and duration of treatment. In a retrospective analysis of a phase II Mayo Clinic trial,[16] 56% of patients were identified as having developed symptoms of peripheral neuropathy. Neuropathy improved in 27% during the treatment phase with/without dose reduction or after cessation of thalidomide. Fifteen percent of patients worsened despite dose reduction or stopping thalidomide while 52% remained stable during treatment. Most patients experienced grade 1 neuropathy only, but 11% of all patients had grade 2 neuropathy and 2% had grade 3 neuropathy. Predominant symptoms of neuropathy were tingling and numbness involving both the upper limb and lower limbs. Small subsets of patients complained of hearing loss and erectile dysfunction. In view of the toxicity profile of thalidomide, its analogue lenalidomide was developed with the aim of retaining its clinical efficacy but improving the toxicity profile.

Lenalidomide *(Revlimid)*

Lenalidomide belongs to a class of drugs known as IMiDs (immunomodulatory drugs) that are structurally related to thalidomide, but have relatively increased potency and differing side effect profiles. Results from phase I and II studies have shown lenalidomide to have significant and durable single-agent activity in the relapsed setting with responses seen in 14% to 29% of patients.[17,18]

When combined with dexamethasone in a phase III randomized study involving more than 140 relapsed or refractory multiple myeloma patients, Weber et al[19] demonstrated greater efficacy in the lenalidomide plus dexamethasone group compared with dexamethasone alone, achieving a response rate of 59% vs. 21% (P<.001) and a CR rate of 13% vs. <1% (P<.001). With these encouraging results, lenalidomide has been investigated in the upfront setting.

Lenalidomide combinations in the frontline setting

Phase II studies have investigated the use of lenalidomide combinations in newly diagnosed multiple myeloma. In 34 newly diagnosed multiple myeloma patients, Macy et al[20] demonstrated an astonishing overall response rate of 90% at 4 months with 48% of patients achieving CR or VGPR. Ninety percent of patients remained alive after 2 years and the 2-year PFS was 59%. Aspirin was an effective DVT prophylaxis.

Under the auspices of ECOG, Rajkumar et al further investigated first line use of lenalidomide and dexamethasone in a phase III setting.[21] ECOG E4A03 compared high dose dexamethasone (i.e. standard dose at 480 mg/cycle) vs. low dose dexamethasone (i.e. 160 mg/cycle) in combination with lenalidomide. More than 400 patients had been recruited at the time of writing. At the second pre-planned interim analysis presented at the American Society of Hematology (ASH) Meeting in 2007, OS was significantly superior with the lenalidomide plus low dose dexamethasone arm compared to the lenalidomide plus high dose dexamethasone arm, with a 1-year survival at 96% vs. 87% (P<.001), respectively. The 18-month survival rate was 91% versus 80%, respectively.

Although there was a significantly greater incidence of DVT/pulmonary embolism in the high-dose arm (18.4% vs. 6.3%, P<.001), further analysis of the data showed that the poorer overall survival of the high-dose dexamethasone arm could not be explained by this adverse event alone. The increased mortality in the high-dose dexamethasone group was due to disease progression (myeloma deaths) as well as increased toxicity. Thus, the study has major implications for the use of high-dose dexamethasone in the treatment of newly diagnosed multiple myeloma (Table 4).

Clinical trials are currently being performed assessing lenalidomide in combination with other agents. Lenalidomide and melphalan/prednisolone has been

Table 4. Results of ECOG E4A03-Phase III Trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma.[21]

Grade 3/4 Adverse Events, (%)	High-dose dexamethasone arm (n=223)	Low-dose dexamethasone arm (n=222)	*P*
Dexamethasone dose	40 mg D1-4, 9-12, 16-20 Total: 480 mg/cycle	40 mg D1, D8, D15, D22 Total: 160 mg/cycle	
DVT /pulmonary embolism	18.4	6.3	<.001
Infection/pneumonia	16.1	9.0	.031
Fatigue	11.7	4.1	.004
Hyperglycemia	5.8	2.3	.090
Neuropathy	0.4	1.4	.372
Any non-hematologic	54.3	39.6	.002
Any toxicity (≥ grade 4)	19.3	11.3	.025
Death (grade 5)	4.9	0.5	.006

investigated in elderly patients with newly diagnosed multiple myeloma.[22] Preliminary results show that the combination produces at least a partial response in 81% of patients with 47.6% of patients achieving VGPR and 24% achieving CR. Hematologic adverse events were frequent but noted as manageable. Non-hematologic adverse events were low. Aspirin appeared to provide adequate anti-thrombosis prophylaxis.

Side effects of lenalidomide

Studies show that lenalidomide is better tolerated than thalidomide in several aspects of its toxicity profile. Clinically significant somnolence, constipation and neuropathy rarely occurred in prior studies. Myelosuppression, mainly in the form of neutropenia and thrombocytopenia are the most common grade ≥ 3 toxicities,[18] but are manageable with dose reduction and growth factor support. As seen in thalidomide, the risk of thromboembolic events is also higher in combination with dexamethasone and anti-thrombotic prophylaxis is advised.

Bortezomib *(Velcade)*

Bortezomib is a novel, first-in-class proteasome inhibitor that has anti-proliferative, pro-apoptotic, anti-angiogenic and anti-tumor activity through the inhibition of proteasomal degradation of numerous regulatory proteins.[23,24] Pre-clinical studies have demonstrated synergistic or additive anti-tumor activity with agents commonly used in the treatment of multiple myeloma.

Bortezomib with or without dexamethasone was shown to be active in two phase II studies in patients with relapsed/refractory myeloma.[25,26] The international, randomized phase III Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial recruited patients with relapsed multiple myeloma following 1 to 3 prior therapies.[27] It showed that single-agent bortezomib provides a significantly longer TTP, higher response rate and superior survival compared with high-dose dexamethasone. The combined complete and partial response rates were 38% for bortezomib and 18% for dexamethasone (P<.001), and the CR rates were 6% and <1%, respectively (P<.001). Median TTP in the bortezomib and dexamethasone groups were 6.22 months (189 days) and 3.49 months (106 days), respectively (hazard ratio, 0.55; P<.001). Substantial activity has also been demonstrated in bortezomib-based combinations in the relapsed/refractory setting.

Bortezomib combinations in the frontline setting

Bortezomib-based therapies have demonstrated encouraging activity in at least 13 studies in the frontline setting,[28] both as induction therapy prior to stem cell transplantation and as therapy for patients not proceeding to, or not eligible for transplant. In total, more than 700 patients involved in these trials have shown high response rates and consistently higher CR/nCR rates than that seen in conventional induction regimens and conventional therapies.

The double regimen of bortezomib plus dexamethasone has been investigated as induction therapy in at least 3 trials.[29-31] In a single-arm phase II study, Jagannath et al[29] investigated the use of bortezomib, as a single agent and in combination with dexamethasone in the first-line setting. Thirty-two consecutive patients received bortezomib for a maximum of six 3-week cy-

Table 5. Results from bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma.[29]

Response rate (%)	Bortezomib alone (2 treatment cycles)	Bortezomib+dexamethasone (4 treatment cycles)	Bortezomib+dexamethasone (6 treatment cycles)
Overall response	49	78	88
Partial response	37	57	49
Very good partial response	2	6	20
Complete response, near complete response	10	14	18

Table 6. Recommended dose modifications of bortezomib in the event of peripheral neuropathy.[38]

Severity of peripheral neuropathy	Modification of dose and schedule
Grade 1 (paresthesias or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or grade 2 (interferes with function but not with ADL)	Reduce to 1.0 mg/m^2
Grade 2 with pain or grade 3 (interferes with ADL)	Withhold treatment until toxicity resolves, then reinitiate at a dose of 0.7 mg/m^2 once weekly
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

Abbreviation: ADL, activities of daily living.

cles with oral dexamethasone 40 mg added if a less than a partial response was achieved after two cycles or a less than CR was achieved after four cycles. The response rate (CR+PR) was 88%, with undetectable paraprotein (CR) in 6% and paraprotein detected by immunofixation only (nCR) in 19%. All 32 patients completed the first two cycles of bortezomib alone, of whom 3% achieved CR, 9% nCR, and 28% PR. Most patients responded within 4 cycles with the median-time-to-response of 1.9 months. It is noteworthy that bortezomib treatment did not affect stem cell mobilization in eight or transplantation in six patients (Table 5).

The IFM 2005-01 is a large randomized phase III trial comparing bortezomib/dexamethasone vs. VAD as induction therapy prior to autologous stem-cell transplantation. Involving more than 480 patients, it completed accrual in January 2007. Interim analysis of the first 220 patients recruited was presented at the ASH Annual Meeting in 2007 in abstract form.[32] Although the difference in achieving "more than partial response" was insignificant between the VAD and the bortezomib/dexamethasone arm both at post-induction and post-ASCT, significantly more patients in the bortezomib/dexamethasone arm established CR+nCR and VGPR (9% vs. 22%; *P*=.0085; 24% vs. 50%; *P*=.001 respectively) at post-induction. We eagerly await further results from this trial.

Regimens containing bortezomib and doxorubicin have also demonstrated substantial activity. In a phase II study, the combination of bortezomib, doxorubicin and dexamethasone (PAD)[33] yielded a response rate of 95%, including a 29% CR/nCR rate, prior to stem-cell transplantation (SCT). This high response rate was sustained even after SCT and is important as CR status following SCT is associated with longer overall survival time.[34,35] The efficacy of bortezomib and pegylated liposomal doxorubicin (PLD; Doxil) has been validated in a randomized phase III international trial in the refractory or relapsed setting.[36] Median time-to-progression was increased from 6.5 months for bortezomib to 9.3 months with the PLD+bortezomib combination (*P*=.000004; hazard ratio, 1.82 [monotherapy v combination therapy]; 95% CI, 1.41 to 2.35) but as yet, no survival advantage has been demonstrated to date.

In June 2008, based on the pivotal phase III VISTA trial[37] involving 682 patients, bortezomib was approved by the FDA in combination with melphalan and prednisolone in the frontline setting for patients who are ineligible for SCT. This phase III multi-center open label study randomized patients to receive bortezomib in addition to melphalan and prednisolone (VMP) versus a control group of the dual combination of melphalan and prednisolone (MP). Interim analysis showed

a CR rate of 35% with the triple-drug combination, compared with 5% with the control arm ($P<.000001$). Median duration of response was 24 months for patients with a CR after VMP, compared with 13 months after MP; the time-to-disease progression was 24 months and 17 months ($P=.0000001$), respectively. In addition, the triple-drug combination demonstrated a statistically significant improvement in OS, with a 40% reduction in the risk for death ($P=.0078$).

Side effects of bortezomib

Most common toxicities associated with bortezomib treatment include fatigue, gastrointestinal events and peripheral neuropathy. The most commonly reported grade ≥3 toxicities are peripheral neuropathy and myelosuppression with anemia, thrombocytopenia and neutropenia. Bortezomib-related peripheral neuropathy is an important dose-limiting toxicity,[38] but was shown to be reversible in the majority of patients. Based on the earlier two phase II trials of bortezomib in the refractory setting,[25,26] a dose modification guideline in the event of neuropathy has been developed (Table 6).

Conclusions

Prior to the advent of these novel agents, extensive work performed by the French IFM group and Barlogie et al[39] advocated tandem stem-cell transplants as the standard of care to achieve a higher CR rate, especially in the younger population. However, with the availability of novel agents, the treatment paradigm of multiple myeloma has changed dramatically. With the introduction of these therapies in the first-line treatment setting, the number of objective responses has increased dramatically and consistently, as has the number of complete responses. The results indicate that combining a novel agent with standard chemotherapy increases the number of complete and near complete responders to 20% or 30%, a number that was previously unheard of outside of a transplant. Notably, this is usually achieved without compromising the dose of either the novel agent or standard chemotherapy. In view of these encouraging results, the role of autologous stem-cell transplant, especially in the older population, is now being called into question. The ultimate impact of novel agents may be to extend survival in younger patients by achieving CR prior to a single autologous transplant as consolidation treatment. The survival of older patients may improve following induction therapy with novel agents without the need for autologous transplant. Further stratification of patients into distinct risk groups based on molecular cytogenetics may also play an important role in deciding treatment options.[40]

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