[haematologica reports]
2006;2(14):17-21

Prolonging time to progression and survival in relapsed/refractory multiple myeloma

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Each year, over 16,500 new cases of multiple myeloma (MM) are diagnosed in the USA alone, making it the second most common type of haematological malignancy after non-Hodgkin's lymphoma.[1] Current treatment options for MM are non-curative, and the 5-year survival rate for all patients with MM has improved only slightly over the last 20–25 years, from 25% to 32%.[1] Conventional therapy for newly diagnosed patients results in a median survival of about 3-4 years.[2] Some patients may be eligible for high-dose chemotherapy with autologous stem cell transplantation (SCT), which may prolong survival. However, even these patients eventually relapse, and treatment options for patients with relapsed and refractory disease are limited.

A *standard* approach to the treatment of relapsed or refractory MM has not been established. Aside from palliative care and enrolment in a clinical trial, options for some eligible patients include conventional regimens based on alkylating agents and/or steroids, or rescue with high-dose chemotherapy and SCT. Newer drugs, such as thalidomide and bortezomib, produce response rates of approximately 35% when used as monotherapy,[3-6] and 50% when combined with dexamethasone.[7] Thalidomide, however, is associated with neuropathy, constipation, somnolence, and teratogenic effects. Bortezomib is also associated with neuropathy, as well as constipation, fatigue, diarrhoea, and thrombocytopenia. Therefore, novel therapies that are safe and effective are needed.

Lenalidomide was recently approved by the US Food and Drug Administration in combination with dexamethasone for the treatment of patients with MM who have received at least 1 prior therapy. Like thalidomide, lenalidomide targets MM cells directly, and also modulates key factors in the microenvironment that affect MM cell growth and survival.[8] Unlike thalidomide, lenalidomide is associated with a low incidence of peripheral neuropathy, somnolence, sedation, and constipation.[9] The approval of lenalidomide was based primarily on the results of 2 similarly designed multinational phase III trials, which are described below.

Clinical studies

Initial phase I studies of lenalidomide in patients with relapsed/refractory MM established that once-daily administration of lenalidomide at a dose of 25 mg was well tolerated and produced some responses in heavily pretreated populations.[10,11] A multicentre, randomised phase II study recently evaluated 2 dosing regimens of lenalidomide: 15 mg twice daily and 30 mg once daily for 21 days of a 28-day cycle.[12] Patients who had progressive or stable disease after 2 cycles received dexamethasone in addition to lenalidomide. An analysis of the first 70 patients indicated that the twice-daily regimen was associated with a higher incidence of grade 3-4 myelosuppression (41% versus 13%; p=0.03); consequently, an additional 32 patients were enrolled and received the once-daily regimen. Based on the total study population, both regimens appeared to have similar activity, with an overall response rate of 29% with the twice-daily regimen and 24% with the once-daily regimen. Grade 3-4 myelosuppression occurred in 80% and 69% of patients, respectively (p=0.3) and occurred more rapidly in patients who received the twice-daily regimen (1.8 months versus 5.5 months; p=0.05). Therefore, the once-daily 30-mg dose regimen was selected for further study. Notably, 20 of 68 patients (29%) who did not respond to lenalidomide alone responded when

Table 1. Patient characteristics in 2 phase III trials (MM-009 and MM-010) of patients with relapsed/refractory MM. (Data from Weber DM, *et al.*[14] and Dimopoulos MA, *et al.*[15])

	MM-009		*MM-010*	
	Lenalidomide/ dexamethasone (n=170)	*Dexamethasone (n=171)*	*Lenalidomide/ dexamethasone (n=176)*	*dexamethasone (n=175)*
Male, %	60	59	59	59
Median age, years	64	62	63	64
ECOG performance status ≤1, %	89	95	85	82
Durie-Salmon stage III, %	67	67	65	63
Lytic bone lesions, %	69	78	77	80
Mean time from diagnosis, years	3.6	3.9	4.2	4.8

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Key results from 2 phase III trials (MM-009 and MM-010) comparing lenalidomide plus dexamethasone with dexamethasone alone in patients with relapsed/refractory MM. (Data from Weber DM, *et al.*[14] and Dimopoulos MA, *et al.*[15])

	MM-009		*MM-010*	
	Lenalidomide/ dexamethasone (n=170)	*Dexamethasone (n=171)*	*Lenalidomide/ dexamethasone (n=176)*	*Dexamethasone (n=175)*
Median time to progression, months	11.1*	4.7	11.3†	4.7
Median overall survival, months	29.6*	20.2	NYR‡	20.6
Overall response (CR + PR), %	59.4†	21.1	59.1†	23.9
CR, %	12.9	0.6	15.0	3.4
Grade 3-4 neutropenia, %	36.2	4.5	27	2
Grade 3-4 thromboembolic events, %	14.1	3.4	9	6

*Abbreviations: CR, complete response; NYR, not yet reached; PR, partial response. *p<0.0001 versus dexamethasone alone. †p<0.001 versus dexamethasone alone. ‡p<0.03 versus dexamethasone alone.*

dexamethasone was added, suggesting that dexamethasone can improve the anti-myeloma effects of lenalidomide.

The safety and efficacy of lenalidomide monotherapy in patients with relapsed/refractory MM was established in a large, multicentre, phase II trial (n=222).[13] All patients had received at least 2 prior regimens, which included thalidomide (80%), SCT (44%), and bortezomib (41%). The overall response rate was 25% and an additional 46% had stable disease, for an overall treatment benefit in 71% of patients. The median time to progression was 22.4 weeks. The most common adverse events that led to dose reductions were neutropenia (40%), thrombocytopenia (23%), fatigue (5%), and anaemia (5%). The incidence of treatment-related neuropathy and deep-vein thrombosis was low.

The combination of lenalidomide and dexamethasone was evaluated in 2 phase III studies. The MM-009 study was conducted in 48 centres in the USA and Canada, and the MM-010 study was conducted in 51 centres in Europe, Australia, and Israel.[14,15] Both trials compared the efficacy and safety of lenalidomide plus dexamethasone with dexamethasone alone in patients with relapsed or refractory MM. In each trial, approximately 350 patients were randomised to dexamethasone 40 mg/day on days 1-4, 9-12, and 17-20 (after the fourth cycle, on days 1-4 only), plus either lenalidomide 25 mg/day on days 1-21 or placebo. Treatment was repeated every 28 days until disease progression. Patients were stratified according to serum β_2-microglobulin level (≤2.5 mg/L versus >2.5 mg/L), prior transplant (0 versus ≥1), and the number of prior regimens (1 versus >1). The primary end-point of each study was time to progression. Secondary end-points included overall survival and response rates. Complete response was defined as no evidence of serum M protein or Bence Jones protein by immunofixation and <5% plasma cells in bone marrow. Partial response was defined as ≥50% reduction in serum M protein or ≥90% reduction in Bence Jones protein.

All patients had relapsed/refractory MM and had received at least 1 prior regimen. Most patients were heavily pretreated: in the MM-010 study, for example, about 68% of patients had received 2 or more prior regimens, including

Table 3. Time to progression according to number of prior therapies in a phase III trial (MM-010) comparing lenalidomide plus dexamethasone with dexamethasone alone. (Data from Dimopoulos MA, *et al.*[16])

	Lenalidomide/ dexamethasone	*Dexamethasone*	*Hazard ratio*	*p value*
Median time to progression, weeks (95% CI), for patients with				
1 prior regimen (n=63)	NE (24.1-NE)	20.1 (12.9-39.9)	2.8	0.003
2 prior regimens (n=130)	78.0 (42.4-NE)	20.1 (13.3-24.1)	3.7	<0.001
3+ prior regimens (n=158)	40.9 (32.1-52.4)	20.1 (16.1-20.9)	2.5	<0.001

Abbreviations: CI, confidence interval; NE, no estimate possible.

Table 4. Efficacy according to prior thalidomide therapy: pooled subgroup analysis of patients from 2 phase III trials (MM-009 and MM-010). (Data from Wang M, *et al.*[17] and Blad J, *et al.*[18])

	Prior thalidomide		*No prior thalidomide*	
	Lenalidomide/ dexamethasone (n=124)	*Dexamethasone (n=145)*	*Lenalidomide/ dexamethasone (n=222)*	*Dexamethasone (n=201)*
Median time to progression, weeks	36.9*	19.7	59.0*	20.3
Overall response, %	53.3*	15.2	62.6*	27.8
Complete response, %	8.1†	1.4	17.6*	2.5

**p<0.001 versus dexamethasone alone. †p=0.02 versus dexamethasone alone.*

SCT (55%), dexamethasone (67%), and thalidomide (34%).[15] In both studies, treatment arms were well balanced with regard to age, performance status, disease stage, and prevalence of lytic bone lesions (Table 1).[14,15] The mean time from diagnosis (disease duration) was approximately 3.8 years in MM-009 and 4.5 years in MM-010.

The median time to progression, the primary end-point of both trials, was significantly greater in patients who received lenalidomide-plus-dexamethasone compared with those receiving dexamethasone alone (Figure 1).[14,15] Overall survival and response rates were also significantly higher in the lenalidomide plus dexamethasone group (Table 2).[14,15] The improvement in time to progression was seen irrespective of the extent of prior therapy, according to a post hoc analysis of the MM-010 study (Table 3),[16] or prior treatment with thalidomide, as shown in a prospective subgroup analysis of the 269 patients from MM-009 and MM-010 who had received prior thalidomide (Table 4).[17,18]

In both studies, the primary side effect related to lenalidomide treatment was grade 3-4 neutropenia, which occurred in about 36% (MM-009) and 27% (MM-010) of patients receiving lenalidomide plus dexamethasone, compared with 5% (MM-009) and 2% (MM-010) in patients receiving dexamethasone alone (Table 2). However, the incidence of grade 3-4 infections was similar in both treatment groups in both studies.

Like thalidomide, lenalidomide treatment was associated with an increased incidence of deep-vein thrombosis and pulmonary embolism. Thromboembolic events occurred in 14% and 9% of patients receiving lenalidomide plus dexamethasone compared with 3% and 6% of patients receiving dexamethasone alone. Neither study required routine thromboprophylaxis. However, it was noted that none of the patients in the MM-009 study who received concomitant aspirin had a thromboembolic event.[14] Unlike thalidomide, lenalidomide treatment was not associated with sedation or neuropathy. The incidence of neuropathy was low in all patients: in the MM-009 study, the incidence of grade 3-4 neuropathy was ≤3% in both treatment arms.[14] The incidence of grade 1-2 neuropathy was 11% in patients receiving lenalidomide pus dexamethasone and 6% in those receiving dexamethasone alone.

Given the improved time to progression, overall survival, and response rates seen in these 2 multicentre phase III trials, it appears that the combination of lenalidomide and dexamethasone is effective in patients with relapsed/refrac-

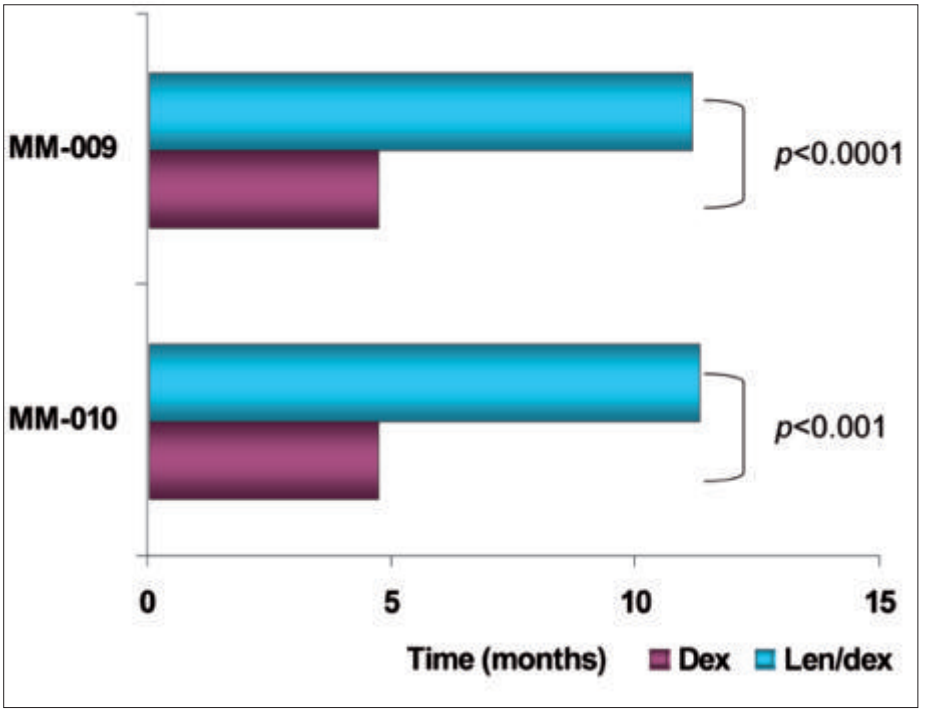

Figure 1. Median time to progression in 2 phase III trials (MM-009 and MM-010) comparing lenalidomide plus dexamethasone with dexamethasone alone in patient with relapsed/refractory MM. (Data from Weber DM, *et al.*[14] and Dimopoulos MA, *et al.*[15])

tory MM. The ease of administering this oral regimen and its manageable toxicity profile indicate that this approach is a promising new treatment option for patients with relapsed/refractory MM.

Lenalidomide in newly diagnosed MM

The activity of lenalidomide plus dexamethasone in the relapsed/refractory setting prompts the question whether this regimen may be beneficial when used as first-line therapy. The combination of thalidomide and dexamethasone produces response rates of up to 76% in patients with previously untreated MM, which are at least as good as those achieved with the traditional VAD regimen of vincristine, doxorubicin, and dexamethasone.[19] In elderly patients or younger patients unable to undergo transplantation, the addition of thalidomide to melphalan and prednisone has been shown to increase response rates and prolong event-free survival.[20] Given that lenalidomide is more potent and has a more favourable safety profile than thalidomide, a phase II study was conducted to evaluate lenalidomide plus dexamethasone in patients with newly diagnosed MM.[21] Lenalidomide was given orally at a dose of 25 mg/day on days 1-21 of a 28-day cycle. Dexamethasone was given orally at a dose of 40 mg/day on days 1-4, 9-12, and 17-20 of each cycle (after the fourth cycle, on days 1-4 only). Of the 34 patients enrolled, 31 achieved an objective response (91%), including 2 complete responses (6%) and 11 near-complete responses (32%).[21] Grade ≥3 non-haematological adverse events occurred in 47% of patients, and consisted primarily of fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). Grade ≥3 haematological adverse events included neutropenia (12%), leucopenia (9%), lymphopenia (6%), and anaemia (6%). All patients received aspirin prophylaxis, and the incidence of deep-vein thrombosis was low (3%). Notably, side effects typically associated with thalidomide, such as sedation, constipation, and neuropathy, were uncommon, and no patient developed grade ≥3 neuropathy.

Based on this initial study, it appears that the combination of lenalidomide and dexamethasone is active and well tolerated in previously untreated patients with MM. Phase III trials conducted by the Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG) are ongoing or planned to evaluate the lenalidomide-dexamethasone combination in this setting. In addition, the Cancer and Leukemia Group B (CALGB) is conducting a phase III trial to evaluate the use of lenalidomide as maintenance monotherapy following autologous SCT. Studies evaluating lenalidomide in elderly patients who are ineligible for SCT are also planned.

Conclusions

The combination of lenalidomide plus dexamethasone represents an effective treatment option for patients with relapsed/refractory MM. The remarkably similar results of 2 phase III international trials demonstrate that this regimen increases response rates and the time to progression. Initial results obtained using lenalidomide plus dexamethasone in previously untreated patients with MM are promising, and phase III studies evaluating lenalidomide plus dexamethasone in this setting are underway. Other trials will continue to explore potential applications of this regimen as maintenance therapy following SCT or as an alternative to SCT for elderly patients who are ineligible for SCT and for whom safe and effective therapies are urgently needed.

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