

Lenalidomide plus dexamethasone is efficacious in patients with relapsed or refractory multiple myeloma

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Two recent studies have shown that lenalidomide in combination with high-dose dexamethasone is significantly more effective than high-dose dexamethasone alone in patients with relapsed multiple myeloma.

Lenalidomide is a more potent analogue of thalidomide that directly induces apoptosis of multiple myeloma (MM) cells and inhibits interactions between MM cells and bone-marrow-stromal cells. In addition, lenalidomide blocks both the constitutive production of cytokines and the production of cytokines induced by the binding of MM cells to bone-marrow-stromal cells. In blocking cytokine production, lenalidomide mediates MM-cell growth and survival, inhibits angiogenesis, and upregulates natural killer and T-cell responses against MM cells.¹ On the basis of preclinical efficacy, phase I and II clinical trials have demonstrated that 25 mg lenalidomide given for 21 days of a 28-day cycle is well-tolerated and induces responses in over 30% of patients with relapsed MM. Moreover, these

responses are enhanced by the addition of dexamethasone.² On the basis of these exciting results, two randomised phase III trials were conducted that compared lenalidomide plus high-dose dexamethasone with high-dose dexamethasone plus placebo in patients with relapsed or refractory MM. Both the North American study by Weber et al. ($n=353$)³ and the international study by Dimopoulos et al. ($n=351$; see opposite) confirmed that the combination regimen was significantly superior to dexamethasone in terms of response rate, time to progression and overall survival.

In the North American study,³ those receiving lenalidomide had significantly improved partial and complete response rates (61% and 14.1%, respectively) and time to progression and overall survival were significantly prolonged (11.1 months and

29.6 months, respectively). The corresponding partial and complete response rates in those receiving dexamethasone were 19.9% and 0.6%, respectively, and time to progression and overall survival were 4.7 months and 20.2 months. The results of the Dimopoulos study were very similar. Oral lenalidomide plus dexamethasone was active in patients who had previously received bortezomib, high-dose therapy and stem-cell transplantation, or thalidomide. A tolerable toxicity profile was observed in both studies. These studies provided the basis for the rapid approval of lenalidomide plus dexamethasone by the FDA and the European Medicines Agency for the treatment of patients with relapsed MM following initial induction therapy.

Notably, the study by Dimopoulos et al. confirmed that deep vein

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Synopsis

M Dimopoulos, A Spencer, M Attal et al. (2007) **Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.** *N Engl J Med* 357:2123–2132

Background. Lenalidomide is a more-potent and less toxic derivative of thalidomide. When lenalidomide is combined with dexamethasone this combination is more effective than either agent alone in the treatment of refractory myeloma.

Objective. To investigate the efficacy of lenalidomide plus dexamethasone in patients with relapsed or refractory myeloma.

Design. This multicentre, randomised, placebo-controlled phase III trial recruited 351 patients with multiple myeloma (MM) from centres in Europe, Israel and Australia between September 2003 and September 2004. All patients had received at least one previous antimyeloma treatment. Other eligibility criteria included age at least 18 years, an Eastern Cooperative Oncology Group performance status of 2 or less and an absolute neutrophil count of at least 1,000 mm³. Patients who experienced disease progression while being treated with high-dose dexamethasone or who had hypersensitivity to previous treatment with thalidomide or dexamethasone were excluded.

Intervention. Patients were randomly assigned to receive either 25 mg oral lenalidomide ($n=176$) or placebo ($n=175$) on days 1 to 21 of a 28-day cycle. All patients received 40 mg oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for four cycles; after the fourth cycle, dexamethasone was administered on days 1 to 4 only. Patients continued to receive the assigned regimen until disease progression or the development of unacceptable toxic effects.

Outcome measures. Time to disease progression was the primary endpoint of this trial. Secondary endpoints included overall survival, rate of response and safety.

Results. The median time to progression was significantly longer in patients treated with lenalidomide plus dexamethasone than in patients treated with placebo plus dexamethasone (11.3 months vs 4.7 months; $P<0.001$; hazard ratio for time to progression 2.85). In total, 106 patients in the lenalidomide group achieved at least a partial response, compared with 42 patients in the placebo group ($P<0.001$). A complete response was achieved in 28 patients receiving lenalidomide and in 6 patients receiving placebo ($P<0.001$). The median duration of response in the lenalidomide group was 16.5 months compared with 7.9 months in the placebo group ($P=0.02$). Patients who received lenalidomide had significantly improved overall survival (hazard ratio for death 0.66; $P=0.03$). A higher incidence of grade 3 neutropenia, grade 3 or 4 thrombocytopenia and venous thromboembolism was reported in the lenalidomide group than in the placebo group.

Conclusion. The combination of lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in the treatment of relapsed or refractory MM.

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thrombosis is an important side-effect of lenalidomide and that optimum prophylactic anticoagulation is required.⁴ In this study, high-dose dexamethasone was used at 40 mg on days 1–4, 9–12 and 17–20 for the first four cycles of treatment. A recent Eastern Cooperative Oncology Group study in patients with newly diagnosed MM has shown a survival advantage with the combination of lenalidomide plus low-dose dexamethasone (40 mg once a week) versus lenalidomide plus high-dose dexamethasone.⁵ This finding raises the question as to whether a weekly dose of dexamethasone could

be used in combination with lenalidomide to treat relapsed MM.

Ongoing studies are evaluating the use of lenalidomide as maintenance therapy after induction therapy or transplantation. Moreover, it is now being combined with melphalan and prednisone to treat newly diagnosed patients who are not transplantation candidates.⁶ Lenalidomide is also being combined with monoclonal antibody therapy to enhance antibody-dependent cellular cytotoxicity. Finally, preclinical studies showing induction of dual apoptotic signaling and synergistic cytotoxicity have led to

investigations into the combination of lenalidomide with bortezomib. The current study provides further clinical validation of the novel treatment paradigm – targeting the MM cell in its bone marrow microenvironment to overcome drug resistance to conventional therapy. These studies represent a key advance in the treatment of MM and an extraordinary example of rapid, collaborative bench-to bedside research to improve patient outcome in MM.

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