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## Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma

MELETIOS DIMOPOULOS, ANDREW SPENCER, MICHAEL ATTAL, MILES PRINCE, JEAN-LUC HAROUSSEAU, ANNA DMOSZYNSKA, JESUS SAN MIGUEL, ANDRZEJ HELLMANN, THIERRY FACON, ROBIN FOA, ALESSANDRO CORSO, ZVENYSLAVA MASLIAK, MARTA OLESNYCKYJ, ZHINUAN YU, JOHN PATIN, JEROME B. ZELDIS, ROBERT D. KNIGHT

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### INTRODUCTION

Multiple myeloma is a neoplastic disease of plasma cells. It accounts for 10% of all haematological malignancies. Currently, patients under age of 65 years with advanced myeloma (stage II-III) are best treated with initial 3 to 4 cycles of thalidomide plus dexamethasone followed by autologous peripheral blood stem cell transplantation (ASCT). Patients above 65 years or those not suitable for ASCT are treated with melphalan, prednisolone and thalidomide(MPT). Following therapy, about 60-70 % achieve significant response including complete response in 15-20%. Patients who fail to respond or relapse after initial response, have a poor outcome. Recently, vortezomib, a proteosome inhibitor and lenalidomide, a thalidomide derivative have been added for the treatment of refractory / relapsed myeloma.

This phase 3, placebo-controlled trial evaluated the efficacy of lenalidomide plus

dexamethasone in the treatment of relapsed or refractory multiple myeloma.<sup>2</sup> Between Sept. 2003 to Sept 2004, a total of 351 patients (176 in lenalidomide plus dexamethasone arm and 175 in placebo plus dexamethasone arm), who had received at least one previous antimyeloma therapy were included. Eligibility criteria were: Age > 18 years , ECOG performance status of  $\leq 2$ , serum creatinine of  $< 2.5$  mg %, absolute neutrophil counts (ANC)  $>1000/\text{cmm}$ , platelet count  $>75,000$  per cubic millimeter for patients with less than 50% bone marrow plasma cells and more than 30,000 per cubic millimeter for patients with 50% or more bone marrow plasma cells. Exclusion criteria were – history of hypersensitivity to or uncontrollable side effects associated with previous use of thalidomide or dexamethasone, disease progression during previous therapy on regimen containing high-dose dexamethasone (total monthly dose,  $>200$  mg). Patients received either 25 mg of oral lenalidomide or placebo on days 1 to 21 of a 28-

day cycle; all patients received 40 mg of oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles. After the fourth cycle, 40 mg of dexamethasone was administered only for 4 days from days 1 to 4 till the occurrence of disease progression or unacceptable toxic effects. Patients were stratified according to the baseline serum  $\beta$ -2-microglobulin level ( $<2.5$  mg per liter  $\geq 2.5$  mg per liter). previous stem-cell transplantation (none or  $\geq 1$ ) and the number of previous anti myeloma regimen (1 or =2). The primary end point was time to progression. Secondary end points included -overall survival, the rate of response, and safety. Response to therapy was defined as per EBMT criteria.<sup>3</sup> Toxicity was graded as per NCI toxicity grading criteria, version 2. All primary statistical analysis was based on the intention-to-treat analysis. Both the time to progression and overall survival were estimated using Kaplan-Meier methods. Pearson chi-square tests were used to compare the proportions of patients in the two groups who had a response to treatment.

Median age of patients in lenalidomide group was 63 years, with PS 0, 1 or 2, median time since diagnosis was 3.4 years. 65.3 % of patients had stage 3 according to Durie Salmon staging system.<sup>4</sup> 68.2 % of patients had received 2 or more prior therapies, 30.1 % of patients had received thalidomide based regimen, and 55.1 % of patients had undergone prior ASCT. 71 % of patients had serum  $\alpha$ -2 microglobulin level 2.5 mg/l or more. Dose modification of dexamethasone and lenalidomide and use of G-CSF was allowed at the investigator's discretion. Baseline characteristics were comparable between the placebo group and lenalidomide group. Median follow up was 16.4 months. The most common adverse events in both these studies were neutropenia, muscle cramps, constipation, nausea, tremor, dizziness. The incidence of grade 3 or 4 somnolence constipation, or peripheral neuropathy was less than 10% in the two groups & rarely resulted in dose reduction. The proportion of patients who required more than one dose reduction or interruption of lenalidomide or dexamethasone was similar in the two groups. The mean time until the first dose reduction or interruption of a study drug was also similar in the two groups (125 days in the lenalidomide group and 128 days in

the placebo group). Dose reduction or interruption because of adverse events was more common in the lenalidomide group (occurring in 76.1 % of the patients) than in the placebo group (56.9%, P<0.001). The primary reason for the discontinuation of treatment in the two groups was disease progression; 31 patients in the two groups (8.8%) discontinued treatment early because of adverse events.

60 % of patients in the lenalidomide group achieved significant response compared to 24% in the placebo arm; complete- 15.9% vs 3.4%. Time to achieve CR or near CR was 5.1 months compared to 6.9 months and time to progression was 11.3 months in the lenalidomide arm compared to 4.7 months in the placebo arm, p<.001.

#### COMMENTS:

Thalidomide, an immunomodulatory drug was introduced in 1999 for the treatment of relapsed and refractory myeloma. Singhal et al were the first one to report its significant activity in relapsed and refractory disease.<sup>5</sup> Similar observations in subsequent studies<sup>6</sup> resulted in its use as first line treatment along with dexamethasone both for younger and elderly patients. Treatment with thalidomide is associated with sedation, constipation, skin rash, and peripheral neuropathy in about 50 % patients. Thrombo-embolism occurs in about 7 % patients without anti-thrombotic prophylaxis. These toxic effects often require dose reduction and, in some instances, discontinuation of the drug<sup>1</sup>. Lenalidomide, a derivative of thalidomide, is less toxic and more potent than the parent drug. In patients with relapsed or refractory multiple myeloma, lenalidomide can overcome resistance not only to conventional chemotherapy but also to thalidomide, and dexamethasone plus lenalidomide is more effective than either agent alone in refractory multiple myeloma.<sup>7</sup> Apart from myeloma, drug has also shown promising activity in patients with myelodysplastic syndrome; patients with 5q deletion are uniquely sensitive to this drug.

Present study has demonstrated significant responses in myeloma patients who have received one previous therapy including thalidomide. Time to progression and median

overall survival was also significantly longer in lenalidomide arm compared to placebo arm. These results have been echoed by another study by Weber et al from North America<sup>7</sup> published in the same issue of the journal. Table -1 gives comparison of both these studies. Efficacy of lenalidomide was also seen in previously treated patients with thalidomide, bortezomib and patients undergone SCT.

As regards to toxicity, there was lower incidence of constipation, sedation, peripheral neuropathy with lenalidomide, while significantly higher hematological toxicity (grade III-IV neutropenia and thrombocytopenia). There was also increased incidence of thromboembolic episodes (both deep vein thrombosis and pulmonary embolism) compared to placebo arm.

Lenalidomide plus dexamethasone has also shown activity in newly diagnosed myeloma patients . One recent phase 3 randomized trial compared lenalidomide plus low dose dexamethasone versus lenalidomide plus high dose dexamethasone, showing significantly lower adverse events in low dose dexamethasone arm.<sup>8</sup> Thus, the results of these two trials in relapsed/refractory myeloma patients have confirmed that lenalidomide is effective in relapsed and refractory myeloma, including patients pre-treated with thalidomide. Based on these results Lenalidomide plus dexamethasone has been approved by Food and Drug Administration (USA) for the treatment of relapsed multiple myeloma. Relatively less side effects of lenalidomide, call for its use in front line

**Table-1 : Lenalidomide + dexamethasone in Multiple Myeloma :**

Characteristic	Dimopoulos et al (2)		Weber et al(8)	
	Lenalidomide + Dexa	Placebo + Dexa	Lenalidomide + Dexa	Placebo + Dexa
No of patients	176	175	177	176
Complete response	15.9%	3.4%	14.1%	0.6% ,p<.001
CR +PR	60.2%	24%, p<.001	61%	19.9%,p<.001
Time to progression	11.3 mm	4.7, p<001	11.1 mm	4.7,p<.001
Median overall survival	Not reached	20.6 , p<.04	29.6	20.2,p<.001
<b>Toxicity</b>				
Gr III-IV Neutropenia	29.5%	2.3%	41.2%	4.6%,p<.001
Gr III Thrombocytopenia	11.4%	5.7%		
Infections	3.4%	none		
Thrombo-embolic episodes	11.4%	4.6%	14.7%	3.4%,p=.14

Dexa - dexamethasone, CR - complete response, PR - Partial response, mon - months

treatment of myeloma. Toxicity to lenalidomide and dexamethasone combination is likely to be reduced further with use of low dose dexamethasone.<sup>9</sup> Whether to use thalidomide plus dexamethasone (current standard) or lenalidomide plus low dose dexamethasone as upfront treatment for myeloma is likely to be answered in future studies.

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**Deepak Dabkara & Jyoti Bajpai**

Department of Medical Oncology  
Institute Rotary Cancer Hospital  
All India Institute of Medical Sciences  
New Delhi 110029  
E mail : deepakdabkara@yahoo.com

