

# Thalidomide and Dexamethasone: A New Standard of Care for Initial Therapy in Multiple Myeloma

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In this issue of the *Journal of Clinical Oncology*, Rajkumar et al report on the results of a randomized phase III clinical trial of thalidomide plus dexamethasone compared to high-dose dexamethasone alone in newly diagnosed multiple myeloma.<sup>1</sup> In this study, coordinated by the Eastern Cooperative Oncology Group, 207 patients were randomly assigned to either thalidomide plus dexamethasone or high-dose dexamethasone alone. Response rate, the primary end point, was significantly higher with thalidomide plus dexamethasone than single-agent high-dose dexamethasone (63% v 41%, respectively,  $P = .002$ ); however, this benefit was associated with important toxicities, including deep vein thrombosis (DVT) and treatment-related mortality, which were 5% and 4%, respectively.<sup>1</sup>

For many years, the combination of melphalan and prednisone has been standard therapy for multiple myeloma with response rates of approximately 50% and a median survival of about 3 years.<sup>2</sup> The advent of high-dose therapy and autologous peripheral blood stem cell transplantation as an effective treatment modality for younger multiple myeloma patients necessitated the development of initial therapy, that minimized alkylator exposure to facilitate successful stem cell collection.<sup>3,4</sup> The combination of vincristine, doxorubicin, and dexamethasone (VAD) was typically used for a number of years as a pretransplant induction therapy for such patients.<sup>5</sup> Despite significant activity, however, VAD administration is associated with disadvantages including treatment-emergent neuropathy, cardiac toxicity, alopecia, mucositis, neutropenia, as well as the necessity for central line placement to allow for continuous infusion of anthracycline, with its attendant risk of catheter-related infection and thrombosis. Furthermore, the high-dose dexamethasone in this regimen is largely responsible for its activity; as a result, high-dose dexamethasone as an oral therapy has gained considerable popularity as a more convenient alternative.<sup>6</sup>

Thalidomide, a first in-class immunomodulatory orally bioavailable drug, was found to have significant single agent activity in relapsed refractory multiple myeloma.<sup>7</sup> Extensive preclinical studies elucidated several novel biologic mechanisms of action: direct pro-apoptotic effects and G1 growth arrest of multiple myeloma cells; down-regulation of binding of multiple myeloma cells to bone marrow stromal cells (BMSCs), which confers cell adhesion-mediated drug resistance (CAM-DR); and inhibition of multiple myeloma growth factors including IL-6, TNF $\alpha$ , and vascular endothelial growth factor (VEGF).<sup>8,9</sup> Antiangiogenic effects, medi-

ated via inhibition of VEGF and beta fibroblast growth factor (FGF), are also an important component of its activity in multiple myeloma.<sup>10</sup> Especially noteworthy are its immunomodulatory effects, evidenced by upregulation of natural-killer cells through the release of interferon gamma and IL-2, in both preclinical studies and in patients on clinical protocols.<sup>11,12</sup> Importantly, thalidomide and dexamethasone are synergistic in vitro and have impressive clinical activity in relapsed refractory multiple myeloma patients, even in patients in whom either agent alone has failed.<sup>9,13</sup> Moreover, three phase II clinical trials have demonstrated response rates ranging from 65% to 70% with manageable toxicities from combined therapy, although DVT, including pulmonary embolism, occurred in 15% of patients.<sup>14-16</sup>

When this Eastern Cooperative Oncology Group study was initiated, the need for DVT prophylaxis for this combination had not been established and it was therefore not administered. Given the high rates of DVT and pulmonary embolism seen in this study and in others, it is now recommended that DVT prophylaxis should be used in all patients starting therapy with thalidomide plus dexamethasone. Prophylactic doses of low molecular weight heparin, full-dose anticoagulation with oral warfarin, and aspirin at doses from 81 mg to 325 mg per day have all been effective.

In this randomized comparison, the addition of thalidomide to high-dose dexamethasone did not compromise the ability to harvest autologous peripheral blood stem cells, supporting its use as an appropriate induction regimen in stem cell candidates. However, the treatment-related mortality rates in both arms highlight limitations of this approach due, at least in part, to high-dose dexamethasone. Therefore, strategies aimed at decreasing toxicity by reducing the dose-intensity of dexamethasone would seem rational. The authors recommend initial single-agent high-dose dexamethasone, with the addition of thalidomide later in lower risk patients, as an alternate approach, with the combined therapy reserved for those patients with advanced disease and high risk features at presentation.

A recent retrospective analysis compared thalidomide and dexamethasone to VAD as induction therapy before high-dose therapy and autologous stem cell transplantation.<sup>17</sup> Thalidomide and dexamethasone resulted in both a significantly higher response rate (76% v 52%, respectively) and a greater reduction in monoclonal proteins. Toxicities included 15% DVT with thalidomide and dexamethasone and 12% granulocytopenia with VAD. As observed in the

current study, stem cell collection was successful in both groups. This analysis complements the current study in establishing thalidomide and dexamethasone as an effective and relatively well-tolerated alternative front-line therapy for multiple myeloma.<sup>17</sup>

Long-term outcome after thalidomide and dexamethasone is not possible to ascertain in the current study, since the trial was intended to examine this regimen as a pretransplant induction therapy. Nonetheless, a subset analysis in 24 patients not proceeding to transplant shows an encouraging median progression-free survival of 19 months.<sup>18</sup> Ongoing, larger multicenter studies will provide more information on progression-free survival and overall survival post-thalidomide and dexamethasone.

While thalidomide and dexamethasone have become a standard combination therapy as an oral alternative to intravenous induction regimens for newly diagnosed multiple myeloma, the opportunity afforded by lenalidomide, a potent analog of thalidomide with a more favorable safety profile, is considerable.<sup>19-21</sup> This is reflected in the upfront setting by encouraging results from a recent phase II clinical trial, also led by Vincent Rajkumar.<sup>22</sup> Response rates were remarkably high in this study at 90% and no treatment-related deaths were reported. However, significant toxicities were encountered in approximately one third of patients, again due to the high-dose dexamethasone. Large phase III trials are therefore now ongoing to investigate the role of lenalidomide plus either low-dose or high-dose dexamethasone in newly diagnosed multiple myeloma. In this respect, the impact of bortezomib in the upfront setting is also of considerable interest, and a series of phase II trials of bortezomib-based induction therapies have shown considerable promise with response rates ranging from 67% to 94% and with manageable toxicity.<sup>23-25</sup> Intriguingly, an ongoing phase I trial of the combination of lenalidomide and bortezomib has shown promising activity and a favorable adverse effect profile, providing a strong rationale for combining lenalidomide, bortezomib, and lower doses of dexamethasone in an attempt to enhance cytotoxicity and decrease toxicity of multiple myeloma induction therapy.<sup>26</sup>

In conclusion, this important randomized phase III trial of thalidomide and dexamethasone represents a major advance and confirms the impact of novel biologically derived therapies in the management of newly diagnosed multiple myeloma.

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## REFERENCES

- Rajkumar SV, Blood E, Vesole D, et al: A randomized phase III clinical trial of thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 24:10.1200/JCO.2005.03.0221
- Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. *J Clin Oncol* 16:3832-3842, 1998
- Attal M, Harousseau JL, Stoppa AM, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 335:91-97, 1996
- Child JA, Morgan GJ, Davies FE, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 348:1875-1883, 2003
- Alexanian R, Barlogie B, Tucker S: VAD-based regimens as primary treatment for multiple myeloma. *Am J Hematol* 33:86-89, 1990
- Alexanian R, Dimopoulos MA, Delasalle K, et al: Primary dexamethasone treatment of multiple myeloma. *Blood* 80:887-890, 1992
- Singhal S, Mehta J, Desikan R, et al: Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 341:1565-1571, 1999
- Hideshima T, Anderson KC: Molecular mechanisms of novel therapeutic approaches for multiple myeloma. *Nat Rev Cancer* 2:927-937, 2002
- Hideshima T, Chauhan D, Shima Y, et al: Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 96:2943-2950, 2000
- Gupta D, Treon SP, Shima Y, et al: Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: Therapeutic applications. *Leukemia* 15:1950-1961, 2001
- Davies FE, Raju N, Hideshima T, et al: Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 98:210-216, 2001
- Lentzsch S, LeBlanc R, Podar K, et al: Immunomodulatory derivatives of thalidomide inhibit growth of B-cell hematologic malignancies and angiogenesis *in vivo*. *Leukemia* 17:41-44, 2003
- Weber DM, Gavino M, Delasalle K, et al: Thalidomide alone or with dexamethasone for multiple myeloma. *Blood* 94:604a, 1999 (suppl 1; abstr 2686)
- Rajkumar SV, Hayman S, Gertz MA, et al: Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 20:4319-4323, 2002
- Weber D, Rankin K, Gavino M, et al: Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol* 21:16-19, 2003
- Cavo M, Zamagni E, Tosi P, et al: Combined thalidomide-dexamethasone as first line therapy for newly diagnosed multiple myeloma. *Hematol J* 4:S244, 2003 (suppl 1)
- Cavo M, Zamagni E, Tosi P, et al: Superiority of thalidomide and dexamethasone over vincristine-doxorubicin dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. *Blood* 106:35-39, 2005
- Rajkumar SV, Dingli D, Nowakowski G, et al: Thalidomide and dexamethasone in newly diagnosed multiple myeloma: Long term results in patients not undergoing autologous stem cell transplant. *J Clin Oncol* 23:5935, 2005 (abstr 6632)
- Richardson PG, Schlossman RL, Weller E, et al: Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* 100:3063-3067, 2002
- Zangari M, Tricot G, Zeldis J, et al: Results of a phase I study of CC-5013 for the treatment of multiple myeloma patients who relapse after high dose chemotherapy. *Blood* 98:775a, 2001 (abstr 3226)
- Richardson P, Jagannath S, Schlossman R, et al: A multicenter, randomized phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (dexamethasone) for the treatment of relapsed or relapsed refractory multiple myeloma. *Blood* 102:235a, 2003 (abstr 825)
- Rajkumar SV, Hayman SR, Lacy MQ, et al: Combination therapy with CC-5013 (lenalidomide; Revlimid (TM)) plus dexamethasone (Rev/Dexamethasone) for newly diagnosed myeloma. *Blood* 104:98a, 2004 (abstr 331)
- Jagannath S, Durie B, Wolf J, et al: Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. *Br J Haematol* 129:776-783, 2005
- Oakervee HE, Popat R, Curry N, et al: PAD combination therapy (PS-341, doxorubicin and dexamethasone) for untreated multiple myeloma. *Br J Haematol* 129:755-762, 2005
- Harousseau JL, Attal M, Leleu X, et al: Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: Results of an IFM phase II study. *J Clin Oncol* 23, 2005 (abstr 6653)
- Richardson PG, Schlossman R, Munshi N, et al: A phase I study of the safety and efficacy of lenalidomide and bortezomib in relapsed and refractory multiple myeloma: The RevVel study. *Haematologica* 90:26, 2005 (suppl 1, abstr PL5.04)

**Authors' Disclosures of Potential Conflicts of Interest**

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