



## ASH evidence-based guidelines: what is the role of maintenance therapy in the treatment of multiple myeloma?

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**A 51-year-old male was diagnosed with an IgA multiple myeloma (MM) after having back pain for several months. His bone marrow showed 30% involvement with plasma cells and his cytogenetics showed t(4:14). His  $\beta$ 2-microglobulin was 6.5 mg/dL at diagnosis and he had multiple lytic lesions, along with a creatinine of 2.3 mg/dL and significant anemia. Induction therapy with lenalidomide, bortezomib and dexamethasone was used, and he was able to achieve complete remission after 4 cycles of therapy. He then went on to receive high-dose chemotherapy with a single autologous stem cell transplant. He tolerated it well and now comes to discuss follow-up treatment plans. He wants to discuss maintenance therapy.**

**D**espite recent advances in its care, MM remains an incurable disease, although an operational cure may be achieved in some patients. Even with modern induction regimens and stem cell transplantation relapse will usually occur within 3 to 5 years, suggesting that effective maintenance therapy is needed to control or delay disease progression.<sup>1</sup> Studies in the relapsed or refractory setting, which use thalidomide, bortezomib and lenalidomide and continue therapy until progression, have shown high responses with long duration.<sup>2-4</sup> Despite these positive results, maintenance therapy post-induction has not been extensively studied. For this article, we performed a Medline search for all the clinical trials that included maintenance therapy in multiple myeloma using the terms “maintenance therapy, myeloma, and clinical trials.” We also reviewed recent abstracts accepted in the American Society of Hematology and the American Society of Clinical Oncology. A total of 218 manuscripts were identified. Review articles were excluded and original clinical trials were included as shown below (**Table 1**).

Mandelli et al performed the first trials of maintenance therapy. They studied the role of interferon-alpha 2b in MM.<sup>5</sup> Interferon significantly improved the response duration (26 vs 14 months) with no significant improvement in overall survival (OS; 52 vs 39 months).<sup>5</sup> However, follow-up studies failed to confirm these results.<sup>6,7</sup> A meta-analysis on the use of interferon, both as maintenance and as part of the induction therapy, showed that progression-

free survival (PFS) and response duration were improved compared with no maintenance; conversely, patients who received interferon as maintenance therapy had decreased OS ( $P = .007$ ).<sup>8</sup>

Based on the observation that MM is often responsive to steroids, a randomized trial (Southwest Oncology Group [SWOG] No. 9210) evaluated the benefit of prednisone maintenance therapy in 125 patients.<sup>9</sup> Patients who received high-dose steroids had significantly longer PFS (14 vs 5 months) and OS (37 vs 26 months). However, given the small sample size and the long-term toxicities observed with steroids, this maintenance regimen has not been widely adopted. Phase 3 studies of steroids in conjunction with thalidomide are ongoing. When used alone prednisolone alternate-day therapy was inferior to prednisolone and thalidomide.<sup>10</sup>

Thalidomide has been considered for maintenance. The randomized phase III French Myeloma Intergroup (IFM-99 02) trial assessed the impact of thalidomide maintenance on duration of response post-stem cell transplantation in 780 patients.<sup>11</sup> At a 29-month median follow-up from randomization (2 months after the second transplant), patients randomized to thalidomide (Arm 3) demonstrated improvement in event-free survival (EFS) compared with those patients randomized to no treatment (Arm 1) or to pamidronate alone (Arm 2) (52% in Arm 3 vs 36% in Arm 1 and 37% in Arm 2;  $P = .002$ ). In addition, there was a

**Table 1. Summary of agents and grade of recommendation.**

Agent	Study	Results	Recommendation	Level of evidence
Interferon	Mandelli et al <sup>5</sup>	PFS and response duration were improved; but interferon decreased OS	Not recommended	Grade 2A
Prednisolone	SWOG study <sup>9</sup> Spencer et al <sup>10</sup>	High toxicity Thalidomide was superior	Recommended, but not used widely because of toxicity concerns.	Grade 2A
Thalidomide	IFM-99 02 <sup>11</sup>	3 randomized studies showing benefit to thalidomide in PFS	Recommended but not used widely because of toxicity concerns.	Grade 2A
Lenalidomide	Ongoing studies	No data	Not recommended until data matures and results are available	Grade 1C
Bortezomib	HOVON <sup>14</sup> Ongoing studies by Richardson et al and Kumar et al	Bortezomib had superior response and PFS in the PAD arm compared to thalidomide in the VAD arm.	Not widely used until data from ongoing studies are available	Grade 1B

PFS indicates progression-free survival; OS, overall survival; PAD, bortezomib, adriamycin, dexamethasone ; VAD, vincristine, adriamycin, dexamethasone

substantial improvement in OS for the patients randomized to receive maintenance thalidomide compared with the other two arms (87% in Arm 3 vs 77% in Arm 1 and 74% in Arm 2;  $P = .04$ ).<sup>11</sup> Patients who had at least a very good partial response did not benefit from thalidomide ( $P = .4$ ).<sup>11</sup> Barlogie et al randomized patients to thalidomide or no thalidomide during induction therapy and as maintenance in combination with dexamethasone and interferon following tandem transplants.<sup>12,13</sup> When initially reported with a median follow-up of 42 months, complete response rate and EFS were superior among the 323 patients randomized to thalidomide, whereas OS was indistinguishable from that of the 345 patients treated on the control arm. With further follow-up of 72 months, a trend to increased OS with thalidomide was seen. In a post-hoc, subgroup analysis, thalidomide reduced the hazard of death by 41% among patients with abnormal cytogenetics ( $P = .008$ ).<sup>13</sup> Spencer et al randomized 269 patients post-autologous stem cell transplantation to receive indefinite prednisolone maintenance therapy (control group) and 114 to receive the same in addition to 12 months of thalidomide consolidation (thalidomide group).<sup>10</sup> After a median follow-up of 3 years, the post-randomization 3-year PFS rates were 23% and 42% ( $P < .001$ ) and the OS rates were 75% and 86% ( $P = .004$ ), respectively. Thus, three separate phase III studies found thalidomide maintenance to improve OS. Despite these findings thalidomide is not being widely used for maintenance, presumably reflecting concerns about cumulative toxicity. Lenalidomide may offer the same advantages with less toxicity, and large randomized trials are now addressing its role both after melphalan in the post-transplantation setting and in the management of more elderly patients.

Bortezomib has been used in maintenance therapy following stem cell transplantation in a large phase III randomized study.<sup>14</sup> This study randomized patients to vincristine, adriamycin and dexamethasone (VAD) or bortezomib, adriamycin and dexamethasone (PAD), with maintenance using thalidomide (50 mg/daily) in the VAD arm, or bortezomib twice a month in the PAD arm post-stem cell transplantation. The response rates were significantly higher on the PAD arm. Current studies using weekly bortezomib maintenance therapy after 8 cycles of therapy, such as in the phase I/II trial of bortezomib, lenalidomide and dexamethasone study conducted by Richardson et al and the phase I/II study of bortezomib, lenalidomide, cyclophosphamide and dexamethasone conducted by Kumar et al, will help delineate the role of bortezomib in maintenance therapy.

The 51-year-old patient looking for advice regarding maintenance therapy had high-risk disease but was already in a complete remission; thus, thalidomide is of unknown utility. The available data suggest that patients may benefit from this approach with higher response rates and improved PFS and, in some studies, OS. The patient elected to participate in a cooperative group post-stem cell transplantation trial comparing low-dose lenalidomide with placebo. Based on our review, we recommend the use of maintenance thalidomide for patients who are not in a complete remission after induction therapy. However, due to concerns about the toxicity of thalidomide, further clinical trials using alternative novel therapeutic agents such as lenalidomide and bortezomib should be explored to better define the efficacy, toxicity and quality of life during maintenance therapy in patients with MM.

## Disclosures

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## References

1. Rotta M, Storer BE, Sahebi F, et al. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. *Blood*. 2009;113:3383-3391.
2. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352:2487-2498.
3. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2133-2142.
4. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.
5. Mandelli F, Avvisati G, Amadori S, et al. Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med*. 1990;322:1430-1434.
6. Salmon SE, Crowley JJ, Grogan TM, Finley P, Pugh RP, Barlogie B. Combination chemotherapy, glucocorticoids, and interferon alfa in the treatment of multiple myeloma: a Southwest Oncology Group study. *J Clin Oncol*. 1994;12:2405-2414.
7. Blade J, San Miguel JF, Escudero ML, et al. Maintenance treatment with interferon alpha-2b in multiple myeloma: a prospective randomized study from PETHEMA (Program for the Study and Treatment of Hematological Malignancies, Spanish Society of Hematology). *Leukemia*. 1998;12:1144-1148.
8. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Ann Oncol*. 2000;11:1427-1436.
9. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood*. 2002;99:3163-3168.
10. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol*. 2009;27:1788-1793.
11. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.
12. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354:1021-1030.
13. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood*. 2008;112:3115-3121.
14. Sonneveld P, van der Holt B, Schmidt-Wolf GH, et al. First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycin, dexamethasone (PAD) Vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM) [abstract]. *Blood*. 2008;653.