The Role of Maintenance Therapy in the Treatment of Multiple Myeloma

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Key Words

Autologous stem cell transplantation, interferon, thalidomide, bortezomib, lenalidomide

Abstract

Maintenance therapy in multiple myeloma has been under investigation for more than 3 decades, without evidence of clear benefit until recently. Chemotherapy maintenance offers no benefit after conventional or high-dose treatment. Interferon-based maintenance is associated with minimal improvements in clinical outcomes, but is poorly tolerated. Results of corticosteroid maintenance studies have been conflicting; at least one randomized trial showed improved survival with prednisone maintenance after conventional chemotherapy. The role of the novel agents thalidomide, lenalidomide, and bortezomib as maintenance is emerging. Most reported maintenance studies have evaluated thalidomide, alone or in combination with a corticosteroid. Several of these studies suggest that thalidomide-based maintenance prolongs overall survival after autologous stem cell transplantation. Important questions that have not yet been resolved include the optimal dose and duration of thalidomide, whether clinical benefit depends on response to induction therapy and risk for relapse, and whether reported benefits are caused by cytoreduction or eradication of minimal residual disease, especially with bortezomib maintenance. Ongoing randomized trials are evaluating lenalidomide and bortezomib maintenance therapies to better define the role of these drugs as maintenance in multiple myeloma. (*JNCCN* 2010;8[Suppl 1]:S21–S27)

Maintenance therapy in multiple myeloma (MM) comprises any therapy given “following completion of induction treatment in responding or nonprogressing patients, with the goal of prolonging survival.”¹ However,

er, maintenance therapy practice patterns vary considerably because of conflicting data about its effectiveness. Currently, NCCN recommends thalidomide (category 1 recommendation) with or without prednisone (category 2B) for maintenance therapy; the roles of interferon and corticosteroids are less clear (category 2B).² This article summarizes the results of many clinical trials that have been designed to evaluate maintenance after conventional chemotherapy and high-dose therapy and identifies areas of current controversy in an effort to understand the role of maintenance therapy in managing patients with newly diagnosed MM.

Maintenance After Conventional Chemotherapy

Because of the increased risk for acute myeloid leukemia with prolonged alkylating agent therapy, alternatives to this approach were being sought as early as the 1980s. Interferon-alpha was the subject of numerous trials that produced inconclusive results. Two meta-analyses, one performed using individual patient data and the other using published data, found a small but statistically significant survival benefit when interferon maintenance was used after conventional therapy.^{3,4} However, few patients can tolerate the substantial toxicities of interferon therapy, and therefore interferon maintenance is rarely used.

Several studies have evaluated corticosteroids, with or without interferon, as maintenance, but the data are insufficient to draw firm conclusions. When compared directly with interferon maintenance, dexamethasone, 20 mg/m², given orally on days 1 to 4 of a 28-day cycle produced a similar median duration of remission, but significantly fewer patients treated with dexamethasone maintenance responded to repeat melphalan/dexamethasone at relapse relative to those treated with in-

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terferon maintenance (44% vs. 82%; $P = .001$).⁵ In the MY.7 study by the National Cancer Institute of Canada (NCIC), dexamethasone maintenance improved median progression-free survival (PFS) based on a hazard ratio (HR) of 0.61 (95% CI, 0.47–0.79), but not overall survival (OS; HR, 0.88; 95% CI, 0.65–1.18), relative to no maintenance.⁶ Similarly, when added to interferon, thrice-weekly prednisone, 50 mg, improved median PFS but not overall survival (OS), relative to interferon alone in the SWOG 9028 trial.⁷

Only one trial, SWOG 9210, has shown a survival benefit with corticosteroid maintenance therapy.⁸ In this randomized trial, a prednisone regimen of 50 mg every other day significantly improved median PFS (14 vs. 5 months; $P = .003$) and OS (37 vs. 26 months; $P = .05$) relative to a physiologic dose regimen (10 mg every other day). These data support the use of steroids in this setting, although the efficacy of the SWOG 9210 regimen has not been confirmed in another controlled clinical trial.

Recently, several trials have focused on the role of novel agents as maintenance therapy. Offidani et al.⁹ conducted a randomized comparison of maintenance with either thalidomide (100 mg/d) plus dexamethasone (20 mg/d for 4 days per month) or interferon thrice weekly plus dexamethasone in 103 patients who experienced response to induction therapy with ThaDD (thalidomide, dexamethasone, and pegylated liposomal doxorubicin). Both 2-year PFS and OS rates were significantly better with thalidomide-based maintenance (PFS, 63% vs. 32%; $P = .024$; OS, 84% vs. 68%; $P = .030$). The low-dose thalidomide regimen was generally well-tolerated, with peripheral neuropathy (6%) and constipation (4%) the most commonly reported grade 3/4 toxicities. More patients were compliant with thalidomide therapy long-term relative to interferon.

Preliminary data have been reported for maintenance therapy in elderly patients who experienced stable disease or better with thalidomide/dexamethasone or melphalan/prednisone induction.¹⁰ A total of 111 patients with nonprogressive disease were randomized to maintenance with thalidomide, 100 mg daily, with thrice-weekly interferon or interferon alone. At a median follow-up of 17.2 months, median survival from the start of maintenance was 53.1 months in the thalidomide/interferon arm and not yet reached in the interferon-alone arm ($P = .49$).

Data on bortezomib-based maintenance strategies are beginning to emerge. A randomized phase III trial conducted by the Italian Multiple Myeloma Group is comparing bortezomib/melphalan/prednisone/thalidomide (VMPT) induction followed by bortezomib/thalidomide maintenance to bortezomib/melphalan/prednisone (VMP) induction without maintenance in elderly patients with newly diagnosed myeloma.¹¹ Results presented at the 2008 American Society of Hematology Annual Meeting showed a higher response rate for VMPT relative to VMP (complete response [CR] rate, 31% vs. 16%; $P = .003$; very good partial response [VGPR] rate, 55% vs. 42%; $P = .02$) but no difference in OS at 3 years.

Maintenance After Autologous Stem Cell Transplantation

Chemotherapy and Interferon Maintenance After Autologous Stem Cell Transplantation

As with conventional induction regimens, chemotherapy is not currently recommended as a maintenance strategy after autologous stem cell transplantation (ASCT).² Interferon is currently considered a maintenance option in the NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org), based on low-level evidence and non-uniform NCCN consensus (category 2B).² However, given the lack of clear activity and substantial toxicity associated with interferon and the availability of new agents, research into interferon maintenance has been largely abandoned.

Novel Agents After ASCT

Thalidomide is the best studied of the novel agents in the post-ASCT maintenance setting, although randomized clinical trials of bortezomib and lenalidomide are underway (Table 1).¹² Four randomized phase III trials have been completed to establish the role of thalidomide-based maintenance after ASCT (Table 2).^{13–16} In all 4 studies, improvements in response (CR) and PFS were seen. Of the 4 trials, 3 also reported significant improvements in OS, and a meta-analysis of these data showed a trend toward improved survival with maintenance thalidomide after ASCT (Figure 1).¹⁷ When the trial that in-

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Table 1 Ongoing Randomized Phase III Trials of Maintenance Therapy After ASCT in Patients With Newly Diagnosed Multiple Myeloma

Clinical Trial and Accrual Goal	Primary Treatment	Maintenance Regimen(s)	Primary End Point
NCIC MY.10 (N = 324) [NCT00049673]	ASCT	<ul style="list-style-type: none"> • Thalidomide daily with alternate-day prednisone • Observation Maintenance × 4 y	OS
NHLBI/ BMTCTN0102 (N = 710) [NCT00075829]	Tandem transplantation (no HLA-matched sibling) or ASCT followed by mini-allogeneic SCT (HLA-matched sibling)	<ul style="list-style-type: none"> • Thalidomide/dexamethasone • Observation Maintenance × 1 y; only administered to patients undergoing tandem transplantation	3-y PFS
CALGB 100104 (N = 462) [NCT00114101]	ASCT	<ul style="list-style-type: none"> • Lenalidomide • Placebo Maintenance continues as tolerated or until progression; only administered to patients with stable or responding disease after ASCT	TTP
IFM 2005-02 (N = 614) [NCT00430365]	ASCT	<ul style="list-style-type: none"> • Lenalidomide • Placebo Duration not specified	Duration of post-ASCT response
Gesellschaft für Medizinische Innovation (N = 194) [NCT00891384]	ASCT Consolidation: lenalidomide, 25 mg, days 1–21 q4w × 6	<ul style="list-style-type: none"> • Lenalidomide, 5 mg, days 1–21 q4w • Lenalidomide, 25 mg/d, days 1–21 q4w Maintenance continues until disease progression	EFS
HOVON-65/GMMG-HD4 (N = 825) ¹²	Induction: VAD vs. PAD Stem cell collection: CAD ASCT: HDM	<ul style="list-style-type: none"> • Thalidomide 50 mg/d • Bortezomib 1.3 mg/m² q2w Maintenance × 2 y	PFS
PETHEMA GEM05 (N = 390) [NCT00461747]	Induction: VBMCP-VBAD-bortezomib vs. TD vs. VTD followed by ASCT	<ul style="list-style-type: none"> • Interferon • Thalidomide • Thalidomide plus bortezomib Maintenance × 3 y	Not stated

Abbreviations: ASCT, autologous stem cell transplantation; CAD, cyclophosphamide/doxorubicin/dexamethasone; EFS, event-free survival; HDM, high-dose melphalan; HLA, histocompatibility leukocyte antigen; OS, overall survival; PAD, bortezomib/doxorubicin/dexamethasone; PFS, progression-free survival; SCT, stem cell transplantation; TD, thalidomide/dexamethasone; TTP, time-to-progression; VAD, vincristine/doxorubicin/dexamethasone; VBMCP-VBAD, vincristine/carmustine/melphalan/cyclophosphamide/prednisone alternating with vincristine/carmustine/doxorubicin/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

cluded thalidomide during induction was excluded, the OS benefit became significant (HR, 0.49; 95% CI, 0.32–0.74).¹⁷ Peripheral neuropathy complicated the treatment course in all 4 studies, and, unsurprisingly, the incidence was highest when the duration of thalidomide maintenance was prolonged. None of the studies, however, determined the optimal dose or duration of thalidomide-based maintenance after ASCT.

A recent update to one of the trials, conducted at a median follow-up of 6 years, suggests that thalidomide may benefit patients with high-risk myeloma.¹⁸ The estimated OS rate at 5 years was 56% for patients with cytogenetic abnormalities treated with thalidomide versus 43% for those with cytogenetic

abnormalities in the control group ($P = .02$).

Results from other randomized trials of thalidomide maintenance were presented at national meetings within the past year, none of which supports an improvement in OS. The United Kingdom Medical Research Council (MRC) Myeloma IX study evaluated thalidomide maintenance after primary treatment of myeloma (either ASCT or conventional chemotherapy, depending on the clinical situation).¹⁹ A total of 820 patients were randomly assigned to thalidomide maintenance (100 mg/d until relapse) or no maintenance, making this the largest trial conducted. Overall, PFS was numerically higher in the thalidomide arm, but the improvement was statistically significant only among patients who ex-

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Figure 1 Overall survival with maintenance thalidomide. (A) All trials. (B) Excluding Barlogie 2006.

Abbreviations: HR, hazard ratio; OS, overall survival; SE, standard error.

Adapted from Hicks LK, Haynes AE, Reece DE, et al. A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma. *Cancer Treat Rev* 2008;34:442–452, with permission from Elsevier.

perienced less than a VGPR with induction therapy (HR, 1.9; $P = .007$). OS was not significantly improved in any subgroup. Moreover, subgroup analyses showed that patients with 17p deletions had a significantly worse OS when treated with thalidomide maintenance (HR, 4.55; $P = .02$), leading the researchers to conclude that 17p deletion is a contraindication to thalidomide maintenance.

Two small studies presented at the XII International Myeloma Workshop in 2009 showed significant improvements in PFS, but not OS, with thalidomide-based maintenance. Mounier et al.²⁰ compared an intermittent dexamethasone/thalidomide maintenance regimen with no maintenance after ASCT in 108 patients and observed median event-free survival of 32 versus 17 months, respectively ($P = .02$). Maiolino et al.²¹ compared dexamethasone maintenance with dexamethasone plus thalidomide, 200 mg daily, after ASCT in 212 patients. Thalidomide significantly reduced the risk for progression relative to dexamethasone alone (HR, 2.43; $P = .03$), but OS was similar in the 2 arms (65% vs. 74% with dexamethasone and dexamethasone/thalidomide, respectively).

Therefore, although data support a role for thalidomide-based maintenance therapy after ASCT, several important questions remain, such as whether thalidomide given post-transplantation truly maintains response versus early initiation of

salvage therapy. Two large studies have reported that the survival benefits with thalidomide were limited to patients who did not experience at least a VGPR, supporting the hypothesis that post-transplantation thalidomide provides additional cytoreduction rather than eradication or suppression of minimal residual disease. Currently, however, initial response to therapy should not be used to guide maintenance treatment decisions.

Furthermore, the optimal dose and duration of maintenance thalidomide remains to be determined. The incidence of neuropathy is clearly cumulative and dose-related, partly leading to the recommendation that thalidomide not be used throughout the entire treatment course. Doses of 200 mg daily or more are difficult to administer on a long-term basis.^{22,23} Lower-dose (100 mg/d) and time-limited therapy (6–12 months) were efficacious in studies by the Tunisian Multiple Myeloma Study Group (TMMSG) and Australasian Leukaemia and Lymphoma Group (ALLG), but the United Kingdom MRC Myeloma IX study did not show a survival benefit with a 100-mg daily thalidomide maintenance regimen.

Another intriguing issue is whether patients who begin maintenance treatment with less than a VGPR should discontinue therapy once they experience VGPR or CR, given that those with VGPR/CR before maintenance therapy did not seem to benefit from additional therapy in some trials. The NCCN

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Table 2 Published Randomized Trials of Thalidomide-based Maintenance Therapy After ASCT

Study	Regimens	Thalidomide Regimen	Efficacy	Safety
TT2 ¹³ Newly diagnosed progressive or symptomatic MM, ≤ 75 y (N = 668)	Induction: 4 cycles of chemotherapy, with or without thalidomide ASCT: tandem transplantation with melphalan-based preparative regimens, with or without thalidomide Consolidation: randomized to 1 of 3 regimens, with or without thalidomide Maintenance: IFN tid; with or without thalidomide; cycles of dexamethasone, 40 mg, given on days 1–4, 9–12, 17–20 q3mo for 4 cycles, first year only	Induction: 400 mg/d ASCT: 100 mg/d, initiated after platelet recovery Consolidation: 200 mg/d Maintenance: 100 mg/d for the first year and 50 mg/d thereafter	Thalidomide vs. observation: CR: 62% vs. 43%; $P < .001$ 5-y EFS: 56% vs. 44%; $P = .01$ MST after relapse: 1.1 vs. 2.7 y; $P = .001$	> Grade 2 AEs, thalidomide vs. observation: Thromboembolism: 30% vs. 17%; $P < .001$ PN: 27% vs. 17%; $P < .001$ Bowel obstruction: 14% vs. 8%; $P = .02$ Tremor: 13% vs. 6%; $P = .003$ Syncope: 12% vs. 4%; $P < .001$
IFM 99-02 ¹⁴ MM without or with one adverse prognostic factor, < 65 y (N = 708)	Induction: VAD × 3–4 cycles ASCT: tandem transplantation with melphalan-based preparative regimens Randomization to maintenance with: A) no maintenance B) pamidronate, 90 mg, IV q4w until progression C) pamidronate plus thalidomide	Maintenance arm C received thalidomide, 400 mg/d, with reduction to minimum of 50 mg/d allowed for toxicity; thalidomide given until disease progression	Arms A vs. B vs. C: Best response after randomization ($P = .001$): CR/VGPR: 55% vs. 57% vs. 67% PR: 37% vs. 37% vs. 30% MR: 7.5% vs. 5.5% vs. 3% 3-y probability of EFS: 36% vs. 37% vs. 52%; $P < .009$ 4-y probability of OS: 77% vs. 74% vs. 87%; $P < .04$	Grade 3/4 AEs, arm A vs. B vs. C: PN: 1% vs. 2% vs. 7%; $P < .001$ Fatigue: 1% vs. 2% vs. 6%; $P < .001$ Constipation: 0% vs. 0% vs. 1%; $P < .001$ Neutropenia: 0% vs. 1% vs. 6%; $P = .001$ Cardiac: 0% vs. 0% vs. 1%; $P = .04$
TMMMSG ¹⁵ Stage II/III Durie-Salmon MM, < 60 y (N = 202)	Induction: thalidomide with intermittent dexamethasone ASCT: cyclophosphamide/GCSF for stem cell collection Randomization: A) Tandem transplantation with melphalan-based preparative regimens; thalidomide given at progression or relapse B) Single transplantation with melphalan-based preparative regimen, with thalidomide maintenance; second ASCT at progression or relapse	Induction: 200 mg/d for 75 d Tandem transplantation: salvage thalidomide, 200 mg/d Single transplantation arm: 100 mg/d initiated 3 mo post-ASCT and continued for 6 mo	Arm A vs. B: CR/VGPR: 54% vs. 68%; $P = .04$ PR: 39% vs. 27%; $P = NS$ MR: 3% vs. 3%; $P = NS$ 3-y PFS: 57% vs. 85%; $P = .02$ 3-y OS: 65% vs. 85%; $P = .04$	Grade 3/4 AEs, salvage thalidomide (arm A) vs. maintenance thalidomide (arm B): PN: 11% vs. 4% Fatigue: 6% vs. 3% Constipation: 6% vs. 1% Infection: 0% vs. 1%
ALLG MM6 ¹⁶ Newly diagnosed, symptomatic MM, ≤ 70 y (N = 269)	ASCT: Single transplantation with melphalan-based preparative regimen Randomization to: A) Prednisolone, 50 mg, every other day B) Prednisolone plus thalidomide	Arm B received 100 mg/d, increased to 200 mg after 14 days as tolerated for up to 12 mo	Arm A vs. B: CR/VGPR at 1 y: 40% vs. 63%; $P < .001$ 3-y PFS: 23% vs. 42%; $P < .001$ 3-y OS: 75% vs. 86%; $P = .004$	Grade 3/4 AEs, arm A vs. arm B: PN: 0% vs. 10%; $P < .001$ Constipation: 0% vs. 4%; $P = .047$

Abbreviations: AEs, adverse events; ALLG, Australasian Leukaemia and Lymphoma Group; ASCT, autologous stem cell transplantation; CR, complete response; EFS, event-free survival; GCSF, granulocyte colony-stimulating factor; IFN, interferon-alpha; MM, multiple myeloma; MR, minimal response; MST, median survival time; NS, not significant; OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy; PR, partial response; TT2, Total Therapy 2; TMMMSG, Tunisian Multiple Myeloma Study Group; VAD, vincristine/doxorubicin/dexamethasone; VGPR, very good partial response.

* Assessed 6 months after second transplantation in arm A and 3 months after thalidomide maintenance in arm B.

guidelines currently do not address the dose or duration of maintenance thalidomide. Most centers currently continue patients on thalidomide for 1 to 2 years, depending on the patient's tolerance.

Finally, more research is needed to determine whether cytogenetics can be used to identify appropriate candidates for post-transplantation maintenance. Subgroup analyses from Total Therapy 2 suggest that thalidomide maintenance reduced the risk for death in patients with metaphase cytogenetic abnormalities, a well-known adverse prognostic factor, but not in those without these abnormalities.¹⁸ The IFM 99-02 trial showed that thalidomide was not effective in patients with del(13), and the United Kingdom MRC Myeloma IX trial showed that risk for death was significantly increased with thalidomide maintenance in patients with del (17p).¹⁴

As these authors describe elsewhere in this supplement, increasing evidence suggests that the novel agents bortezomib and lenalidomide may overcome the poor prognosis associated with cytogenetic abnormalities in myeloma.²⁴ How these findings from the induction setting translate into the maintenance setting remains to be determined in appropriately designed clinical trials.

Conclusions

The role of maintenance therapy after conventional chemotherapy remains to be determined, but there is a paucity of ongoing research in this setting. Much work is needed to evaluate maintenance therapy after ASCT, yet the optimal treatment regimen has not been identified. Thalidomide is the first novel agent to be studied as a maintenance therapy and shows the most promise. However, it may work through a direct cytoreductive effect rather than a true maintenance effect, given that several trials showed benefit only in patients who had not experienced at least a VGPR before initiating maintenance treatment. The optimal dose and duration of thalidomide maintenance remains to be determined, as does the appropriate patient population for routine treatment. Moreover, whether thalidomide should be used as maintenance or at relapse remains a matter of debate. More robust results of trials with lenalidomide and bortezomib maintenance therapies are eagerly awaited.

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