Is Maintenance Therapy for Everyone?

Ajay K. Nooka, Sagar Lonial

Abstract

Although myeloma remains an incurable disease among majority of myeloma patients, the prognosis has significantly improved after the introduction of novel agents. While more agents are being explored for their anti-myeloma activity, the more familiar agents with a better tolerability profile have been tested in the maintenance arena. Lenalidomide and bortezomib so far have shown promise as effective maintenance agents in prolonging PFS, and also OS in some studies. The current review aims at describing the clinical data supporting various maintenance therapies and also at providing some clarity to a few concerns associated with maintenance therapies.

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Introduction

The question of whether to offer maintenance therapy for myeloma patients is a very important one, especially in the context of current thinking that induction therapy followed by stem cell transplant is not a curable approach for the majority of myeloma patients. Offering maintenance therapy after induction and consolidation therapies among myeloma patients has resulted in delaying progression, thereby resulting in prolonged progression-free survival (PFS) and, in a few studies, pronged overall survival (OS).[1] However, certain considerations need to be well thought-out while planning on initiating maintenance therapy. First, it is quite uncertain which patient phenotype benefits the most. Secondly, there is a theoretical concern for development of resistant clones on prolonged exposure to the maintenance agent. More importantly, other factors such as drug costs, side effects with prolonged use of maintenance agents can present as potential challenges to utilizing routine use of maintenance therapy. An ideal maintenance agent should exert certain characteristics: be able to deepen the responses with the ultimate goal of not only to attain minimal residual disease (MRD) negativity but also to sustain the treatment response achieved as well; have a good safety and tolerability profile in long-term use, be convenient and easily administrable for patients. Importantly, the maintenance agent should not reduce the efficacy or preclude the use of other subsequent anti-myeloma therapies used as future treatments.

Division of Bone Marrow Transplant, Winship Cancer Institute, Emory University, Atlanta, GA

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Address for correspondence: Ajay K. Nooka, MD, MPH, FACP, Assistant Professor, Division of Bone Marrow Transplant, Winship Cancer Institute, Emory University, 1365 Clifton Rd NE, C4010, Atlanta, GA 30322
E-mail contact: anooka@emory.edu

Several questions of significance arise when determining the choice, timing, and duration of maintenance therapy. What is the optimal time to initiate maintenance therapy (upfront vs. salvage setting)? Is there a benefit to offering maintenance therapy prior to a transplant, thereby deferring the option of transplant for a future time (before vs. after transplant)? What is the optimal duration of maintenance therapy (fixed duration vs. continuous therapy until relapse)? Is there a role for alternating maintenance agents? And last but not least, what is the best choice of maintenance agents (single agent vs. combination therapy)? In this article we will review the available clinical trial data to address a few of the questions.

Historical Perspective

Historically, several agents exerting anti-myeloma effects have been evaluated in the maintenance setting with an intent to gain an incremental benefit in the disease state with minimal residual myeloma burden. Unfortunately, the toxicities of the older anti-myeloma agents precluded their use over prolonged periods. First, the cytotoxic agents that used to be the mainstay of myeloma therapy were evaluated as maintenance agents. With no survival improvement observed with these therapies and the association of long-term alkylator therapy with secondary myelodysplastic syndromes and acute myeloid leukemias well established, cytotoxic therapies have fallen out of favor.[2] Subsequent randomized trials have evaluated α-interferon as maintenance therapy, but the reported results were inconsistent. A meta-analysis of 12 randomized control trials undertaken by The Myeloma Trialists Collaborative Group, involving 1543 patients from 13 maintenance trials and evaluating the role of α-interferon demonstrated a marginal benefit in PFS and OS, more restricted to smaller trials. Poor compliance owing to the side effect profile rendered it prohibitive for routine usage.[3] The Southwest Oncology Group (SWOG) evaluated the role of glucocorticoids as maintenance therapy using oral prednisone

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at 2 different doses (10 mg vs. 50 mg every alternate day) in the SWOG9210 study. The higher-dose steroids had a benefit in PFS and OS, but prolonged steroid use resulted in significant toxicity with long-term use.[4] One of the newer agents, thalidomide, was evaluated in 6 randomized trials. All studies showed PFS benefit, although there was no consistent OS benefit. A meta-analysis (illustrated in Figures 1 and 2) resulted in a 39% reduction in risk of progression ($P < .00001$) and a 20% reduction in risk of mortality ($P = .001$).[5] Long-term cumulative toxicities of neuropathy, high discontinuation rates, negative impacts on health-related quality of life,[6] and the availability of newer well-tolerated immunomodulatory agents limits the use of thalidomide maintenance for routine use, at least in the United States, but the observed survival benefits with thalidomide maintenance make a clear case for deriving benefits of maintenance therapy.

Maintenance Therapy With Newer Agents

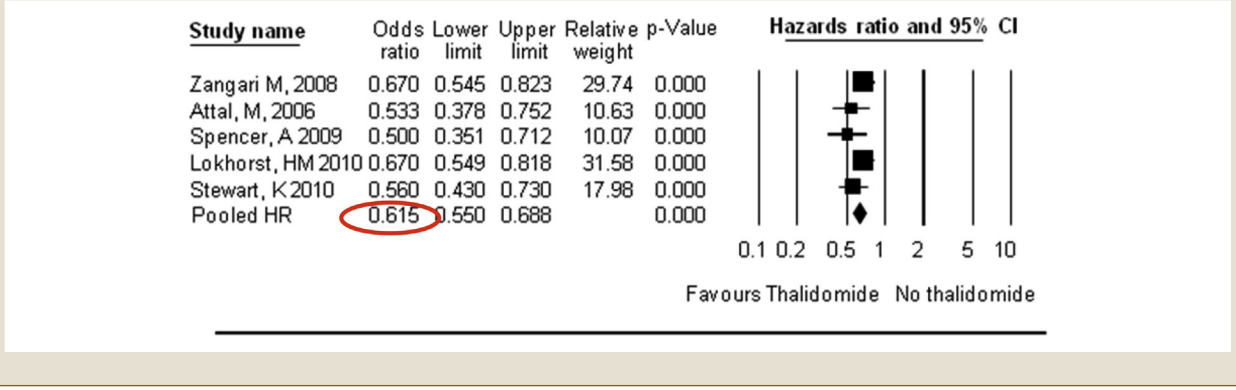
Lenalidomide-Based Maintenance Strategies

Lenalidomide as maintenance therapy has been evaluated in 4 phase III randomized control trials in patients who were transplant-eligible, in the post-transplant setting as illustrated in Table 1. In 2 of these 4 trials, lenalidomide maintenance therapy was initiated between 3 and 6 months posttransplant among nonprogressers.[7,8] The Intergroupe Francophone du Myélome (IFM) 2005-02 trial protocol was designed to receive consolidation treatment with 25 mg daily lenalidomide (days 1-21 every 28 days for 2 months), followed by maintenance treatment with lenalidomide, given at a dose of 10-15 mg daily for a fixed duration of 2 years, or placebo for the same duration of time. The median PFS from randomization favored the lenalidomide arm compared with the placebo arm (PFS, 46 months vs. 24 months; hazard ratio [HR], 0.52; $P < .001$), although there was no OS difference seen between the arms (> 80 months).[7] In the second trial by the Cancer and Leukemia Group B (CALGB), which followed a similar design to the IFM with the difference being that lenalidomide maintenance was continued until disease progression, the median time-to-progression (TTP) favored the lenalidomide arm compared with the placebo arm (PFS, 53 months vs. 26 months; HR, 0.54; $P < .001$), and the median OS also favored the lenalidomide arm (OS, not reached [NR] vs. 76 months; HR, 0.60; $P = .001$).[8] The observed OS benefit in the CALGB trial but not in the IFM trial supports continuous maintenance therapy rather than fixed-duration maintenance. One can also argue that the higher incidence of high-risk patients in the lenalidomide maintenance arm of the IFM trial can explain the loss of OS benefit, but the unavailability of similar cytogenetic characteristics in the CALGB trial does not allow for adequate cross-trial comparison.

Two additional phase III studies also evaluated the beneficial effect of lenalidomide maintenance after transplant. The RV-MM-PI-209 study, in its first randomization, assigned patients to receive a transplant or to receive the melphalan, prednisone, and lenalidomide (MPR) regimen. In the second randomization, patients received lenalidomide maintenance or no maintenance therapy. Maintenance therapy with lenalidomide was associated with a significant improvement in median PFS (41.9 months vs. 21.6 months; $P < .0001$), as well as a trend toward 5-year OS benefit (75% vs. 58%; $P = .14$).[9] More importantly, the median PFS was the highest, at 54.7 months, for patients that underwent transplant and then received lenalidomide maintenance. This median PFS was similar to that of the lenalidomide maintenance arm of the CALGB study, suggesting that this may the best approach at this point in time to obtain the PFS and OS benefits.[8,9] Another recently published study aimed to compare the efficacy and safety of consolidation with chemotherapy (cyclophosphamide and dexamethasone) and lenalidomide versus transplant, followed by lenalidomide maintenance versus lenalidomide and prednisone maintenance. In this 1:1:1:1 randomization, patients received lenalidomide or lenalidomide and prednisone maintenance. Median PFS did not significantly differ with the addition of steroids in maintenance therapy, and the 3-year OS trended towards favoring the lenalidomide-alone group (83% vs. 88%).[10]

Using the same concept of lenalidomide maintenance, the IFM group, in a phase II pilot study, also utilized triplet therapy with lenalidomide, bortezomib, and dexamethasone (RVD) in the induction setting, which was then followed by transplant and lenalidomide maintenance. This study enrolled 31 patients, showing impressive

Figure 1 Progression-free Survival Improves With Thalidomide Maintenance



Abbreviation: CI = confidence interval.