

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Maintenance Therapy in Multiple Myeloma



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H&O How has the use of maintenance therapy evolved over the years in multiple myeloma?

SK Maintenance therapy in multiple myeloma comprises any treatment administered after completion of a planned set of initial therapy (with or without transplantation) in responding or nonprogressing patients. The concept of maintenance therapy in myeloma is not new. Several studies have demonstrated improved progression-free survival (PFS) with maintenance therapy and some have also shown improved overall survival (OS). 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; improved survival with prednisone maintenance was demonstrated in at least 1 randomized trial. Thalidomide is the first among the newer agents that has been studied, with variable improvements in survival and significant toxicity. The role of novel agents as maintenance is emerging.

H&O What are the goals and drawbacks to maintenance therapy?

SK The goal of maintenance therapy is to keep the tumor volume down and potentially eradicate residual tumor to prevent relapse or need for retreatment. Ultimately, with continuous maintenance treatment, we hope to improve survival. Maintenance treatment with novel agents is emerging as a new strategy to sustain disease control and delay disease progression; however, longer follow-up is needed to assess the optimal duration and OS benefit. The optimal treatment approach should provide a good balance of efficacy and safety against costs. Quality of life should also be evaluated, because this is not captured by the response criteria. Novel agent-based combinations are

resulting in deeper and longer remissions, but we also need optimized tools to monitor our patients (minimal residual disease assessments, novel imaging techniques, etc) in parallel with the development of new drugs.

There are several potential drawbacks of maintenance therapy. Unnecessary exposure to chemotherapy can lead to side effects, increased costs, and potential secondary malignancies. If we are no longer able to reduce the amount of residual disease or improve immune surveillance against the tumor clone, continuing maintenance treatment might be dangerous as it could select a more resistant clone. Thus, a major step for researchers moving forward is to determine for how long maintenance therapies should be administered.

H&O What were some areas of controversy regarding maintenance therapy at this year's American Society of Hematology (ASH) meeting?

SK Some debates at this year's ASH meeting concerned the role of maintenance therapy in myeloma. Michel Attal presented the longer-term results of the IFM 2005-02 trial. This randomized, placebo-controlled phase 3 trial investigated the efficacy of lenalidomide (Revlimid, Celgene) maintenance after transplantation in 614 myeloma patients younger than 65 years whose disease had not progressed after first-line autologous stem cell transplantation. As expected, the results showed improved length of remission with lenalidomide maintenance; however, there was no OS benefit. In the new analysis, median PFS from randomization was 46 months with lenalidomide and 24 months with placebo ($P < .001$), but median OS was still not significantly improved with maintenance, despite the longer 77 months of follow-up. Median OS was 81 and 82 months in the 2 study arms, respectively ($P = .80$).

Potential reasons for the lack of survival benefit included the use of 2 months of lenalidomide consolidation

Table. Lenalidomide Maintenance vs No Maintenance

Study	Setting	Comparison	N	Consolidation	Lenalidomide Maintenance
IFM 05-02	Post-ASCT	Placebo	614	Len-dex × 2 cycles	10 mg daily × 3 months, increased to 15 mg daily if tolerated, until disease progression
CALGB 100104 ^a	Post-ASCT	Placebo	460	No	10 mg daily (up to 15 mg daily), until disease progression
MM-015	Post-MPR induction in nontransplant-eligible patients	Placebo	459	No	10 mg daily on days 1-21 of 28-day cycle until disease progression or unacceptable toxicity
RV-MMPI209	2 × 2 design comprising both ASCT and nontransplant arms	No maintenance	402	No	10 mg daily on days 1-21 of 28-day cycle until disease progression or unacceptable toxicity

^a Allowed crossover after study unblinding.

ASCT, autologous stem cell transplantation; dex, dexamethasone; len, lenalidomide; MPR, melphalan, prednisone, lenalidomide.

after transplant, which was administered to all patients (including those with no maintenance therapy). The intriguing question that this study brought up is whether we can get away with a very short duration of a more intense treatment after transplant instead of continuing therapy for a long period.

H&O Can you please discuss your ASH presentation on lenalidomide maintenance?

SK We conducted a meta-analysis of data pooled from 4 randomized controlled trials involving nearly 2000 multiple myeloma patients to evaluate role of lenalidomide as maintenance (Table). There was a significant improvement in PFS and a trend toward improvement in OS associated with lenalidomide maintenance. However, there was considerable heterogeneity among the studies for OS rate estimates, including lack of uniform access to lenalidomide upon disease progression in the placebo/no maintenance arms. Our meta-analysis also confirmed an increased risk of grade 3/4 adverse events with lenalidomide maintenance, including a nearly 2-fold increase in the risk of second primary malignancies.

H&O What were the limitations of your study?

SK As noted, there was significant heterogeneity across studies for OS estimates. Data on high-risk patients were not uniformly reported, and complete data for the subgroup analysis of transplant vs nontransplant arms were unavailable. In addition, quality-of-life data were not reported in most of the studies. There was also limited information regarding access to lenalidomide at the time of relapse.

H&O What are the biggest remaining challenges?

SK The biggest remaining challenge in multiple myeloma is to better understand its biology and what aspect of the

biology contributes to the heterogeneity of this disease. From there, we must determine how to devise therapies to specifically target the different subgroups of myeloma, and I think that is the only way we are going to get closer to curing this disease. I do not believe that there will be 1 treatment that will appropriately benefit every patient. If we can continue working toward using acquired knowledge regarding disease biology and applying that knowledge to individualize therapy for various patient subsets, there is much to be hopeful about in the treatment landscape.

Suggested Readings

Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma: follow-up analysis of the IFM 2005-02 trial. Presented at: 2013 Annual Meeting of the American Society of Hematology; December 7-10, 2013; New Orleans, LA. Abstract 406.

Boccardo M, Cavallo F, Gay F, Di Raimondo F, Nagler A, Montefusco V. Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) plus lenalidomide maintenance or no maintenance in newly diagnosed multiple myeloma (MM) patients [ASCO abstract 8509]. *J Clin Oncol*. 2013;31(suppl 15).

Facon T, Dimopoulos MA, Dispenzieri A, et al. Initial phase 3 results of the first (frontline investigation of lenalidomide + dexamethasone versus standard thalidomide) trial (MM-020/IFM 07 01) in newly diagnosed multiple myeloma (NDMM) patients (pts) ineligible for stem cell transplantation (SCT). Presented at: 2013 Annual Meeting of the American Society of Hematology; December 7-10, 2013; New Orleans, LA. Abstract 2.

Gay F, Hajek R, Diramondo F, et al. Cyclophosphamidelenalidomide-dexamethasone vs autologous transplant in newly diagnosed myeloma: a phase 3 trial. *Clin Lymphoma Myeloma Leuk*. 2013;13(suppl 1):S40.

McCarthy PL. Multiple myeloma: strategies for induction, transplantation, consolidation, and maintenance for transplant-eligible patients. Education Program presented at: 2013 Annual Meeting of the American Society of Hematology; December 7-10, 2013; New Orleans, LA.

Palumbo A, Magarotto M, Bringhen S, et al. A phase III study of ASCT Vs cyclophosphamide-lenalidomide-dexamethasone and lenalidomide-prednisone maintenance vs lenalidomide alone in newly diagnosed myeloma patients. Presented at: 2013 Annual Meeting of the American Society of Hematology; December 7-10, 2013; New Orleans, LA. Abstract 763.

Singh PP, Kumar SK, LaPlant BR, et al. Lenalidomide maintenance therapy in multiple myeloma: a meta-analysis of randomized trials. Presentation at: 2013 Annual Meeting of the American Society of Hematology; New Orleans, LA; December 7-10, 2013. Abstract 407.