Role of Maintenance Therapy After Autologous Stem Cell Transplant for Multiple Myeloma: Lessons for Cancer Therapy

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Recently, in an attempt to determine the role of maintenance therapy, 2 large studies reported longer progression-free survival (PFS) in patients undergoing an autologous stem cell transplant who were then randomized to lenalidomide (Revlimid; Celgene, Summit, NJ) vs placebo.[1,2] After a single autologous stem cell transplant for symptomatic multiple myeloma, 614 patients were given consolidation with lenalidomide followed by randomization to maintenance with either lenalidomide or placebo. Progression-free survival from the time of randomization improved to 42 months with lenalidomide maintenance therapy vs 24 months with placebo. The 5-year postdiagnosis overall survival (OS) was 83% in both arms.[1] In another study of 460 patients who received an autologous stem cell transplant and were then randomized to receive lenalidomide or placebo, time to progression was 42 months for lenalidomide vs 22 months for placebo. No survival data have been reported.[2] In keeping with the principles of primum non nocere ("First, do no harm"), physicians should carefully consider a number of points about maintenance therapy in patients with myeloma. A discussion of these principles and their potential application to other cancers follows.

Overall Survival

Although PFS is prolonged in the lenalidomide treatment arms, one must first demonstrate a convincing and meaningful increase in OS before advising maintenance therapy. Progression-free survival can be useful as a regulatory end point when introducing a new drug for the treatment of multiple myeloma; however, a meaningful OS improvement is necessary when evaluating maintenance therapy. Progression-free survival is a valid regulatory end point in myeloma for new drug approval because it is a reasonable marker of clinical benefit. In fact, if one did not use PFS in evaluating new drugs, one would be required to wait an inordinate period of time to ascertain a survival advantage. This would unnecessarily delay the introduction of new agents for the treatment of multiple myeloma. Such is not the case with maintenance therapy using an approved agent, where the question is not whether a new drug is useful but rather whether a drug already on the market offers clinical benefit. Patients in the placebo arm must receive lenalidomide at the time of relapse. Failure to give lenalidomide in this population may shorten OS. Patients who initially respond to lenalidomide are highly likely to respond subsequently to the agent after relapse on placebo. Patients who eventually relapse while receiving lenalidomide maintenance therapy may be resistant to future lenalidomide therapy. In this context, prolongation of PFS has not been shown to be indicative of clinical benefit and has not been a reliable predictor of improved OS in myeloma.[3,4]

Adverse Effects

Lenalidomide is quite well tolerated. Cytopenias, fatigue, and other adverse effects are rather easily managed. However, lenalidomide is a complex immunomodulatory drug. As with any other new drug, we do not know if serious adverse effects will occur in the future. Could there be deleterious effects from lenalidomide that would be recognized only with long-term use? For example, it took 12 years from the introduction of melphalan (1958)[5] to the recognition that myelodysplasia/acute leukemia might be related to melphalan.[6] Similarly, the nucleoside analogues fludarabine and cladrabine have been found to induce myelodysplasia or transformation to a large-cell lymphoma in some patients with Waldenström macroglobulinemia after long-term follow-up.[7] A few cases of myelodysplasia/acute myeloid leukemia have been reported in patients who have received lenalidomide, but these patients also received melphalan, which is a known leukemogenic agent. Much more follow-up is required before arriving at any definite conclusions. In fact, warning signs have already started to appear. At the Annual Meeting of the American Society of Hematology in December 2010, the Intergroupe Francophone du Myélome reported that 5.5% of patients receiving lenalidomide maintenance therapy developed a malignancy compared with 1% of those receiving placebo.[1] The Cancer and Acute Leukemia Group B study reported an incidence of second cancers of 6.5% in patients treated with lenalidomide compared with 2.6% for those receiving placebo.[2] It is essential that both arms of the protocols be followed up carefully for the occurrence of malignancy.

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Quality of Life

Although lenalidomide is quite well tolerated, patients must be followed up by the physician at regular intervals. This entails office visits and blood cell counts. Thus, patients are under close medical surveillance and may feel that they are ill. In contrast, patients who have undergone autologous stem cell transplant need not be followed up so frequently. The modest adverse effects of lenalidomide (eg, fatigue) may also impair the quality of life of patients. Quality-of-life studies need to be conducted to determine whether prolonged PFS is associated with improved patient-reported quality-of-life outcomes.

Cost

Lenalidomide is an expensive agent, costing a patient in the United States approximately $80,000 to $100,000 annually. Can the medical system afford this cost in a disease for which the physician cannot guarantee a cure?

Consistent Availability and Access to Lenalidomide at Relapse

Unfortunately, in both recent trials, lenalidomide was not routinely given as part of the protocol for patients in the placebo arm at first relapse. It is therefore essential to ensure that patients receiving placebo be given lenalidomide at the time of relapse. Failure to give lenalidomide, even in a subset of patients in the control population, may shorten survival and render the study results difficult to interpret.

Maintenance therapy may be indicated in patients with multiple myeloma who have adverse prognostic features, such as unfavorable cytogenetic abnormalities or a high-risk gene expression profile. Currently, no clear evidence supports a benefit of maintenance therapy for standard risk posttransplant patients, who represent at least 80% of patients with myeloma. Continued studies are needed to ascertain whether long-term maintenance therapy is beneficial in these patients.

These caveats regarding the role of maintenance therapy in multiple myeloma may also apply to its use in other cancers that are currently considered incurable (eg, chronic lymphocytic leukemia, low-grade non-Hodgkin lymphoma), because these cancers likewise raise the question of whether expensive medications should be used early or whether their use should be delayed. Early use of an active drug will most likely demonstrate improvement in surrogate end points; however, unless meaningful OS improvements can be shown, such improvement may not necessarily reflect clinical benefit.

References

1. Attal M, Cances Lauwers V, Marit G, et al. Maintenance treatment with lenalidomide after transplantation for MYELOMA: final analysis of the IFM 2005-02 [abstract 310]. *Blood (ASH Annual Meeting Abstracts).* 2010;116(21):310.
2. McCarthy PL, Owzar K, Anderson KC, et al. Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous hematopoietic stem cell transplantation (AHSCT) for multiple myeloma: CALGB 100104 [abstract 37]. *Blood* (*ASH Annual Meeting Abstracts).* 2010;116(21):37.
3. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. 2010;28(30):4621-4629.
4. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010;376:2075-2085.
5. Blokhin N, Larionov L, Perevodchikova N, Chebotareva L, Merkulova N. Clinical experiences with sarcolysin in neoplastic diseases. *Ann N Y Acad Sci*. 1958;68(3):1128-1132.
6. Kyle RA, Pierre RV, Bayrd ED. Multiple myeloma and acute myelomonocytic leukemia. *N Engl J Med*. 1970;283(210:1121-1125.
7. Leleu X, Tamburini J, Roccaro A, et al. Balancing risk versus benefit in the treatment of Waldenstrom's Macroglobulinemia patients with nucleoside analogue-based therapy. *Clin Lymphoma Myeloma*. 2009;9(1):71-73.