EDITORIAL

Current Treatment for Multiple Myeloma

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In the past decade, we have witnessed dramatic changes in the treatment of multiple myeloma. Proteasome inhibitors such as bortezomib and carfilzomib target the ubiquitin pathway, resulting in cytotoxic injury due to disruption of protein degradation in myeloma cells. The immunomodulatory agents thalidomide, lenalidomide, and pomalidomide target myeloma cells through several mechanisms including direct cytotoxicity, antiangiogenic effects, and activation of antitumor immunity. Initial studies both with proteasome inhibitors and with immunomodulatory drugs in patients with relapsed or refractory disease have shown highly encouraging results.[1,2] In patients 65 years of age or younger, high-dose chemotherapy with autologous stem-cell transplantation has been widely accepted as the standard of care as part of initial therapy. Phase 2 studies of regimens combining proteasome inhibitors with immunomodulatory agents have shown complete response rates that approximate those previously only achievable with high-dose chemotherapy,[3] raising the question as to whether autologous transplantation would be rendered obsolete in the era of new therapies.

To address this critical question, in this issue of the *Journal*, Palumbo et al.[4] report on a randomized phase 3 clinical trial in which patients 65 years of age or younger with newly diagnosed multiple myeloma received induction therapy with lenalidomide and dexamethasone and were then randomly assigned to receive consolidation therapy with two cycles of high-dose melphalan (at a dose of 200 mg per square meter of body-surface area) followed by autologous stem-cell transplantation or six 28-day cycles of standard-dose melphalan–prednisone–lenalidomide (MPR). The study showed that tandem courses of high-dose chemotherapy, as compared with consolidation therapy with MPR, resulted in improved progression-free survival (the primary end point) and overall survival (a secondary end point). Despite a lack of difference in complete response rates between the group of patients who underwent stem-cell transplantation and those who did not, melphalan plus stem-cell transplantation was associated with improved progression-free survival. Notably, the difference in survival was observed despite the use of high-dose chemotherapy as salvage therapy in many patients who were initially assigned to the MPR group. The authors speculate that this may have been due to the lack of feasibility of transplantation at the time of relapse in many patients. It is also possible that high-dose chemotherapy is less effective later in the disease course; this may be due to clonal drift resulting in increased resistance to cytotoxic therapy.

Randomized, controlled studies of the role of maintenance therapy with lenalidomide after autologous transplantation have also shown improved progression-free survival but conflicting results regarding its effect on overall survival and the potential risk of secondary cancers.[5,6] In the current study by Palumbo et al., patients who received consolidation therapy with high-dose chemotherapy or MPR were subsequently randomly assigned to receive no maintenance therapy or lenalidomide maintenance therapy until the time of disease progression. As in previous studies, lenalidomide maintenance therapy was associated with improved progression-free survival after either high-dose or standard-dose consolidation therapy. Consistent with the find-

ings of two of the three previously reported randomized studies,[5-7] maintenance therapy did not improve overall survival. In addition, maintenance therapy, as compared with standard-dose therapy, did not alter the superior outcomes associated with high-dose therapy. A sizeable number of patients who were enrolled in the study were excluded before randomization because of an inadequate response to primary induction therapy; this suggests that the study population was biased toward patients with more responsive disease. The study did not examine the use of bortezomib or combination therapy during consolidation or maintenance therapy. A randomized study comparing early consolidation therapy with bortezomib, lenalidomide, and dexamethasone or a single high-dose chemotherapy cycle is being conducted (ClinicalTrials.gov number, NCT01208662).

In transplant-ineligible patients, the addition of both immunomodulatory agents and proteasome inhibitors to melphalan and prednisone therapy has been shown to enhance progression-free and overall survival.[8,9] In another article in this issue of the *Journal*, Benboubker et al.[10] examine outcomes after treatment with melphalan, prednisone, and thalidomide (MPT), as compared with lenalidomide and low-dose dexamethasone in transplant-ineligible patients. In addition, the authors assess the role of continuous therapy with lenalidomide–dexamethasone until disease progression as compared with a predetermined number of cycles of therapy with lenalidomide–dexamethasone (18 cycles) or MPT (12 cycles). The study showed that as compared with a defined course of either lenalidomide–dexamethasone or MPT, continuous lenalidomide–dexamethasone therapy was associated with improvement in progression-free survival and a modest but significant improvement in overall survival. Although the response was higher with both lenalidomide–dexamethasone regimens than with MPT, improved outcomes were noted only with continuous therapy. The study suggests that treatment until disease progression is preferable to suspending treatment after achieving a maximal response.

These two articles considerably further our understanding of therapy for myeloma and how to best integrate new agents to treat this disease. In patients who are 65 years of age or younger, high-dose chemotherapy with stem-cell transplantation remains a standard of care associated with prolongation of progression-free and overall survival. Maintenance therapy after transplantation or standard-dose therapy has a clear effect on the duration of remission, but there is conflicting evidence regarding its impact on long-term outcomes. Finally, in transplant-ineligible patients, new agents with acceptable toxicity provide the opportunity for continuous therapy that may offer some advantage over a defined course of treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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