Novel Agents for Initial Therapy of Multiple Myeloma: Comparable results with continued initial therapy and delayed transplantation at relapse versus early transplantation

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Dr. Kumar, you made a presentation at the 51st annual meeting of the American Society of Hematology (ASH) about your investigation into the place of autologous stem cell transplantation in the era of novel agents in multiple myeloma. What can you tell us about this study?

Autologous stem cell transplantation has been an important part of multiple myeloma therapy since randomized trials showed improved survival with transplant compared to conventional therapy. However, the conventional treatment of myeloma has changed with the introduction of new drugs like IMiDs and proteasome inhibitors and there has been an increasing trend towards delaying transplant. While clinical trials in the pre-novel agent area have shown equivalent outcomes with early or delayed transplant, it is not clear if this holds true when the new drugs are used in the beginning. Patients treated with new drugs have had an understandable concern regarding the value of transplant once their myeloma relapses.

We studied the disease course among 410 patients seen at Mayo Clinic between 2001 and 2008. The patients included 123 (43%) individuals who received initial therapy with thalidomide-dexamethasone (TD) and 167 (57%) patients who were treated with lenalidomide-dexamethasone (LD). In 290 (71%) patients, a stem cell harvest was attempted and these patients were considered transplant eligible for this study (i.e., started on growth factor irrespective of collection success and whether or not they ended up having a transplant).

The early transplant group included 174 (60%) patients undergoing transplant within 12 months of diagnosis, and in whom the SCT was performed within 2 months of stem cell harvest. The remaining 118 (40%) patients were considered in the delayed transplant group, irrespective of whether a transplant was actually performed (45 patients from the delayed SCT group have been transplanted to date from among 68 who had a second line therapy). The median estimated time to SCT was 5.3 months among the early group compared to 39 months in the delayed group. At baseline, the groups were comparable for age, gender and other relevant clinical features.

What differences in efficacy did you find between the upfront and delayed transplant groups in the Mayo Clinic study?

In this group of newly diagnosed patients treated with TD or LD as initial therapy, an approach of continued initial therapy and delayed transplant at the time of first relapse appears to have comparable
efficacy to upfront transplant. Most importantly, the overall survival of patients was comparable whether they received the transplant in an early or delayed fashion. The time to disease progression appears comparable following transplant, likely reflecting the fact that these patients had not received previous treatment with melphalan type drugs. However, the overall survival post-SCT appears to be lower for the delayed SCT group reflecting fewer options for salvage therapy. The timing of transplant in the era of novel agents remains the top question on the mind of both physicians and patients, and this is the first study to examine this very important question.

**Did the retrospective study uncover a clear rationale when selecting early versus delayed transplant?**

The rationale governing the decision to go forward with an early or delayed transplant is difficult to ascertain for any particular patient in this retrospective study. The retrospective nature of our study precludes understanding reason for the early versus delayed decision in any particular patient. Clearly, randomized prospective studies are needed to confirm these findings. Transplantations should be considered a “regimen” for myeloma therapy, not a platform to base all therapy on.

Also, it is important to note that our retrospective study did not address quality of life (QOL) issue, and this should be assessed in future studies as such consideration clearly plays an important role in the decision of early versus delayed SCT.
Overall survival from diagnosis

Median OS for early group was 86 mos (95% CI: 80.88) vs. NR (95% CI: 54, NR) for delayed group (P = 0.3)

Post-SCT Overall survival

Trend to better OS post SCT for early SCT group, 80 mos vs. 43 mos, P = 0.04 (Breslow Gehan), P = 0.16 (logrank)