

# ADVANCES IN LLM

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

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## Optimal Timing for Transplant in Multiple Myeloma

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**H&O** What are the current forms of available transplant, and how do they affect patient survival rates?

**SR** Transplantation for myeloma could be either autologous or allogeneic. Allogeneic transplantation remains controversial because its impact on overall survival is not established. On the other hand, autologous stem cell transplantation (ASCT) likely prolongs overall survival in multiple myeloma. There are 2 approaches to performing ASCT: either early in the course of the disease following initial diagnosis, or at the time of first relapse. Studies have shown both strategies to be useful.

**H&O** What are the options for initial treatment in patients eligible for ASCT, and do you think it is necessary as part of initial therapy for all eligible patients with myeloma?

**SR** ASCT has been shown to prolong survival in multiple myeloma in randomized, controlled trials. The bigger unanswered question is whether patients should receive ASCT as part of their initial therapy or delay it until the time of first relapse. In terms of overall survival, there does not appear to be any significant difference when the transplant is done early or at the time of first relapse, based on the 3 randomized trials that have tested this question so far. My sense is that ASCT should be offered to all patients who are eligible for the procedure, but there should be flexibility in the timing of the procedure, and the choice of early versus delayed will depend on the

patient's age, risk characteristics, preferences, etc. Even if a delayed approach is contemplated, stem cells must be collected early in the disease course and cryopreserved.

**H&O** What are some new agents being studied that could change the role of transplantation?

**SR** Newer agents—particularly bortezomib (Velcade, Millennium Pharmaceuticals), lenalidomide (Revlimid, Celgene), and combinations of these drugs—are achieving improvements in surrogate endpoints, such as response rate and complete response, that rival the results obtained with ASCT. If approved, additional new drugs such as carfilzomib (Onyx), oral proteasome inhibitors, and pomalidomide (Celgene) may extend these gains further. Thus, it may be possible to develop initial therapy regimens that are highly effective and well tolerated so that transplantation could serve a second-line role. We have a sense that this is already happening, because more patients are deciding the timing of their transplant. At Mayo Clinic, for example, approximately 50% of patients who are eligible for the procedure are choosing to have it postponed to the time of first relapse, since their initial therapy is already working so well.

**H&O** Can you describe the risk-adapted therapy strategy?

**SR** The risk-adapted therapy strategy is essentially an attempt to individualize treatment based on the level of disease aggressiveness and expected survival. Some say that

a risk-adapted strategy is unproven in myeloma. However, so are many of the treatment strategies currently in use. For example, there are no clear data from randomized trials to determine whether performing a transplant earlier versus later in the disease course yields different results. Similarly, many common combinations advocated today have not shown a survival advantage over simpler, less toxic regimens. In the absence of such data, instead of treating all patients based on small phase II trials or improvements in surrogate endpoints, my colleagues and I prefer a risk-adapted approach. The rationale for this strategy, termed mSMART (Mayo Stratification of Myeloma and Risk-adapted Therapy), is to improve survival and at the same time help maximize the patient's quality of life. Rather than simply use a "favored method of treatment" for all patients in a one-size-fits-all model, what we have done is classify patients into 3 risk groups. Approximately 75% of myeloma patients have standard-risk myeloma, characterized cytogenetically by the presence of hyperdiploidy, t(11;14) or t(6;14). These patients have a median survival of 7–10 years, and we approach them in a different manner than in which we approach intermediate-risk patients, who have the t(4;14) translocation, or high-risk patients, who have deletion 17p, t(14;16), t(14;20), or a high-risk gene expression profiling signature at baseline. For the low-risk patients, our goals are to maximize quality of life and ensure that patient preference is maintained. This includes preferences regarding initial therapy, timing of transplantation, the number of transplants, and whether or not to use maintenance therapy. For example, low-risk patients can be treated with either lenalidomide-based therapy or bortezomib-based initial therapy, and can receive either an early or a delayed transplantation. Complete response in these patients, although desirable, is not a stated treatment goal. In the intermediate-risk group, we recommend the use of bortezomib as initial therapy, followed by ASCT, and then bortezomib-based maintenance therapy for at least 2 years, since data show that such an approach can bring their survival to almost the same level as that of the standard-risk patients. High-risk patients (comprising approximately 15% of all myelomas) have a median survival of 2–3 years, despite the use of intense induction therapy and double ASCT. Therefore, we are willing to engage in more experimental treatments for this group, and pursue complete response as a goal of therapy.

### **H&O** What is lacking in current data and/or clinical trials that makes determining the best treatment strategy difficult?

**SR** In myeloma, with few exceptions, there are limited phase III data to show that one treatment strategy is superior to another. Wherever such data are available, we have

incorporated that as the standard of care. Comparative trials that have included bortezomib and/or lenalidomide in both treatment arms have not shown survival differences between one regimen versus another. All we have are either survival improvements compared to old standards (eg, melphalan/prednisolone, infusional vincristine, doxorubicin and dexamethasone, or thalidomide/dexamethasone) or changes in surrogate endpoints. Similarly, we do not have survival data on the optimal timing of transplant for patients who are eligible for the procedure. We are thus limited to surrogate endpoints or expert opinion at the moment. Data concerning solid, clinical benefit endpoints, such as overall survival or quality of life, have yet to emerge.

### **H&O** Can you discuss your recent study on survival outcomes in myeloma patients who received upfront ASCT?

**SR** There is a lot of interest in trying to determine whether maximizing the depth of response achieved in myeloma can prolong survival. As a hypothesis that needs to be tested in clinical trials, this is a laudable goal and something that we need to pursue. However, for clinical practice, it is a strategy that still needs more proof. The study by Kapoor and colleagues, presented at the 2011 annual meeting of the American Society of Clinical Oncology (abstract 8069), demonstrated that patients who had a stringent complete response (defined as an eradication of clonal cells of bone marrow and normalization of the serum free light chain assay) have better overall survival post-transplant compared with patients who do not achieve that degree of complete response. Dr. Kapoor is doing additional landmark-type analysis to make sure that the results are not biased. Others, such as the GEM (Grupo Español de MM) and PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna) Cooperative Study Groups, have shown that a molecular complete response is better than a regular complete response. Although interesting, these studies still have drawbacks. They compare patients who achieve a certain type of response to patients who do not; thus, they are not randomized comparisons. The studies show that increased depth of response may be a key prognostic factor, but do not prove that changing therapy or its intensity to achieve this result will cause prolongation of survival. The latter requires a randomized comparison of 2 treatment strategies: one with a fixed type of treatment versus another in which therapy is modified to achieve a predefined response depth. However, these studies are providing hypotheses that would be worthwhile to test in randomized trials.

### H&O What other current studies are showing promise in this area?

**SR** The Dana Farber Cancer Institute and the Inter-Groupe Francophone du Myélome are conducting an important study that compares early transplantation to bortezomib, lenalidomide, and dexamethasone. The results will go a long way in clarifying the role of transplantation versus standard dose therapy. Other studies are focusing on post-transplant strategies designed to delay or prevent relapse. Overall survival results are anticipated from phase III maintenance trials that recently tested lenalidomide in the post-ASCT setting.

### H&O Where should we focus our efforts for the future in multiple myeloma treatment?

**SR** Patients want improvement in their quality of life and in overall survival. I think those endpoints should be pursued rigorously. We should try to ensure that future trials look at risk categories more closely, because myeloma is a heterogeneous disease with various cytogenetic categories, each of which have an outcome that may be quite different from the others. We need to design trials that will enable us to choose the best

drug for the given patient. I think patients will soon be coming in with their full genome sequence, and asking us how their treatment can be modified based on that particular profile. We should be prepared for that. As far as transplantation is concerned, I think we need to improve the conditioning regimen. We are still using the same conditioning regimen that we were using 10–15 years ago, which is high-dose melphalan. Researchers are looking at ways to improve this conditioning regimen using agents such as lenalidomide and bortezomib. The transplant window may allow us to administer not just high-dose melphalan, but also other drugs at optimal doses, in order to try and eradicate the myeloma clone.

### Suggested Readings

Kapoor P, Kumar S, Dispenzieri A, et al. Survival outcomes of patients with multiple myeloma (MM) achieving stringent complete response (sCR) following upfront autologous stem cell transplantation (SCT). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 8069.

Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. *Blood*. 2011; Epub ahead of print.

Clinicaltrials.gov. Randomized study comparing conventional dose treatment using a combination of lenalidomide, bortezomib and dexamethasone to high-dose treatment with ASCT in the initial management of myeloma in patients up to 65 years of age. Identifier NCT01191060. <http://clinicaltrials.gov/ct2/show/NCT01191060?term=ifm%2Fdfci&rank=1>. Accessed August 15, 2011.