An update on HCT research and clinical trends in multiple myeloma to help guide treatment choices.

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HCT Research on Multiple Myeloma

Welcome to Transplant Connection, The University of Kansas Cancer Center (KUCC) newsletter focusing on trends in the treatment of hematologic malignancies. This edition focuses on perspectives on multiple myeloma with new ASBMT recommendations, treatment strategies for high-risk patients and survival trends. Stay up to date by viewing additional short summaries of the latest research in multiple myeloma and other hematologic malignancies. Visit BeTheMatchClinical.org/Research.

HCT for Multiple Myeloma: Updated Guidelines from the ASBMT

— Siddhartha Ganguly, MD, FACP; University of Kansas Medical Center

Therapeutic strategies for multiple myeloma (MM) have changed dramatically over the last decade. The American Society for Blood and Marrow Transplantation (ASBMT) recently updated its guidelines for using hematopoietic cell transplantation (HCT) in the treatment of MM based on an extensive review of recent literature. [1] In this evidence-based review, the ASBMT guidelines committee makes recommendations on several aspects of transplantation for MM, including patient selection, timing of transplantation, autologous vs. allogeneic HCT, and post-transplant follow-up strategies.

Timing of transplant: Early vs. late

A significant survival advantage of autologous HCT over conventional chemotherapy has been shown in many earlier studies. However, controversy exists regarding proper timing of referring patients with MM to a transplant center. There is no published prospective randomized study answering this question, and in the era of novel agents, previous clinical practices may need to be revisited.

Earlier prospective data by French groups showed an autologous HCT benefit in event-free survival and time without symptoms. [2] And retrospective studies show that delayed transplant is feasible in the modern era, but these results are not a substitute for prospective randomized data.

The multi-center DFCI 10-106 (NCT01208662) trial is structured to answer the exact same question in the era of novel combination therapy. Until the reports are available, the ASBMT guidelines committee recommends continuing with the practice of early (up-front) autologous HCT in MM.

What about those patients who are refractory or failed to attain at least a PR from the initial induction therapy?

Status at the time of transplantation correlates well with the remission status after transplantation. Patients who are refractory or fail to attain at least a partial remission (PR) after an initial combination therapy pose a challenge to treating physicians. Results of earlier retrospective studies demonstrated that additional therapy or changing therapy did not seem to change survival. Although prospective data are lacking, the ASBMT guidelines committee recommends consideration of first autologous HCT in refractory disease.

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Review: How to Treat High-Risk Myeloma

In this installment of the “How I treat ...” series in Blood, the authors take a case-based approach to review the treatment of patients with genetically or clinically defined high-risk myeloma, and discuss their clinical decision-making process when selecting among treatment options for these patients. [1]

The authors note that the best long-term outcomes are achieved if physicians identify high-risk myeloma patients at the time of disease presentation, so that patients can receive aggressive combination therapy followed by long-term maintenance therapy. The authors outline risk-stratification using disease stage, chromosomal abnormalities, disease biology, and gene expression.

Conventional chemotherapy in various combinations is insufficient to overcome or even mitigate the impact of high-risk myeloma, according to the authors. Their suggested treatment algorithm begins with high-dose therapy with early autologous transplantation and continues with risk-adapted maintenance therapy.

Aggressive induction therapies discussed in this review include RVD (lenalidomide, bortezomib, and dexamethasone), VTD (bortezomib, thalidomide, and dexamethasone), CTD (cyclophosphamide, thalidomide, and dexamethasone), and CRD (carfilzomib, lenalidomide, and dexamethasone), as used in the large cooperative group trials in Europe and the United States. Such therapies avoid the use of alkylating agents and are designed to prevent the emergence of drug resistance, with the ultimate goal of suppressing clonal evolution.

A key aspect of treating this aggressive disease is an aggressive monitoring schedule, according to the authors, who note that “any opportunity the tumor is given to grow and develop drug resistance represents a potential source for tumor escape.” They therefore recommend minimizing the period with no therapy to 60 days rather than the conventional 100 days for the initiation of maintenance therapy.

Finally, the role of transplantation in these patients is reviewed with recommendations for which patients with high-risk myeloma would benefit most from high-dose therapy and autologous transplantation, planned tandem autologous transplantation, or allogeneic transplantation within a clinical trial. The NMDP/Be The Match and ASBMT guidelines on the timing for transplant consultation are listed in Table 1.

### Transplant consultation guidelines for Multiple Myeloma

<table>
<thead>
<tr>
<th>Event</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>At first progression</td>
<td>All patients after initiation of therapy</td>
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Table 1. View complete guidelines at [BeTheMatchClinical.org/guidelines](http://BeTheMatchClinical.org/guidelines)


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**HCT for Multiple Myeloma: continued from page 1**

### Role of second transplantation as a salvage therapy for relapsed MM

Unfortunately, the majority of patients after first autologous HCT will eventually relapse. Although there are several available options for patients with relapsed disease, a second autologous HCT should be considered for select patients, especially for those who relapse later than 12 months after the first autologous transplant. National Comprehensive Cancer Network (NCCN) guidelines recommend collecting for at least two autologous grafts for eligible patients in the event a second transplant is needed for salvage after relapse.

Progression-free survival is an acceptable outcome in a relapsed setting. Based on this observation, and review of retrospective data, the ASBMT guidelines committee states that second autologous transplant is safe and efficacious for patients with relapsed MM and should be considered in a salvage setting.

### Who needs maintenance after transplantation?

In the era of novel agents, maintenance and consolidation are attractive options after autologous transplantation for MM. Two large prospective randomized trials (IFM/French and CALGB/USA) showed improvement in time to progression for patients on lenalidomide maintenance compared to placebo after transplantation. [3,4] In addition, the CALGB/USA trial showed overall survival advantage as well for patients taking maintenance lenalidomide.

In a meta-analysis of 8 randomized trials, a benefit in both progression-free and overall survival were noted in patients on immunomodulatory drug-based maintenance strategy. [5] The ASBMT Guidelines recommend lenalidomide-based maintenance unless a contraindication exists. In high-risk disease with renal failure or with adverse chromosome changes, consolidation and maintenance with a bortezomib-based regimen may be considered.

**Improved Survival in Multiple Myeloma Over Time**

**Primary improvement in patients >65 years**

A large-scale and long-term study of patients with multiple myeloma has shown that overall survival has significantly improved since 2001. [1] The study analyzed the outcomes of 1,038 patients who were started on therapy within 30 days of their diagnosis of symptomatic multiple myeloma at the Mayo Clinic in Rochester, Minn., between 2001 and 2010.

The researchers grouped patients into two time periods: between 2001 and 2005 (n=477) and between 2006 and 2010 (n=561). Mean age at diagnosis was 66 years. The median follow up for the entire patient cohort was 5.9 years.

Improved survival is benefitting older patients and early mortality in this disease has been reduced considerably.

Median overall survival (OS) for the entire cohort was 5.2 years. The median overall survival of patients in the more recent group was significantly longer compared with the earlier cohort: 6.1 years vs. 4.6 years, respectively (p=0.002). The estimated 6-year OS for the recent cohort was significantly higher compared to the earlier cohort: 51% vs. 40%, respectively (p<0.001).

Among the entire cohort, 393 patients (37%) received an autologous hematopoietic cell transplant (auto-HCT) at some point during the disease course, with a median time to transplant of 5.9 months (range, 2-95). A higher percentage of patients ≤65 years received an auto-HCT (277 of 498, or 56%). Researchers performed a 6-month landmark analysis to examine the impact of auto-HCT on OS. The median OS for patients who underwent auto-HCT was not reached, compared with 4.9 years (95% CI; 4.2, 5.3) for those not receiving an auto-HCT (p<0.001).

The study authors also noted that the improvement in survival was primarily seen among patients >65 years, with 6-year OS improving from 31% to 56% (p<0.001). Additional results show improvements in early post-transplant mortality over time, with only a 10% incidence during the first year post-transplant in the 2006-2010 group, compared with 17% in the 2001-2005 cohort (p<0.01).

The authors concluded that the improved outcomes were linked closely to FISH-based risk stratification, use of one or more new agents in initial therapy, such as the IMiD and proteasome inhibitor classes of drugs, and the use of bortezomib for patients with high-risk translocations and 17p deletion.


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**Invited national experts:**
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- Helen Heslop, MD, Center for Cell and Gene Therapy, Houston
- Stephanie Lee, MD, Fred Hutchinson Cancer Research Center, Seattle

**Event details:**
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- **Location:** Overland Park Convention Center, 6000 College Blvd., Overland Park, KS 66211
- **Cost:** Free, Preregistration: required