Ask ACCC's Community Resource Centers

Even with the advent of novel agents and autologous peripheral blood stem cell transplants therapy (ASCT), multiple myeloma (MM) is still an incurable disease; most patients relapse, even those patients placed into complete remission (CR). In the absence of a high curative potential, long-term disease control remains the most important part of MM treatment. Clinicians have disagreed on whether standard-risk patients who will survive a long time need to be treated as aggressively as high-risk patients, but all agree that high-risk patients require a complete remission for long term overall survival (OS) and an aggressive strategy to reach that goal.[1] Leona A. Holmberg MD, PhD, Fred Hutchinson Cancer Research Center, discusses current standard of care and what the future holds for patients with MM post-ASCT.

THOUGH UNDERUTILIZED FOR treating MM, ASCT remains the most common reason for transplant. Unfortunately, relapse of MM remains a major problem after transplant. Possible explanations for relapse include: incomplete eradication of endogenous disease or infusion of tumor contaminated stem cell products.[2,3] Attempts to improve outcomes by further dose intensification of conditioning to date with a single ASCT have led to an increase in transplant-related morbidity and mortality without a significant reduction in both relapse rates and improvement in OS.[4]

Clinicians also face challenges determining minimal residual disease (MRD) status in MM patients. Molecular and multi-parameter flow cytometry techniques have not yet been standardized in MM and the most sensitive assays are not well accepted by providers. In addition, determining PCR (polymerase chain reaction) status is time consuming and requires specific primers from patients. Although other diseases have seen the advent of deep sequencing, its role in MM has still to be addressed.

Genetic profiling also plays an important role in treating MM patients. Unfortunately, standardization and easy use of gene expression profiling signature to help identify those patients with more indolent MM that may require less aggressive therapy does not yet exist. MRD must be combined with genetic assessment to develop a powerful medical risk-assessment tool. In other words, before using MRD to make clinical decisions, providers need to standardize the tests and the criteria used to determine response and then validate their relevance in clinical outcomes.

Clinicians have commonly used additional therapy post-ASCT to try to improve outcomes for MM patients. These therapies have fallen into different approaches of consolidation with or without maintenance therapy or maintenance therapy alone. Consolidation therapy has been defined as improving on response and accepting more toxicity; maintenance therapy has been defined as maintaining response with less toxicity (see table 1, page 61).

In the era of novel agents, improved outcomes after ASCT and induction therapy have been realized. ASCT followed by consolidation therapy and maintenance therapy appears to be the standard approach to induce remission status in MM patients.[5–8] While thalidomide works best in good-risk disease, peripheral neuropathy has made it hard for patients to comply with this therapy.[9]

Optimal duration of maintenance therapy may be drug specific. For example, the optimal use of lenalidomide may be for as long as tolerated or until disease progression. Newer agents, such as carfilzomib, are being studied, looking at not only the combination of agents, but giving them alone or sequentially.

ACCC's Community Resource Centers for Multiple Myeloma

- **The Nebraska Medical Center, Omaha, Nebraska**
- **Seattle Cancer Care Alliance, Seattle, Washington**
- **Winship Cancer Institute of Emory University, Atlanta, Georgia**

Contact them at: www.accc-cancer.org/resources/MultipleMyeloma-CRC.asp.

For future studies as effective salvage therapies continue to come on board, overall survival (OS) is going to be problematic as an endpoint. So, as a community, we need to decide whether TTP (time to progression) and EFS (event free survival) are reasonable endpoints for future studies of consolidation and maintenance therapy after ASCT.

Additionally, clinicians have not yet answered the question as to whether all patients need therapy post-ASCT or if there are groups of patients that do not need to be treated. A standardized clear definition of MRD and a process to identify accurately who still has the disease may help clinicians make that choice.

Current studies have not yet clearly delineated good-risk and bad-risk patients or the role of additional therapy post-ASCT in patients who require more than one induction regimen to get good response before ASCT or patients who are undergoing ASCT in the relapsed delayed transplant setting.

Still, it is premature to say that all patients should not be offered therapy if in CR (complete remission) after ASCT. Data shows that patients with bad-risk parameters at diagnosis, such as elevated beta 2 microglobulin or bad-risk cytogenetics, or those who require more than one induction regimen may benefit from additional therapy post treatment—even if they are in complete remission.

Our old definitions of CR still have high-relapse rate; the median TTP (time to progression) from ASCT for sCR (stringent complete remission) is 50 months vs. 20 months for CR and 19 months for near CR.[10] Thus, if clinicians maximize the use of sCR after ASCT, we may—with the current standard technology and use of clinical information, such as good-risk factors at presentation—identify a group of patients who (with adequate counseling) do not need additional therapy post-ASCT.

In the future, clinicians need to assess the best therapy to use post treatment based on previous therapy and cytogenetic and other risk factors. In other words, we need to learn how to choose therapy based on toxicity of drugs and underlying toxicity that patients have from previous therapy, especially in a setting where we are not curing disease but treating it as a chronic illness.

Future studies should address risk stratification approaches, and we need to do head-to-head comparisons of different regimens to determine the best treatment with specific MM patients post-ASCT.

Finally, clinicians must establish the appropriate duration of treatment with different agents. We need to standardize MRD criteria and design studies to address this question appropriately with other risk factors to maximize the use of additional post transplant therapy. But, for patients with bad-risk factors at presentation and even those in good-risk category that do not achieve sCR after ASCT, the strategy of non-cross resistant therapy to induce deeper remissions and sustain them over time is the goal and currently is reached by novel agent combination induction therapy, ASCT, and additional novel agent therapy post treatment.

Table 1. Consolidation vs. Maintenance Therapy

Consolidation Therapy	Maintenance Therapy
Accept more toxicity	Well tolerated with easily manageable toxicity
Limited time use	Long term use
Effective	Effective
Need not be simple to give	Simple to give
Deepen response	Maintain response

References

1. Haessler J, et al. Benefit of complete response in multiple myeloma limited to high-risk subgroup identified by gene expression profiling. *Clin. Cancer Res.* 2007;13:7073-7079.
2. Brenner MK, et al. Gene-marking to trace origin of relapse after autologous bone-marrow transplantation. *Lancet*. 1993;341:85-86.
3. Stewart AK, et al. Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. *J Clin Oncol*. 2001;19:3771-3779.
4. Moreau P, et al. Comparison of 200 mg/m2 melphalan and 8 Gy total body irradiation plus 140 mg/m2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood*. 2002;99:731-735.
5. Attal M, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.
6. McCarthy PL, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *NEJM*. 2012;366:1770-1781.
7. Attal M, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *NEJM*. 2012;366:1782-1791
8. Sonneveld P, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. [Erratum appears in *J Clin Oncol*. 2012 Oct 10;30(29):3654]. *J Clin Oncol*. 2012;30:2946-2955.
9. Krishnan A, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol*. 2011;12:1195-1203.
10. Kapoor P, et al. Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma. *J Clin Oncol*. 2013;31:4529-4535.