Re: Tandem vs Single Autologous Hematopoietic Cell Transplantation for the Treatment of Multiple Myeloma: A Systematic Review and Meta-analysis

Kumar et al. (1) recently reported results of a meta-analysis of tandem vs single autologous hematopoietic cell transplantation (HCT) for patients with multiple myeloma. The authors should be commended for trying to address an important and topical issue regarding HCT for multiple myeloma. However, we disagree with their conclusions, which we believe are based on incorrect interpretation of data derived from a meta-analysis of heterogeneous trials. Their analysis was based on extrapolations from 2 meeting abstracts and 4 clinical peer-reviewed journals rather than from primary sources of data.

The authors studied six randomized clinical trials with a total of 1803 patients. They stated that tandem HCT yielded neither overall survival (OS) nor event-free survival (EFS) benefit. Unfortunately, one of the four fully published trials included in the analysis was not designed to compare tandem vs single HCT but instead compared single HCT followed by maintenance thalidomide vs tandem autologous HCT without maintenance (2). Thalidomide maintenance is associated with improved progression-free survival (PFS) and OS after a single autologous HCT (3). Indeed, when the authors excluded the trial by Abdelkefi et al., EFS was longer in patients treated with tandem HCT. Inclusion of the Dutch HOVON 24 study is also questionable because the design compares two cycles of attenuated nonablative doses of melphalan vs the same regimen followed by HCT with cyclophosphamide and total body radiation, an outdated modality, due to its lack of demonstrated benefit and increased morbidity and mortality when given as part of HCT (4,5).

The observation that tandem HCT is associated with better EFS but not definitive improvement in OS is likely the result of effective salvage therapy for patients treated with a single HCT (including novel agents), second autologous HCT, or an allogeneic HCT. Therefore, EFS and PFS are appropriate outcomes to evaluate effectiveness of multiple myeloma therapy (6).

The conclusions and recommendations of the authors, that is, that use of tandem autologous HCT did not result in improved EFS and that the routine use of tandem transplants in its current form is not justified without considering the caveats mentioned above are unwarranted and have negative implications for the field. These conclusions are often used by third-party payers to deny coverage for tandem autologous HCT of patients enrolled in clinical trials in United States and elsewhere. Participation in prospective, randomized, multi-institutional clinical trials should be encouraged to appropriately answer this question of efficacy of tandem autologous HCT in the era of novel agents for multiple myeloma. Indeed, such a trial developed by a collaboration of National Cancer Institute-sponsored cooperative groups and the Blood and Marrow Transplant Clinical Trials Network will compare single HCT vs single HCT followed by consolidation with novel agent combinations (including lenalidomide and bortezomib) vs tandem HCT. All patients will receive maintenance with lenalidomide for 3 years. The study has the potential to provide a definitive answer to questions posed by the authors and will be applicable to current treatment options for multiple myeloma.

Sergio Giralt
David H. Vesole
George Somlo
Amrita Krishnan
Edward Stadtmueller
Philip McCarthy
Marcelo C. Pasquini
on behalf of the Blood and Marrow Transplant Clinical Trials Network Multiple Myeloma Working Group

References

Notes
Affiliations of authors: Department of Stem Cell Transplantation and Cellular Therapy (SG), University of Texas, MD Anderson Cancer Center, Houston, TX; Blood and Marrow Transplant Program (DHV), Loyola University, Stritch School of Medicine, Chicago, IL; Department Hematology and Hematopoietic Cell Transplantation (AK) and Department of Medical Oncology and Therapeutics Research (GS), City of Hope Cancer Center, Los Angeles, CA; Department of Medicine, University of Pennsylvania, PA (ES); Bone Marrow Transplant Program, Roswell Park Cancer Institute, Buffalo, NY (PM); Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI (MCP).

Correspondence to: Marcelo C. Pasquini, MD, MS, Center for International Blood and Marrow Transplant Research 9200 W. Wisconsin Ave, CC5600, Milwaukee, WI 53226 (e-mail: mpasquin@mcw.edu).

Dr A. Krishnan is on the speakers bureaus of Celgene Corporation and Millennium Pharmaceuticals Incorporated. Dr S. Giralt is on the advisory boards and speakers bureau of Celgene Corporation, Millennium Pharmaceuticals Incorporated, Novartis Pharmaceutical Corporation and Genzyme Corporation.

DOI: 10.1093/jnci/djp126
© The Author 2009. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.