Biol Blood Marrow Transplant 19 (2013) 333–337

The Bottom Line

Digging Deeper with Allogeneic Transplantation in Multiple Myeloma

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Article history:
Received 14 December 2012
Accepted 21 December 2012

The treatment paradigms for myeloma have dramatically changed in the past decade with availability of more effective drugs, and patients are living substantially longer [1]. These changes, along with a better understanding of the genetic underpinnings of the disease, have changed our approach to management of patients with myeloma. The study by Kroger and colleagues [2] highlights two of the most debated questions in myeloma today: What should be the goal of myeloma therapy and how do we approach patients with high-risk multiple myeloma?

The increasing depth of response seen with the new drug combinations and increasing use of post-transplant consolidation and maintenance approaches have seen nearly 100% of patients getting a partial response and nearly half of patients obtaining a complete response (CR), as defined by the International Myeloma Working Group (IMWG) response criteria [3,4]. These high response rates have pushed the boundaries of the current response criteria, highlighting the need for better markers of residual tumor given that most patients in CR eventually relapse. In response to this, the IMWG criteria was revised to add a category of stringent CR that required normalization of serum free light chains as well as lack of clonally restricted plasma cells in the marrow [4]. However, it is clear that more sensitive and specific markers of minimal residual disease are needed.

Two methodologies have been studied extensively, although no consensus exists as to the exact methodologies and definitions for minimal residual disease negativity [5,6]. Polymerase chain reaction–based methods clearly have a high sensitivity and specificity but suffer from the inability to create patient-specific primers in nearly half of patients. Flow cytometry–based methods have gained significant foothold in the recent years due to several technological advances such as six- and eight-color flow cytometers, the ability to automate the process and study over million cells from individual samples, and the development of new fluorochromes and better antibodies [7].

There have been different algorithmic approaches to defining presence of minimal residual disease in a flow cytometry sample. Some centers used baseline aberrant expression of a panel of antigens such as CD28, CD117, CD33, or CD20 to "fingerprint" myeloma cells at baseline followed by serial examination for phenotypically similar cells to detect residual myeloma cells [8]. Others have depended on the typical antigenic profile of myeloma cell followed by clonality determination using kappa and lambda expression [9]. An additional method used by Kroger et al. is to examine the plasma cell chimerism; however, this methods requires additional validation.

Consensus has eluded this area, but with increasing utilization of this technique in recent years, we will likely see uniform standards being developed in this area. However, increasing sensitivity of the tests are likely to elevate the debate in the field as to how deep a response the goal of therapy should be. Deeper responses have always transformed into longer disease control, and most studies also suggest that attainment of deeper states of response leads to better overall survival [10]. However, the studies so far have not been able to definitively answer the question as to whether additional therapy with the goal of inducing a CR in a given patient translates to better outcome, thus proving that the impact of CR is not just a reflection of the disease biology. Clinical trials examining response-adapted treatment strategies are needed to answer this question definitively.

The second area of considerable importance addressed by Kroger et al. is the outcome of patients with high-risk myeloma. Nearly 25% of patients with myeloma die in the first 3 years of diagnosis despite improvements in median survival for all patients exceeding 8 years currently. Even intense approaches such as total therapy protocols have failed to make much of a dent in this high-risk population [11]. Although randomized trials of allogeneic transplantation have not shown overall survival benefit in myeloma, high-risk myeloma is an area where allogeneic approaches may have a distinct role [12,13]. Unfortunately, randomized trials of allogeneic transplantation in myeloma have not strictly defined the high-risk population as we currently do with fluorescence in situ hybridization–based abnormalities such as 17p deletion and the t(4;14), t(14;16) and t(14;20) transplantations.

Kroger et al. were unable to demonstrate any difference in progression-free survival for the high-risk group, which is an encouraging finding. Clearly, this is a rather small, retrospective study that included patients during a time where treatments for the disease have dramatically changed. However, these results should spur interest in developing randomized trials examining the utility of this modality in these patients.

Finally, there has been increasing skepticism about the ability of reduced-intensity regimens to induce meaningful responses in myeloma. Kroger et al. demonstrated the ability

Financial disclosure: See Acknowledgments on page 336.

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1083-8791/$ – see front matter
http://dx.doi.org/10.1016/j.bbmt.2012.12.020

to induce molecular remissions in a proportion of patients, which in turn has translated to improved progression-free and overall survival. Their results underscore the importance of designing prospective trials to better define the role of allogeneic transplant in myeloma, specifically the patient population that might benefit and the conditioning approach that is most appropriate.

ACKNOWLEDGMENTS

Financial disclosure: The author has nothing to disclose.

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Hyperferritinemia in Stem Cell Transplantation

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Article history:
Received 29 December 2012
Accepted 2 January 2013

Since the initial study of Altes and colleagues in 2002 [1], a large number of publications have reported a strong association between elevated serum ferritin before allogeneic hematopoietic stem cell transplantation (HSCT) and decreased post-HSCT overall survival (OS). Although this association is now beyond doubt, many areas of uncertainty remain.

In this context, the study of Dr. Meyer and colleagues [2] in this issue of *Biology of Blood and Marrow Transplantation* adds both light and darkness. They report the dynamic behavior of serum iron parameters, most notably ferritin, among 290 patients who underwent myeloablative HSCT at their center. As previously described, ferritin levels increased in the few months after transplantation and then decreased to below pre-HSCT levels in long-term survivors. They also could confirm that pre-HSCT ferritin is associated with increased nonrelapse mortality (NRM) and decreased OS. However, the most important finding of this study is that an elevated ferritin was associated with increased mortality even in 6-, 12-, and 24-month landmark analyses. This effect appeared to depend on both an increased risk of relapse and an increased risk of NRM in patients with elevated ferritin. This finding can be interpreted in at least three different ways.

First, it is possible that iron overload is indeed detrimental after HSCT, as previously assumed based on ferritin studies and for the reasons previously adduced: increased risk of infection, especially fungal, and liver toxicity. The present study would suggest that this effect extends to long-term survivors of HSCT. However, this seems the least likely explanation. Indeed, long-term mortality after HSCT depends primarily on disease relapse and complications of chronic graft-versus-host disease (GVHD), not liver toxicity (which is a very rare cause of death after the early post-HSCT period) or fungal infection (outside of the context of chronic GVHD and immunosuppression). There has been little evidence to date that hyperferritinemia is associated with the subsequent development of chronic GVHD. In Dr. Meyer's study, the adverse effect of hyperferritinemia on long-term survivors was primarily due to relapse, not NRM, which is

Financial disclosure: See Acknowledgments on page 337.

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1083-8791/$ – see front matter
http://dx.doi.org/10.1016/j.bbmt.2013.01.002