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EDITORIAL

Re-invigorating rather than re-inventing the wheel: augmenting the impact of salvage autologous stem cell transplantation for multiple myeloma in the era of novel agents

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The demonstration of the anti-myeloma activity of high-dose (HD) melphalan (subsequently supported with autologous stem cells; ASCTs) in the 1980s promised a significant advance in the care of patients with this incurable malignancy.[1] As a consequence, the procedure is now considered as the standard of care for the treatment of patients with newly diagnosed multiple myeloma (MM) generally up to the age of 65–70 years without significant comorbidities.[2] However, for the vast majority of patients, cure remains elusive and the disease will eventually relapse. The use of ASCT at relapse (salvage ASCT) presents an appealing option because of the potential for long-term disease control although, until recently, only retrospective, registry-based or single-center analyses investigating the use of salvage ASCT in the relapse setting after a prior ASCT have been published. We recently reported the results of prospective phase 3, randomized, multi-center, open-label trial that delineate the superiority of a salvage ASCT over conventional consolidation, in terms of durability of response.[3] Several questions remain in light of this recent evidence. What is the role of new biological therapies ('novel' agents) in the setting of relapse after a prior ASCT, in the context of salvage ASCT? How can we maximize the effectiveness of salvage ASCT to similar efficacy to that seen in first line? Can conditioning augmentation result in greater therapeutic efficacy, both in terms of depth and of durability of response? In this issue of *Bone Marrow Transplantation*, Gimsin and colleagues present important data delineating the impact of incorporating a novel agent into the conditioning regimen in the salvage ASCT setting.[4] They clearly demonstrate that by augmenting HD melphalan with the proteasome inhibitor (PI), bortezomib, they were able to induce similar disease durability or responses as those seen by the same patients during their first line ASCT. Although patients enrolled into the study were bortezomib-naive at first relapse, a clinical scenario that in many countries is becoming less common, the study does highlight an interesting avenue of clinical research.

The availability of new biological targeting agents (Immuno-modulatory drugs, IMiDs: thalidomide, lenalidomide and pomalidomide; PI: bortezomib and carfilzomib) in the induction setting for transplant-eligible patients has resulted in significantly deeper disease responses pre-ASCT, translating into more durable responses post ASCT in the frontline setting.[5] In the relapse setting, emerging data support the incorporation of novel agents to regain control of disease prior to salvage ASCT.[3,6] In the present study, where patients' original response to induction therapy was compared with their response to bortezomib-containing re-induction therapy, an improved depth of response was demonstrated. It is worthy of note that this study enrolled patients who were naive to novel agents, especially a PI, in the first line, so the relevance to current day practice remains speculative. Furthermore, as most, if not all, transplant-eligible patients will be exposed to novel agents in frontline treatment in current clinical practice, there is a need to determine what is the optimum re-induction therapy when salvage ASCT is planned. Currently this is not known and whether there is a role for combined novel agent regimens (triplets such as bortezomib/thalidomide/dexamethasone[7] or bortezomib/lenalidomide/dexamethasone[8]) remains to be clarified.

In relation to the conditioning regimen of the ASCT, HD melphalan alone has been the recognized conditioning regimen for several decades, and although the addition of other chemotherapy agents to HD melphalan has been studied, HD melphalan remains the standard.[2] Given the established role of novel agents in myeloma, the incorporation of novel agents into conditioning therapies is an attractive strategy. Pre-clinical data have demonstrated synergy between melphalan and novel agents[9] and such combinations might therefore be expected to yield augmented post-ASCT response rates and durability. In phase I/II studies, combining bortezomib with HD melphalan has shown improved depth of response irrespective of induction therapy.[10,11] A phase I/II dose-escalation study of lenalidomide augmenting high dose melphalan (HDM) is currently under recruitment. The results presented in this issue of *Bone Marrow Transplantation* provide further evidence of the utility of combinational conditioning regimens utilizing novel agents.[4] Conditioning regimens encompassing novel therapies, therefore, show some promise, but prospective randomized trial data are needed to clarify this area of MM therapy.

There remain a number of issues still to be addressed in the setting of salvage ASCT. The first is how best to maximize the durability of response to a salvage ASCT? The role of consolidation and maintenance has been extensively studied in first line ASCT but there is no reported evidence of its efficacy in the savage setting. In particular, given the expanding scope of therapeutic agents with differing modes of delivery (IV vs SC vs oral) combined with the potential for community-based therapy delivery, patient engagement with long-term maintenance strategies becomes a real opportunity. However, an evidence basis for the efficacy and thus the incorporation of further post-ASCT therapy is needed. The second issue is which patients benefit and especially which patients do not benefit from salvage ASCT. There is some evidence that molecular risk stratification at relapse after a prior transplant may delineate sub-groups where a second transplant offers no advantage in terms of durability of response but clearly we need to examine this area in more depth.

The third issue relates to the safety of a salvage ASCT. The salvage ASCT carries a low procedural mortality, at least in the short term, but as yet, we have few data on the impact of salvage ASCT on the incidence of second primary malignancies, especially treatment-related myelodysplasia. Thus, ultimately the appropriate selection of patients for salvage ASCT needs to be defined. The fourth issue relates to whether such therapeutic strategies can influence survivorship. This question has now become somewhat more complex in myeloma, given the expansion of post-relapse treatment strategies and their influence on survivorship. In some patient sub-groups, certain lines of therapy may even have an adverse impact on subsequent response to treatment and even survivorship. This serves to emphasize the need for clarity over

patient stratification and the use of currently evolving technology to delineate key biomarkers of response prediction. This is an area that has yet to be defined in relation to salvage ASCT.

Although salvage ASCT has been utilized in clinical practice for relapsed myeloma after a prior ASCT for many years, it is only in recent times that prospective studies have demonstrated the utility of this compared with a no-transplant strategy, as well as the evolution of investigational-conditioning regimens. The direction of travel is clearly to establish as good a durable response to the second ASCT as to the first ASCT, such that there can be an expected improvement in the overall survivorship. More studies are planned in this setting, which is to be welcomed.

CONFLICT OF INTEREST

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