Allogeneic transplantation for multiple myeloma: Yes, no or maybe?

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In this edition of *Bone Marrow Transplantation*, Ahmad *et al.*[1] report on a cohort of 92 newly diagnosed myeloma patients treated at a single institution from 2001 through 2010, with a planned standard autograft followed by an allograft from a HLA-identical sibling. At induction, 75/92 (82%) of patients were treated with VCR-adriamycin-dexamethasone and only a minority, 18/92 (18%), with bortezomib-based therapies. The conditioning regimen before the allograft consisted of IV fludarabine (30 mg/m^2) and IV cyclophosphamide (300 mg/m^2) for 5 days, followed by G-CSF-mobilised PBSC. The allograft was entirely delivered as an outpatient procedure. No maintenance or consolidation therapy with 'new drugs' was allowed. After a remarkable median follow-up of 8.8 years, probability of 10-year overall survival and PFS were 62% and 41%, respectively. Of note, the cumulative incidence of treatment-related mortality was 10% at 10 years. The cumulative incidence of extensive chronic GvHD was 79%. The majority of long-term survivors were, however, off immunosuppressive drugs at 5 years post transplant.

The results of this well-sized study reported by Ahmad *et al.* allow the following observations. First, despite the fact that the trial predated the introduction of so-called new drugs with a potent anti-myeloma activity, over 40% of patients became long-term survivors in continuous CR and at least a subset may have reached disease eradication due to graft-versus-myeloma. Second, transplant-related mortality was low and this finding clearly shows that the high transplant mortality rates observed decades ago have successfully been overcome. Third, long-term disease control and relapse mortality have become the major causes of treatment failure also in the setting of allografting. Fourth, although the incidence of chronic GvHD was high, most patients were off immunosuppression at year 5 post transplant and this undoubtedly allowed improvement in the quality of life.

In the light of the study by Ahmad *et al.* and of those by other groups, the abandonment of allografting, as some have suggested, appears rather premature even in newly diagnosed myeloma patients. Conversely, the role of allografting should become a matter of sound scientific debate in the myeloma community. Autologous transplantation undoubtedly remains the standard of care for younger medically fit myeloma patients. Three recent large studies that included an autograft followed by maintenance therapy with lenalidomide reported overall survivals of 85% at 3 years, and 73% and 81% at 4 years, respectively.[2, 3, 4] However, there is no clear evidence of cure and in a subset of high-risk patients prognosis remains dismal.

In the early 2000s, as in the study by Ahmad *et al.*, a number of trials employed the frontline tandem approach with an autograft followed by reduced-intensity or non-myeloablatvie allografts.[5,

[6], [7], [8], [9], [10], [11], [12] Some prospective trials also compared allografting with autografting using a biological assignment based on the availability of a HLA-identical donor. Substantial differences in inclusion criteria and treatment schemas partly contributed to conflicting outcomes. One meta-analysis, which included six clinical trials containing 1192 newly diagnosed patients who received tandem auto–auto and 630 who received a tandem auto-non-myeloablative allo, showed that the rates of CR were higher in the auto–allo group.[13] However, this did not translate into a survival advantage in the first 3 years or after 3 years from assignment given the higher non-relapse mortality in the auto–allo group. Follow-up duration greatly varied among studies. Of note, the survival advantage in the auto–allo group, reported in two comparative studies, became statistically significant after a follow-up of at least 3 years. Importantly, a new meta-analysis on the same trials with updated long-term clinical outcomes has been planned (Costa L., personal communication).

All these studies were, however, designed well before potent anti-myeloma agents such as bortezomib, carfilzomib or lenalidomade and pomalidomide became readily available. Although the annual reports of the European Society of Blood and Marrow Transplantation show an important transplant activity in plasma cell disorders in recent years, the real role of the combination of new drugs with graft-versus-myeloma has never been fully explored in this incurable disease. This may partly be attributed to the current limited interest on cell therapy strategies in myeloma. New drugs and graft-versus-myeloma are not mutually exclusive, and their synergy has clearly been shown in relapsed patients.[14]

Patient-risk stratification and depth of response have become important factors to evaluate prognosis and guide treatment decisions in hematological malignancies. In multiple myeloma, the recently Revised International Staging System by the International Myeloma Working Group showed that there is a subset of patients where overall and PFSs are very poor even in the era of new drugs.[15] In this patient subset, new effective treatments should be sought. The negative prognostic impact of high-risk cytogenetics appeared to be partly neutralized by graft-versus-myeloma in two recent studies.[12], [16]

Depth of response is another key factor to predict clinical outcomes in myeloma. Thanks to advanced molecular technology, PCR-based minimal residual disease (MRD) detection currently represents a powerful outcome predictor. In the GIMEMA-VEL-03-096 trial, 39 patients who received consolidation with a combination bortezomib-thalidomide-dexamethasone (VTD) after an autograft were monitored for MRD by qualitative nested-PCR and quantitative PCR (qPCR). After a median follow-up of 8 years, overall survival was 72% for patients in major MRD response versus 48% for those with MRD persistence (P=0.041).[17] This was a hallmark study that clearly showed that molecular remissions could be obtained with new drug-based consolidation treatments. However, the same group recently reported on the long-term outcomes of molecular monitoring after a tandem ‘auto-non-myeloablative allo’ approach.[18] Twenty-six patients were prospectively evaluated by both nested-PCR and qPCR. Specific markers were generated in 19/26. At the median follow-up of 12.1, overall survival for the whole-patient cohort was not reached and event-free survival was 4 years from the allograft. Rate of nested-PCR negativity increased up to 47% at 1 year after the allograft, whereas the molecular response rate was 63% at 2 years by qPCR. At a remarkable median follow-up of 12.1, median overall survival and event-free survival were not reached in patients who achieved nested-PCR negativity while they were 3.3 and 1.5 years, respectively, in the remaining patients. Graft-versus-myeloma appeared to determine prolonged molecular remission rates, higher than those reported after autografting and VTD. Although the number of patients studied was small, one may provocatively infer that, had these findings been obtained with other treatment modalities, they would have been emphasized more in the scientific community.

In summary, despite the recent dramatic improvement in survival, the overwhelming majority of myeloma patients invariably relapse. Given the potentially curative effect of graft-versus-myeloma, it may become ethical to evaluate its combination with potent anti-myeloma agents in young high-risk and/or early-relapsed patients where life expectancy is currently very poor.

Conflict of interest

The author declare no conflict of interest.

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