haematologica
Journal of the Ferrata Storti Foundation

In search for cure of multiple myeloma

by Ralph Wäsch and Monika Engelhardt

Received: October 20, 2023.
Accepted: November 8, 2023.

Citation: Ralph Wäsch and Monika Engelhardt. In search for cure of multiple myeloma. Haematologica. 2023 Nov 16. doi: 10.3324/haematol.2023.284292 [Epub ahead of print]

In search for cure of multiple myeloma

Ralph Wäsch and Monika Engelhardt

Department of Hematology, Oncology and Stem Cell Transplantation, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
Email: ralph.waesch@uniklinik-freiburg.de

Multiple myeloma (MM) is typically considered as an incurable disease, despite the ongoing improvements and the stunning developments of novel therapeutic approaches, the most recent being bispecific antibodies and chimeric antigen receptor (CAR) T-cells. Some patients may still experience long-term remission beyond 15 years (although such cases are rare), and one may consider these patients as cured. One option, which offers the potential for such long-term remission, is allogeneic stem cell transplantation (allo-SCT). Its immunological effects and allogeneic T-cell response against myeloma cells is one key event also currently being used in other T-cell-directed therapeutics in the autologous setting that are receiving much attention. Nevertheless, many physicians treating myeloma consider allo-SCT too toxic because of the immunosuppression, bearing the risk of subsequent infections and the hazard of graft-*versus*-host disease (GvHD), all of which result in a potentially high non-relapse mortality (NRM). Given this, allo-SCT is not routinely performed in MM patients.

Indeed, early studies with myeloablative conditioning had shown high NRM rates of 40-60%, these having decreased to 10-15% in recent years.[1-4] An improved approach to separate toxicities to achieve a lower NRM than with allo-SCT alone seemed to be a tandem-transplantation approach. This uses first a myeloablative high-dose chemotherapy with autologous SCT (auto-SCT) for deep myeloma remission induction, then followed by a reduced-intensity conditioning with allo-SCT to introduce the graft-*versus*-myeloma (GvM) effect. This results in a much lower NRM.[4] In addition, such an approach may not necessarily impair patients' quality of life (QoL), rather than improving QoL in those being in long-term remission. At our center, we had indeed assessed this in 109 consecutive allo-SCT MM patients using the revised-myeloma comorbidity index (R-MCI; www.myelomacomorbidityindex.org) with a dynamic assessment of the five individual R-MCI comorbidity factors of organ function (lung, renal and general constitution [Karnofsky performance status, KPS]), age and frailty.[2] We compared the R-MCI repeatedly in allo-SCT *versus* non-allo-SCT MM patients diagnosed and treated at our center. In a prospective cohort of 280 MM patients, the median R-MCI and KPS were 4 and 80%, similar to a retrospective cohort of 1,054 MM patients with 5 and 70%, respectively.[5] In line with this, the median R-MCI and KPS of our allo-SCT cohort were 4 and 80% at initial diagnosis (ID), which improved prior to allo-SCT and at last follow-up to 3 and 90%, respectively.[2] The single comorbidity factor assessment of all five R-MCI factors in our allo-cohort demonstrated that the estimated glomerular filtration rate (eGFR) decreased with advancing patients' age, but lung and frailty impairment did not whereas the KPS increased and patients' aged from a median of 51 years at ID to 60 years at last follow-up. Formally, the R-MCI improvement from 4 to 3 before allo-SCT and remaining at 3 at last follow-up even implicated a shift from intermediate-fit (R-MCI 4-6) to fitter patients (R-MCI 0-3). Similar results were obtained with a quadruple combination[5] or recent use of bispecific antibody treatment with teclistamab in relapsed/refractory MM patients,[6] here, the QoL likewise improved with treatment response. In our allo-SCT patients, the R-MCI before and after SCT remained at 3; bearing in mind patients' aging by almost a decade, which even underestimated our allo-SCT patients' QoL improvement.[2]

Retrospective studies indicate that it is best to perform allo-SCT in young, fit patients and those with high-risk disease early in the disease course.[3] In this issue of *Haematologica*, Kröger and colleagues report on a prospective phase II-study comparing autologous tandem SCT (auto-TSCT) with autologous-allogeneic tandem SCT (allo-TSCT).[7] SCT was followed by a 2-year intended thalidomide maintenance as upfront treatment for MM, which had not been performed in similar studies before. However, thalidomide discontinuation occurred frequently due to toxicity in both arms. Immunomodulatory drugs (IMiDs) can be especially useful after allo-SCT, since they may induce GvHD and therefore presumably enhance GvM. (Today, lenalidomide or pomalidomide are used as IMiDs rather than thalidomide due to their non- or much lesser polyneuropathy potential.) Studies in this setting using IMiDs before day +100 have even been stopped due to GvHD aggravation,[7] while reinforcing their potential when used at a sufficient interval beyond day +100.

In this ambitious multicenter study from 20 centers in Germany, 217 MM patients were included between 2008 and 2014, with a total of 178 patients who underwent the second SCT (allo n=132

[74%] and auto n=46 [26%]). Although allo-TSCT reduced the rate of recurrence and progression, the difference in progression-free survival (PFS) was marked but not significant with 43% for allo-TSCT and 21% for auto-TSCT after eight years (*P*=0.10). The 8-year overall survival (OS) was comparable with 52% for allo-TSCT and 50% for auto-TSCT, indicating that NRM did outweigh the lower relapse rate after allo-TSCT. Indeed, NRM was 13% after allo-TSCT and 2% after auto-TSCT at eight years after treatment (*P*=0.04), while relapse was reduced almost by half: 44% *versus* 77% (*P*=0.002), respectively.

Unfortunately, the study was not sufficiently powered with substantially fewer patients in the auto-TSCT arm than required: 46 instead of 74 patients. If an allogeneic donor was available, patients received allo-TSCT. This led to a lower number in the auto-TSCT arm than anticipated, due to improved availability of matched-unrelated donors and possibly also due to less MM patients (and treating physicians) who were willing to go forward to the second auto-SCT for the tandem-approach. With this much lower number of auto-TSCT, the observed 22% difference in PFS at eight years did not reach significance (*P*=0.1), also because the overall rate of relapse after auto-TSCT was lower than anticipated.

Therefore, the study was still unable to answer the question as to whether allogeneic transplantation offers any advantage in the treatment of myeloma. However, it again showed long-term benefit in some patients, indicating that it would be important to conduct further studies. Unfortunate in the study was also that the significance of allo-SCT for patients with high-risk (HR) features (i.e. HR-cytogenetics and <50-years of age) remained unsolved due to low number of patients and the maintenance use of thalidomide, which is outdated and was expectedly short-endured. Nevertheless, multicenter allo-SCT trials are rare, and the reduced rate of MM recurrence or progression by 23% after four years and by 33% at eight years was gratifying. The authors themselves suggest, that the 13% NRM after allo-TSCT, although in line with other studies including unrelated donors, is still too high for allo-TSCT to be recommended for all patients, regardless of the lower incidence of relapse. Prof. Kröger is currently performing a large, randomized, multicenter phase III-study to compare allo-SCT with standard triple relapse therapies in myeloma to provide even better answers, and this study has been encouraged by German health authorities.

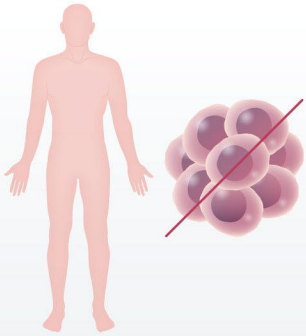
Therefore, until more recent studies provide up-to-date answers, the results of the phase II study on allo-TSCT *versus* auto-TSCT in this issue of *Haematologica* suggest both options as feasible, even though the study failed to reach its primary endpoint of improved PFS of 20% at four years with allo-SCT. Not unusual for clinical trials, insufficient patient numbers were accrued, and although the allo-TSCT arm fared better in PFS (43% vs. 21%), the OS was identical (52% vs. 50%), due to the TRM (13% vs. 2%) which needs further improvement. Before other large studies provide final results, allo-SCT is still rarely performed in young, fit and/or high-risk MM patients. Further prospective trials should be designed with combinations of newer drugs that allow profound cytoreduction before allo-SCT, enhance the efficacy of GVM through immunomodulatory effects after transplantation, and thus lead to long-term disease control and survival even in high-risk MM patients. Subsequent trials and newer CARTs and bispecifics emerge as attractive anti-MM options, with even more novel agents and therapies to be developed in the ever-growing field of MM care. Currently, the myeloma community is extremely enthusiastic about including CAR T-cell therapies and bispecifics in earlier treatment lines in the continued search for cure or very long-lasting remission in a more substantial fraction of MM patients (Figure 1).

References

1. Gahrton G, Svensson H, Cavo M, et al. Progress in allogenic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983--93 and 1994--8 at European Group for Blood and Marrow Transplantation centres. Br J Haematol. 2001;113(1):209-216.
2. Greil C, Engelhardt M, Ihorst G, et al. Allogeneic transplantation of multiple myeloma patients may allow long-term survival in carefully selected patients with acceptable toxicity and preserved quality of life. Haematologica. 2019;104(2):370-379.
3. Greil C, Engelhardt M, Finke J, Wäsch R. Allogeneic Stem Cell Transplantation in Multiple Myeloma. Cancers (Basel). 2021;14(1):55.
4. Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. Blood. 2003;102(9):3447-3454.
5. Waldschmidt JM, Keller A, Ihorst G, et al. Safety and efficacy of vorinostat, bortezomib, doxorubicin and dexamethasone in a phase I/II study for relapsed or refractory multiple myeloma (VERUMM study: vorinostat in elderly, relapsed and unfit multiple myeloma). Haematologica. 2018;103(10):e473-e479.
6. Dieterle MP, Mostufi-Zadeh-Haghighi G, Kus JW, et al. Safe and successful teclistamab treatment in very elderly multiple myeloma (MM) patients: a case report and experience from a total of three octogenarians. Ann Hematol. 2023 Sep 15. [Epub ahead of print]
7. Kröger N, Wulf GG, Hegenbart U, et al. Autologous-allogeneic versus autologous tandem stem cell transplantation and maintenance therapy with thalidomide for patients with multiple myeloma and age <60 years: a prospective phase II-study. Haematologica. xxx
8. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. Blood. 2011;118(9):2413-2419.

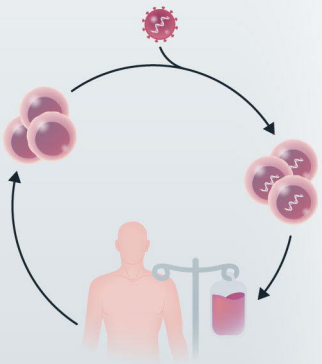
Figure Legend

Figure 1. The long way in the search for myeloma cure. The current promising alternatives to allo SCT are CAR T cells and bispecific antibodies or a combination of these options.



Allo-SCT

Bispecific antibodies



CAR T cell therapy