In search for cure of multiple myeloma

by Ralph Wäsch and Monika Engelhardt

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Multiple myeloma (MM) is typically considered 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 to be 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 that are receiving much attention. Nevertheless, many physicians treating myeloma consider allo-SCT too toxic because of the immunosuppression, bearing as it does 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%, although these have decreased to 10-15% in recent years. 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 a myeloablative high-dose chemotherapy with autologous SCT (auto-SCT), first 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. In addition, such an approach may not necessarily impair patients’ quality of life (QoL), if we consider this in relation to the improvement in QoL in those 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. 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 (5 and 70%, respectively). 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. The single comorbidity factor assessment of all five R-MCI factors in our allo-cohort demonstrated that estimated glomerular filtration rate (eGFR) decreases with advancing patients’ age, but no lung or frailty impairment, or increase in KPS was seen in patients’ aged a median 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 or recent use of bispecific antibody treatment teclistamab in relapsed/refractory MM patients; 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 the fact that patients were almost ten years older, this even underestimated our improvement figures in allo-SCT patients. 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. 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). 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 (IMiD) can be especially useful after allo-SCT, since they may induce GvHD.
and therefore presumably enhance GvM. (Today, lenalidomide or pomalidomide are used as IMiD rather than thalidomide due to their non- or much lesser polyneuropathy potential.) Studies in this setting using IMiD before day +100 have even been stopped due to GvHD aggravation, 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 than anticipated, due to improved availability of matched-unrelated donors, and possibly also due to the fact that less than 2 MM patients (and treating physicians), who were willing to go forward to auto-SCT, underwent tandem-approach transplants. 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. Unfortunately, in this study, 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 the low number of patients and the maintenance use of thalidomide, which is outdated and the use of which was, as expected, short-lived. 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.

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 are 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. In addition, although the allo-TSCT arm showed better PFS (43% vs. 21%), 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, plus newer CAR T-cell therapy approaches 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

Figure Legend

Figure 1. The long way in the search for myeloma cure. The current promising alternatives to allogeneic stem cell transplantation (allo-SCT) are chimeric antigen receptor (CAR) T cells and bispecific antibodies or a combination of these options.