

The stepchild in myeloma treatments: is allogeneic transplantation not so bad after all?

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doi:10.3324/haematol.2018.206987

In this edition of *Haematologica*, two papers from the US and Germany report on the long-term follow up of patients with multiple myeloma (MM) treated with reduced intensity conditioning (RIC) and allogeneic hematopoietic cell transplantation (HCT).^{1,2} Given the armamentarium of highly effective agents and a pipeline of novel therapeutic options, including chimeric antigen receptor T (CAR-T) cells, many hemato-oncologists believe that there is no longer a role for allogeneic HCT in the treatment of MM. Despite remarkable improvements in outcomes with novel drugs, these advances have not yet translated into cure of the disease, even when combined with high-dose chemotherapy and autologous HCT. Patients eventually relapse and die of their underlying disease. The two reports by Maffini *et al.* and Greil *et al.* both show that long-term survival, and potentially a cure, can actually be achieved in a proportion of myeloma patients by an allogeneic HCT, a treatment outcome that so far has not been observed with any other therapeutic strategy.

Maffini *et al.* present the long-term clinical outcomes of 244 patients who underwent allogeneic HCT following non-myeloablative conditioning with fludarabine and total body irradiation (TBI) between 1998 and 2016. In this study, more than half the patients had a chemotherapy-based induction with vincristine-doxorubicin-dexamethasone (VAD), whereas after 2006 mostly immunomodulatory / proteasome inhibitor triplet regimens were given. The majority of patients (86%) received tandem autologous-allogeneic treatment upfront, while 14% had failed previous autologous HCT. After high-dose melphalan and autologous HCT, 26% of patients were in a complete remission (CR), 19% in a very good partial remission (VGPR), 38% in a partial remission (PR), and 17% had progressive disease. Best responses following allogeneic HCT were: CR in 46%, VGPR in 17%, PR in 20% of patients [overall response rate (ORR) 83%], and 17% failed to achieve a response. With a median follow up of 8.3 years (range, 1.0-18.1), 5-year overall survival (OS) and progression-free survival (PFS) rates were 54% and 31%, respectively, and 10-year OS and PFS rates were 41% and 19%, respectively. Non-relapse mortality was low with 2% at day +100 and 14% at five years. The rate of acute graft-versus-host disease (GvHD) was acceptable (33% grade II, 11% grade III / IV), while the cumulative incidence of chronic GvHD was 46%. The key findings of this study were: i) that patients with disease that was refractory to induction and those with high-risk biological features experienced shorter OS and PFS, while among standard-risk patients the median OS was not reached, and the median PFS was 6.5 years. High-risk patients experienced a median OS of 8.4 years with a PFS of 2.5 years; ii) patients who proceeded to tandem HCT after a previously

failed autologous HCT had poor outcomes with a median OS of 1.2 years and a median PFS of 0.4 years; iii) those patients who achieved negativity for minimal residual disease (MRD) had a significantly lower relapse rate as compared with MRD-positive (MRD⁺) patients, indicating that marrow sampling for MRD assessment post HCT is an important tool to guide treatment decisions.

Similar observations were made by Greil *et al.* who report on their single center experience of 109 consecutive patients who received fludarabine-based RIC preparation followed by allogeneic HCT between 2000 and 2017. With a median follow up of 71.5 months (6 years), the authors observed a high ORR of 70% (CR rate 42%), with a median PFS of 14.2 months (1.2 years) and a median OS of 39.2 months (3.3 years). Consistent with the findings of Maffini *et al.*, survival was better in patients with sufficient response to induction therapy with a median OS of 65 months (5.4 years vs. 11.5 months in non-responders) and best in those undergoing allogeneic-HCT within first-line treatment (median OS not reached vs. 21.6 months in relapsed/refractory patients). Accordingly, the cumulative incidence of relapse was considerably lower in patients transplanted in first-line with 11% within the first year as compared to 50.3% after HCT for relapsed /refractory myeloma. Most relapses occurred within the first two years post HCT. Beyond five years, the survival curves appear to have reached a plateau with late relapses rarely occurring (10-year OS 28.4% and 10-year PFS 24%). Also in this cohort, the rate of high-grade GvHD was moderate and the non-relapse mortality low (8.4% within the first year, 12.4% at 10 years).

Both the studies by Maffini *et al.* and Greil *et al.* provide evidence that allogeneic HCT can induce graft-versus-myeloma activity that enables long-term disease control and survival (potentially even a cure) in selected myeloma patients. The following observations stand out and require further reflection and consideration.

1) Induction treatment in both trials was mostly chemotherapy-based. The majority of patients achieved “only” a partial response prior to autologous HCT. Both studies showed that the depth of response prior to HCT is critical, and that outcomes in patients who respond to induction are better when compared with non-responders, also after allogeneic HCT. Depth of response is a well-known parameter that predicts clinical outcomes in myeloma, and in recent years MRD testing by PCR or flow cytometry has become available at many centers. A hallmark study underlining the importance of MRD monitoring was presented in a report on the long-term outcomes of molecular monitoring after a tandem “auto-non-myeloablative allo” approach.³ Twenty-six patients were prospective-

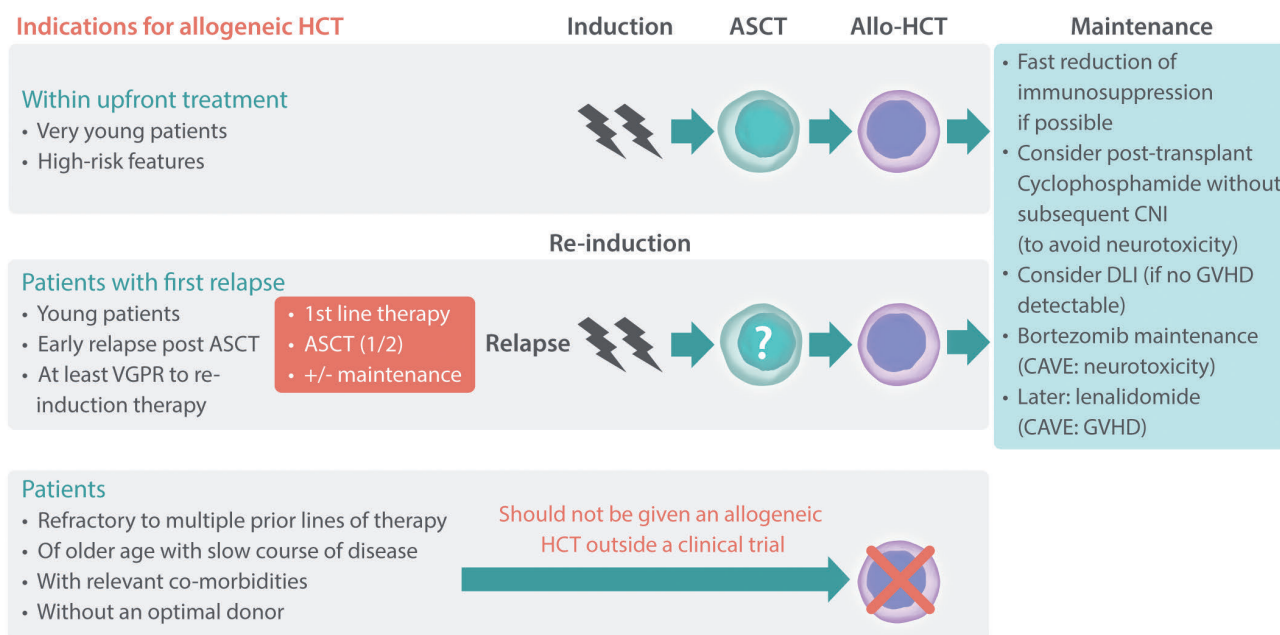


Figure 1. Proposed indication for allogeneic (allo)-hematopoietic cell transplantation (HCT) based on studies by Greil *et al.*,¹ Maffini *et al.*,² and other authors.^{4,7,17} ASCT: autologous stem cell transplantation; DLI: donor lymphocyte infusion, CNi: calcineurin inhibitors; GVHD: graft-versus-host disease; VGPR: very good partial remission; CAVE: possible adverse effect.

ly evaluated by PCR. At a remarkable median follow up of 12.1 years, median OS and EFS were not reached in patients who achieved nested-PCR negativity while they were 3.3 and 1.5 years, respectively, in the remaining patients.

Besides the intuitive recognition that “responders do better than non-responders”, the biological relevance of achieving a deep response prior to allogeneic HCT, and maintaining this response for a certain time post HCT, is that the establishment of graft-versus-myeloma activity requires time. In both studies published in this edition of *Haematologica*, relapses mostly occurred early, during the first 1-2 years post allogeneic HCT, reflecting the ongoing balance between disease biology (aggressiveness) and effectiveness of graft-versus-myeloma activity. The implementation of novel agents not only prior to HCT, but also post HCT, likely results in deeper responses prior to HCT and can help to maintain these responses post allogeneic HCT. Such strategies may translate into lower relapse rates during the first year, and thereby provide time for graft-versus-myeloma effects to establish, particularly once patients are off immunosuppression.

2) Both trials clearly indicate that there is anti-myeloma activity in some patients, as more than 20% were long-term survivors beyond ten years post HCT. Patients who relapsed post HCT appeared to have a relatively long survival, which is consistent with two recently published reports on long-term follow up post autologous versus autologous-allogeneic tandem HCT, in which patients post allografting had a significantly longer OS compared with those with relapse post autologous HCT.^{4,5} The question not answered by the studies published here is whether and how anti-myeloma activity of donor T cells could be enhanced *in vivo*, e.g. by donor lymphocyte infusions (DLI),

immunomodulatory drugs (IMiDs), proteasome inhibitors, monoclonal antibodies, etc. In both studies, not all patients had been treated with novel myeloma drugs as induction or post HCT, in the latter context, mostly for treatment of active disease. Moreover, at relapse, many patients received drugs outside the context of clinical trials depending on which one was readily available at that time. Defined subgroups in available studies were thus too small to provide statistically significant results regarding the impact of novel therapeutics in general or the influence of a specific drug. Newer data show that the application of post-HCT bortezomib is feasible, safe, and effective even in heavily pre-treated, poor-risk patients.^{6,7} IMiDs, in contrast, resulted in higher toxicity, acute GvHD, and early discontinuation in one trial,⁸ whereas in other trials, lenalidomide was given at lower doses and tolerability was good.^{9,10}

3) The current major cause of treatment failure after allografting is disease relapse, not treatment-related mortality. In contrast to early trials, today, under appropriate standard care, transplant procedures are associated with low toxicity and GvHD rates are acceptable. In the early 2000s, a number of trials introduced the tandem approach with an auto-graft for tumor debulking followed by reduced-intensity or non-myeloablative allogeneic HCT, a strategy that was able to lower the toxicity of the regimens. Yet, even today, allogeneic HCTs still bear the negative connotation of high toxicity, morbidity, treatment-related mortality, and a substantial negative impact on the quality of life. Interestingly, using the revised Myeloma Comorbidity Index (R-MCI), an established tool and prognostic instrument for risk prediction in myeloma patients that evaluates renal and lung function, Karnofsky Performance Status impairment, frailty, and age,¹¹ Greil *et al.* showed, that over time, the R-MCI

declined through treatment, indicating that performance status, and accordingly quality of life, was improved by treating the underlying disease. In those patients whose condition deteriorated, such a deterioration was from decreasing renal function and increasing age, and only in a minority was this due to complications from the allogeneic HCT, such as chronic GvHD.

Six prospective trials examined the role of allografting compared with autologous HCT alone.¹²⁻²¹ Substantial differences in inclusion criteria and treatment schemas partly contributed to conflicting outcomes. While most of these trials demonstrated an improved PFS in the allogeneic cohort, in only two studies did this response also translate into a longer OS. Similarly, a meta-analysis of published clinical trials containing 1192 newly diagnosed patients who received tandem auto-auto and 630 who underwent tandem auto-non-myeloablative allogeneic HCT showed that the CR rates were higher in the auto-allo group, but that there was no survival advantage in the first three years.²² Of note, the survival advantage in the auto-allo group, reported in two of the published comparative studies, became statistically significant after a follow up of at least three years. All these studies were conducted prior to the routine implementation of novel drugs into induction therapy; treatment of relapsed disease following HCT varied and was not taken into consideration when analyzing survival rates.

Today, there is remarkable heterogeneity in the use of allogeneic HCTs for patients with myeloma among different countries, and even institutions, and few ongoing clinical trials are studying how to improve allogeneic HCT strategies in myeloma or clarify its role. Trends in the use of HCT in myeloma were published in a large evaluation of the European Group of Blood and Marrow Transplantation (EBMT) over a 25-year period that examined a total of 3405 myeloma patients given allogeneic HCT either as an upfront treatment, within an upfront autologous-allogeneic HCT concept or as salvage treatment after a failed autologous HCT.²³ It was demonstrated that allogeneic HCT is currently mostly used as salvage therapy for myeloma patients after at least one autograft rather than within an intensified upfront induction-auto-allo approach. Similar to the studies by Maffini *et al.* and Greil *et al.*, the EBMT analysis demonstrated that OS rates in the first few years following allogeneic HCT were comparable with novel induction strategies involving new drugs and high-dose chemotherapy with autologous HCT; however, also in the EBMT dataset, long-term survival was observed in more than 20% of patients given allogeneic HCT. Again, patients receiving allogeneic HCT within an upfront auto-allo tandem approach achieved better outcomes, but even later transplants, usually in progression or relapse following autologous HCT, resulted in encouraging long-term outcomes with 25% survivor rates at ten years.

In the light of the studies by Maffini *et al.* and Greil *et al.*, and those by other groups, the abandonment of allografting, as some have suggested, appears rather premature even in newly diagnosed myeloma patients. The two reports draw particular attention to the long-term follow up with potential cure in subsets of patients. Reasons to re-examine the role of allogeneic HCT for patients with myeloma in controlled clinical trials are as follows.

- Today, validated tools are available to identify patients

at high risk in whom OS and PFS are very poor even in the era of new drugs, including the R-MCI,¹¹ the revised International Staging System by the International Myeloma Working Group,²⁴ cytogenetics, etc. For this patient subset, new effective treatments are urgently needed. The negative prognostic impact of high-risk cytogenetics appeared to be partly neutralized by graft-*versus*-myeloma activity in two recent studies.^{15,25}

- Patient preparation, including the achievement of a deep response prior to HCT, has significantly improved over the past decade by incorporating second and third generation proteasome inhibitors, IMiDs, monoclonal antibodies, and histone deacetylase inhibitors. Patients may, therefore, be in better condition (as many of them have not been exposed to toxic chemotherapy), have improved organ function, and be in deeper remission of the disease prior to HCT. These factors all optimize the baseline setting for an allogeneic HCT, reducing treatment-related toxicity, morbidity, mortality, and providing time for graft-*versus*-myeloma activity to be established.

- The role of the combination of new drugs with graft-*versus*-myeloma activity has never been systematically explored in this incurable disease. This may partly be attributed to the limited current interest on cell therapy strategies in myeloma. New drugs and graft-*versus*-myeloma activity are not mutually exclusive and their synergy has clearly been shown in relapsed patients.

In conclusion, despite the recent dramatic improvement in survival, the overwhelming majority of myeloma patients invariably relapse. Given the potentially curative effect of graft-*versus*-myeloma activity, the role of allografting should become a matter of sound scientific debate in the myeloma community. Combinations of allografts with potent anti-myeloma agents pre- and post-HCT should be examined in young high-risk and/or early relapsed patients for whom life expectancy is currently very poor. Modern MRD monitoring tools may guide individual treatment decisions and thereby further improve long-term outcomes.

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