EDITORIAL

Donor specific antibodies (DSA): the only risk factor for primary graft failure?

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In this issue of Blood and Marrow Transplantation, MT Altared et al. report on donor specific antibodies (DSA) having no effect on primary graft failure (PrGF), in patients undergoing a Haploidentical stem cell transplant (HAPLO) [1]. Primary graft failure (PrGF) is defined as the failure to achieve an absolute neutrophil count <0.5 $\times 10^9$/L by day + 28, for marrow (BM) or peripheral blood (PB) grafts, and by day + 42 for cord blood (CB) grafts, together with failure to achieve complete donor chimerism [2]. It is more difficult to define PrGF on the time of platelet engraftment, since platelet counts can be low for a significant number of weeks in about a quarter of patients. PrGF can occur also in matched sibling and unrelated donor transplants, and is associated with significant morbidity and mortality [3].

The rate of PrGF can vary from less than 1–35%, depending on a number of factors, including HLA matching between donor and recipient, intensity of the conditioning regimen, number of CD34+ cells infused, manipulation of the graft with removal of T cells and type of disease (Fig. 1) [2]. More recently donor specific antibodies (DSA) have been identified as an important predictor of PrGF [4–6].

Despite numerous studies connecting DSA to PrGF, Altared et al. in this issue of Blood and Marrow Transplantation, find no association of DSA with PrGF, in 107 JHAPLO transplant, prepared with a myeloablative conditioning regimen [1]: three patients experienced graft failure, and none of them had evidence of DSA pre transplant. Seventeen DSA-positive patients engrafted, similarly to 87 DSA-negative patients. Similar studies, in HAPLO transplant programs, denying an association between DSA and PrGF, have been reported [7, 8]. In one large study [8] PrGF was seen in 19/503 HAPLO transplants (3.8%): it occurred in 1% patients after 12 Gy TBI, 3% after full dose thiotepa, busulfan (3 days) and fludarabine (TBF3) ; 5% after reduced busulfan conditioning (TBF2), and 12% in patients receiving further reduce busulfan dose (TBF1). In a multivariate logistic regression analysis patients receiving the reduced intensity conditioning, had a 3 fold risk of PrGF, as compared to full dose TBI [7]. The proportion of DSA-positive patients among individuals with PrGF was 53%, and a second HAPLO transplant was successful independent of DSA [8]. In this study DSA appeared to play no role, either in predicting PrGF, nor in predicting engraftment after a second HAPLO graft. Similar data were reported from an other transplant group [7].

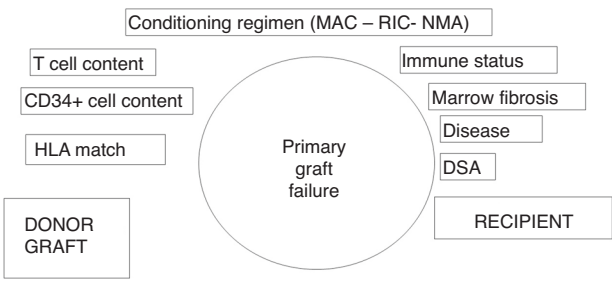

Fig. 1 This figures outlines some of the risk factors for primary graft failure, both in the donor graft (left) and in the recipient (right). Donor specific antibodies (DSA) are one risk factor, but others need to be taken in to consideration, such as the intensity of the conditioning regimen : myeloablative-MAC, reduced intensity-RIC, non myeloablative-NMA.

How can we reconcile these results, with current international guidelines, indicating DSA as a primary predictor of PrGF [5]. One simple answer is the following: the presence of DSA is not the only predictor of PrGF. The intensity of the conditioning regimen plays a major role. In 1986 Prentice and coworkers found that fractionated TBI exposed leukemia patients to a high risk (60%) of rejection as compared to single dose TBI (6%), in HLA matched -T cell depleted grafts [9]. In 1989, Storb and coworkers confirmed these data in a dog model: the risk of PrGF was 11% vs 65%, respectively, in dogs receiving single or fractionated dose TBI [10]. On top of intensity and immunosuppressive effect of the conditioning regimen, and the T cell content of the graft, the immune system and marrow cellularity of the recipient is also very important. In patients with Thalassemia, the immune system is intact and there is a packed marrow: graft rejection can be as high as 38%, when the exposure to busulfan is suboptimal [11]. At the other end of the spectrum, are patients with severe combined immune deficiency (SCID), who will engraft with no conditioning at all [12].

Since HLA mismatch is a known risk factor for graft failure it is clear that in HAPLO transplants, all other confounders need to be closely analyzed: intensity and immunosuppressive effect of the conditioning regimen, T cell content of the graft, the nature of the disease of the recipient, and alloimmunization /DSA.

In conclusion, when performing a HAPLO T cell replete graft for patients with leukemia, following a fully myeloablative regimen, DSA will have little or no effect on trilineage engraftment. On the other hand HAPLO transplant programs with either T cell depletion, non myeloablative conditioning regimens, and a diseases known to have a high risk of rejection, such as aplastic anemia or hemoglobinopathies, the role of DSA may be quite significant, and DSA-negative donors should be selected.

Primary graft failure appears to have a multifactorial pathogenesis (Fig. 1), and DSA may play a role in given transplant platforms, but not in others.

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AUTHOR CONTRIBUTIONS

All contributions are from one single author.

COMPETING INTERESTS

The author declares no competing interests.