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Graft failure after allogeneic hematopoietic stem cell transplantation

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ABSTRACT

Graft failure is a serious complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) defined as either lack of initial engraftment of donor cells (primary graft failure) or loss of donor cells after initial engraftment (secondary graft failure). Successful transplantation depends on the formation of engrafment, in which donor cells are integrated into the recipient's cell population.

In this paper, we distinguish two different entities, graft failure (GF) and poor graft function (PGF), and review the current comprehensions of the interactions between the immune and hematopoietic compartments in these conditions. Factors associated with graft failure include histocompatibility locus antigen (HLA)-mismatched grafts, underlying disease, type of conditioning regimen and stem cell source employed, low stem cell dose, ex vivo T-cell depletion, major ABO incompatibility, female donor grafts for male recipients, disease status at transplantation.

Although several approaches have been developed which aimed to prevent graft rejection, establish successful engraftment and treat graft failure, GF remains a major obstacle to the success of allo-HSCT.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) still remains to be the curative treatment option for various non-malignant and malignant hematopoietic diseases. The outcome of allo-HSCT primarily depends on the engraftment of the graft. Graft failure (GF), is a life-threatening complication which needs the preferential therapeutic manipulation. In this paper, we focused on the definitions of graft failure / poor graft function and also we reviewed the current understanding of the pathophysiology, risk factors and treatment approaches for these entities.

1. Definitions and survival

Engraftment after hematopoietic stem cell transplantation (HSCT), is defined as an absolute neutrophil count greater than 500 cells per liter [(ANC) $> 0.5 \times 10^9$/L] on the first day of three consecutive days. Platelet recovery is defined as a platelet count greater than 20,000 cells per liter [(PLT) $> 20 \times 10^9$/L] on the first day of seven consecutive days without transfusion support.

Primary graft failure is characterized by the absence of initial donor cell engraftment (donor cells less than 95%); peripheral blood ANC $< 0.5 \times 10^9$/L by day + 28 after allo-HSCT from peripheral blood or bone marrow progenitors in the absence of relapse [1] and by day + 42 after umbilical cord blood transplant due to expected delayed engrafment of umbilical stem cells [1,2]. In contrast, secondary graft failure is characterized by loss of donor cells after initial engraftment and recurrent ANC $< 0.5 \times 10^9$/L [1].

GF incidence ranges from 3.8 to 5.6% [3] and varies significantly according to different transplant settings. The cumulative incidence of GF was found to be significantly higher in non malignant disorders in comparison with malignant disorders [4].

It is important to distinguish between poor graft function from primary graft failure. Poor graft function is defined as severe cytopenia of at least two cell lines and/or transfusion requirement in the presence of hypoplastic/aplastic bone marrow with full donor chimerism, and in the absence of severe GVHD or relapse [4]. Poor graft function occurs in 5–27% of patients and is associated with considerably high infections and hemorrhagic complications. The distinctions and definitions of graft failure and poor graft function have been summarized in Table 1.

Overall survival (OS) in patients with malignant hematological disorders and graft failure after allo-HSCT is significantly lower than those with no graft failure. In a study, 5 years OS rates were found to be similar for primary graft failure, primary graft failure with autologous reconstitution and secondary graft failure as 18%, 11% and 13%, respectively.[5] Poor graft function is a life threating complication which may result in poor survival rates. In a study of unmanipulated haploidentical stem cell transplantation, overall survival was significantly lower in patients with PGF compared to those with good graft function (34.6 vs. 82.7%, $p < 0.001$) [6].

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Table 1
Characteristics of graft failure and poor graft function.

		Initial donor engraftment	Initial hematologic recovery	Cytopenias	Bone marrow	Relapse	Chimerism
Graft Failure	Primary	No	No	Yes	Hypocellular	No	Mixed or full recipient
	Secondary	Yes	Yes				
Poor graft function	Primary	Yes	No	Yes	Hypocellular	No	Full donor
	Secondary	Yes	Yes				

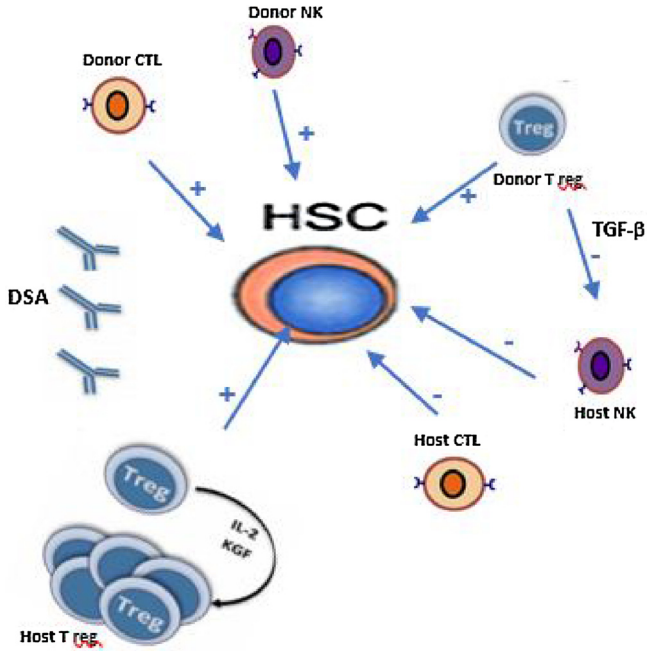

Fig. 1. Pathogenesis of graft failure. Arrows with positive sign indicate facilitating effects and with negative sign indicate inhibitory effects. CTL: cytotoxic T lymphocyte, T reg: regulatory T cell, NK: natural killer, TGF-B: tumor growth factor beta, DSA: donor specific antibody. Adapted from Masouridi-Levrat et al. [3].

2. Graft failure

2.1. Pathogenesis of graft failure in allogeneic hematopoietic stem cell transplantation

Graft failure ocurs as a result of recipient immune response against donor immunohematopoietic cells mediated by residual host immunity persisting after the conditioning regimen. Presence of residual host T cells are considered the most prominent effector cells mediating rejection [7]. However, donor cytotoxic T cells have a facilitative effect on HSC engraftment [8–10] absence of donor T cells in blood and marrow by graft T-cell depletion is associated with increased incidence of GF (Fig. 1). Residual host T-cell mediated graft failure can occur, more often in HLA-mismatched settings [11], in both HLA-matched and HLA-mismatched tranplants [12].

Graft rejection in HLA-matched transplantations can occur due to recognition of minor histocompatibility antigens (MİHA) on donor stem cells by immunocompetent T lymphocytes of recipient origin. After sex mismatched transplantations T-lymphocyte clones that recognize H-Y epitopes on male target cells have been generated during graft rejection [13]. Komatsu et al. revealed that, antigen-primed CD8 + T cells can mediate resistance, preventing allogeneic marrow engraftment in the simultaneous absence of perforin-, CD95L-, TNFR1-, and TRAIL-dependent killing [13].

CD4 + CD25 + Foxp3 + regulatory T cells (Tregs) are crucial immunomodulatory cells providing interactions between immune and hematopoietic cells [14]. In allo-HSCT either host or donor T regs are important to facilitate engraftment [3]. Host T regs produce IL 10 and help HSC to maintain in the bone marrow niche [3]. Removal of host Treg cells, but not $CD8^+$ T cells, significantly enhanced NK cell-mediated bone marow rejection in full MHC-mismatched and hybrid resistance BMT models [15]. Donor T regs can promote engraftment by mediating the NK cell supression through TGF-beta [15].

Natural killer (NK) cells also play a role in graft failure pathogenesis especially in HLA mismatched setting. NK cell mediated graft rejection, is the result of “missing self recognition”. The inhibitory receptors expressed on donor NK cells can not recognize their cognate MHC class I molecule on host cells [16]. Perforin, Fas- and TNF- based cytotoxicity has been found to be important in NK cell mediated rejection [3]. In mouse models, it has been shown that adoptive transfer of donor NK cells activated with human IL-2 can facilitate hematopoietic engraftment and immune reconstitution [17].

The impact of donor specific antibody (DSA) mediated rejection has been under investigation. Presence of DSA mostly as a consequence of previous transfusions, is associated with a 2- to 10-fold increase in GF during HLA mismatched HSCT. This increase is regardless of the stem cell source or the conditioning regimen [18]. DSAs against HLA class I (HLA-A and HLA-B) and class II (HLA-DRB1) Ags can have a deleterious effect on engraftment whereas the role of anti-HLA Abs against HLA-DPB1 and HLA-DQB1 still remains to be uncertain [18]. DSA mediated GF can occur either by antibody-dependent cell-mediated or complement mediated cytotoxicity [18]. The critical role of C1q fixing DSA on graft failure has been shown in haploidentical HSCT setting [18]. Also, in a study, integrated humoral and cellular immunity recognizing the same alloantigen of the donor have been shown to mediate GF in DSA-positive patients [18]. In addition, pretransplant donor-specific antibodies directed against CD34 + /VEGFR-2 + donor stem cells assosiated with higher risk of GF, providing evidence for antibody-mediated rejection [19]. Mean fluorescent intensity (MFI) in DSA positive patients has been found to be associated with GF. In a study, 75% of patients who had MFI > 1500 before haploidentical HSCT had GF whereas only 5% of patients with negative DSA had GF [19].

2.2. Risk factors of graft failure

Risk factors of GF can depend upon disease and transplantation related risk factors. Primary diagnosis of the patients is one of the major disease related risk factors for GF. Olsson et al. revealed three times higher incidence of graft failure in patients with non-malignant hematological diseases in comparison with malignant hematological diseases [20]. Historically graft failure has frequently observed after allogeneic transplants for severe aplastic anemia [21]. In myeloablative allogeneic hematopoietic cell transplantation for hematologic malignancies, an increased risk of primary GF was reported in chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) compared to acute myeloid leukemia (AML) patients. An enlarged spleen in patients with myeloproliferative disease and myelodysplastic syndrome is a also a risk factor for GF. Advanced disease status in patients with hematologic malignancies is found to be associated with increased risk of GF [22,23].

HLA disparity between recipient and donor during allo HSCT is also an important factor for graft rejection. Grafts obtained from matched unrelated and missmatched donors can result in increased GF rates