HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2009 January 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2008 January ; 14(Suppl 1): 165–170. doi:10.1016/j.bbmt.2007.10.025.

Graft Failure after Allogeneic Hematopoietic Cell Transplantation

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Abstract

Graft failure is a significant complication following allogeneic hematopoietic cell transplantation (AHCT). It may be due to rejection caused by recipient T-cells, NK-cells or antibodies. It is increased in HLA-mismatched grafts, unrelated grafts, T-cell replete transplants, sensitized patients and in patients treated with reduced intensity conditioning (RIC). In recipients of unrelated grafts, graft failure is increased in patients receiving major AB0 blood group mismatched transplants (p=0.008). Recent data also suggest that donor-specific antibodies to CD34+/VEGFR-2+ cells may be involved in graft failure after AHCT. Graft failure may be overcome by more intensified conditioning, increased cell dose, or more effective immunosuppression.

With more frequent use of RIC, cord blood grafts and other HLA-mismatched transplants, graft failure is an increasing problem after AHCT.

Keywords

graft failure; rejection; allogeneic hematopoietic stem cell transplantation; major histocompatibility complex; reduced intensity conditioning; cord blood transplant

INTRODUCTION

Graft failure or graft rejection after allogeneic hematopoietic cell transplantation (AHCT) may be manifested as either lack of initial engraftment of donor cells, or loss of donor cells after initial engraftment. In the latter case, autologous recovery may appear or, alternatively, marrow aplasia and pancytopenia may develop. Rejection is a major cause of graft failure and is due to recipient immune response against donor immunohematopoietic cells. Rejection is supported by the presence of recipient lymphocytes, preferentially T-cells, and the absence of donor cells in blood and marrow. Graft failure may also be due to other

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causes, such as viral infections, specifically, cytomegalovirus (CMV), human herpes virus type 6 (HHV6) and parvovirus. Drug toxicity and septicemia can also induce graft failure. In the latter case of graft failure, persistence of donor cells with or without the presence of recipient cells can be detected in blood and marrow.

Several immunological mechanisms may cause graft failure. Most commonly, it is due to immune recipient T-cells, although NK-mediated rejection also has been demonstrated in animal models [1-5]. NK-mediated allograft rejection, to some extent, can be overcome by cyclophosphamide (Cy) or total body irradiation (TBI) administered before transplantation and antimetabolites, such as methotrexate, given after transplantation [6]. Further, pre-treating canine recipients of DLA-mismatched marrow with an antibody to an adhesion molecule, CD44, allowed for sustained engraftment in most cases [1]. Whether antibodies can cause rejection is controversial [7-9]. In mice, antibody-mediated rejection resulted in rejection within three hours in allo-sensitized recipients of MHC mismatched bone marrow [10] in a similar way as antibody-mediated hyperacute rejection of renal allografts. In contrast, studies in a large animal model, transfusion-sensitized random-bred dogs, showed successful marrow engraftment in the presence of circulating cytotoxic antibodies against donor cells [11]. These results point toward cellular rather than humoral mechanisms underlying graft rejection in sensitized recipients. With the use of reduced intensity conditioning (RIC) and a wider application of HLA mismatched donors, graft failure has become an increasing problem. This article will summarize our present knowledge of graft failure/rejection in AHCT with a focus on recent advances.

Risk Factors for Graft Failure

Of major importance for allograft rejection is disparity between recipient and donor within the major histocompatibility complex (MHC). In patients with leukemia receiving myeloablative conditioning, the rejection rate was 0.1% in patients given HLA-identical sibling transplants, compared to 5% in those given HLA-mismatched grafts [12]. Recipients of stem cells from unrelated donors also have an increased risk of graft failure, compared to patients receiving grafts from HLA-identical siblings. Using unrelated donors, HLA class I disparity between donor and recipient was associated with an increased risk of rejection [13].

Patients sensitized by blood transfusions, but also by pregnancy are at increased risk of rejection. In immunized patients, rejections are likely caused by memory T-cells though some investigators have implicated antibodies that recognize major or minor histocompatibility antigens on donor cells. Patients with nonmalignant blood disorders, such as aplastic anemia and thalassemia major, who have been treated with multiple transfusions before transplant, had rejection probabilities in the range of 5 – 60% in earlier transplant series [14,15]. A low marrow cell dose was reported to be associated with an increased probability of graft failure [16]. Transfusion-induced sensitization can be largely averted in the MHC-identical setting by leuko-depletion [17]and in vitro irradiation [18,19] of transfusion products. An increased risk of graft rejection is also seen in recipients of T-cell depleted grafts[20].

Reduced intensity conditioning (RIC) is used in elderly patients and those with comorbidity who cannot tolerate full myeloablative conditioning [21,22]. However, with lower doses of chemo-radiation therapy, the host immune system may persist, resulting in an increased risk of allograft rejection. In this setting, the intensity of the conditioning seems important for the frequency of graft failure. Thus, using non-myeloablative conditioning, 6/24 patients experienced graft failure compared to 1/34, using more intense chemotherapy in the setting of RIC (p=0.02) [23].

HLA-Haploidentical Transplants

Only one third of the patients have HLA-identical sibling donors. With an unrelated donor pool of 10 million volunteer donors, 80% of Caucasian patients have access to well-matched unrelated donors. For the remaining patients, HLA-haploidential or partially mismatched related donors are ready available possibilities in most patients, especially in children, where parents may be motivated to serve as donors. HLA-haploidentical donors have been used also in adults, using effective T-cell depletion and overcoming graft rejection with a megadose of stem cells [24]. It has been postulated that, in this setting, graft rejection may be overcome by donor NK-cells, which may eliminate recipient immunocompetent cells. In experimental animals, it has been known for a long time that adding T-cells to the marrow inoculum could overcome the MHC barrier to engraftment [25,26].

Cord Blood Transplants

Almost all patients are potentially eligible for cord blood transplants, because tissue typing requirements are less stringent, and up to two HLA-antigen mismatches are acceptable [27,28]. Engraftment is delayed and graft failure is increased using cord blood transplants compared to bone marrow [29]. The cell dose is important for outcome and should be above 2×10^7 nucleated cells/kg recipient weight. When the cell dose is too low, double cord blood transplants may overcome this problem[30]. Today, using different strategies, it is possible to find a graft for all patients in need of AHCT. Therefore, using HLA-mismatched cord blood transplants, antibody-mediated microcytotoxicity using recipient serum and donor lymphocytes may need to be analyzed before transplant in multiply transfused recipients. A positive test raises a flag, heralding either the risk of antibody-mediated or, more likely, T-cell based acute rejection.

Major AB0 Blood Group Mismatch and Graft Failure

Among 224 leukemic patients receiving unrelated grafts, it was found that patients with major AB0 blood group mismatches had an incidence of graft failure of 7.5%, compared to 0.6% in recipients of minor AB0 mismatched or AB0 compatible grafts (p=0.02) [31]. In multivariate analysis, major AB0 mismatch (p=0.008) and HLA allele mismatch (p=0.03) were associated with graft failure.

This provocative observation has as yet not been reported by others [32]. While red blood cell antigens are not known to act like transplantation antigens and their expression is restricted to red blood cells and their more mature precursors, it is conceivable that transplantation methods used to overcome the ABO barriers might contribute to graft failure.

For example, red blood cell depletion of the graft might lead to losses of both stem cells and T lymphocytes, thought to be critical for sustained engraftment.

Antibodies against CD34+/VEGFR-2+ cells

Recipient T and NK cells are presumed to be the primary effector cells that mediate rejections after AHCT, but other immunological mechanisms may also contribute to the elimination of donor cells.

After organ transplantation alloantibodies may mediate a substantial proportion of organ allograft rejection episodes, contributing to both early and late graft loss [33,34]. Antibody-mediated rejection may also occur after AHCT [7]. Some studies have also indicated an inferior survival due to graft failure in patients with a positive crossmatch prior to AHCT [35].

It has recently been indicated that CD34+/VEGFR-2+ cells from adult bone marrow or cord blood may generate both haematopoietic and endothelial cells in vitro [36]. This cell population also seem to be of importance for engraftment after AHCT [37].

In a recent study By Nordlander *et al.*, we studied 19 patients without and 11 with rejection after AHCT and 20 non-transplanted healthy individuals [38]. Sera taken pre and post-transplantation from patients receiving AHCT were studied for the presence of donor CD34+/VEGFR-2+cell-specific antibodies. Significantly higher numbers of patients with rejection 9/11 (81 %), compared to 1/19 (5%) (p=0.001) without rejection had antibodies against donor $CD34^+$/VEGFR-2+ cells, but not CD34-/VEGFR-2- cells. In eight of the patients studied, antibodies against donor $CD34^+$/VEGFR-2+ cells were detected prior to transplantation. Purified IgG fractions from patients who rejected their grafts, but not controls significantly decreased the ability of these cells to form hematopoietic and endothelial colonies. The specific antigen for these antibodies is currently unknown.

In conclusion, donor-specific antibodies to CD34+/VEGFR-2+ cells may be involved in graft failure after AHCT.

Molecular Diagnosis of Engraftment

PCR amplification of variable number tandem repeats (VNTR) loci enables a sensitive technique to identify donor and recipient cells after AHCT [39,40]. For instance, using immunomagnetic beads, T-cells, B-cells and myeloid cells and others can be separated to increase the sensitivity and specificity of the method [41]. An increase in recipient T-cells precedes graft rejection [42]. In the setting of RIC, it may be especially valuable to follow T-cell chimerism, where high numbers of recipient T-cells on day +28 may be an indicator of graft rejection [43-45].

Prevention of Graft Failure

In patients with an increased risk of graft failure, graft rejection can be overcome by more intensified conditioning regimens, such as those using total lymphoid irradiation, thoraco-abdominal irradiation or TBI [46]. In patients with thalassemia major with class III disease receiving multiple transfusions and with cirrhosis, the risk of rejection was 30% in HLA-

identical siblings receiving conditioning with busulphan and Cy [47]. By adding hydroxurea, azathioprine and fludarabine to this regimen, the risk of rejection decreased to 8%. Increasing the cell dose by giving donor buffy coat transfusions, or giving G-CSF-mobilized peripheral blood stem cells (PBSC) instead of bone marrow, may also reduce the rates of graft rejection. [48,49]. PBSC have a 10-50 fold higher T-cell and NK-cell dose compared to bone marrow and a twofold higher CD34 cell dose [50]. PBSC is the stem cell source of choice using RIC.

The use of antithymocyte globulin in combination with Cy during conditioning in patients with aplastic anemia may increase the immunosuppressive effect of the conditioning and result in a lower incidence of graft rejection with corresponding enhanced rates of overall survival [51,52].

Cellular Therapy to Overcome Graft Failure

Donor lymphocyte infusions (DLI) have been increasingly used to treat relapse, especially molecular relapse, in patients with chronic myeloid leukemia, but may also be used to overcome rejection in cases of decreasing donor T-cell chimerism [53,54]. Side effects of DLI include GVHD and, in some cases, marrow aplasia. DLI have a potent immunological effect and, combined with monoclonal anti CD3 receptor antibody (OKT3), may reverse an impending rejection, even in patients who recieve 5/6 HLA antigen mismatched unrelated grafts [55]. In patients with aplastic anemia undergoing rejection, conditioning with a combination of cyclophosphamide and antithymocyte globulin before second AHCT has resulted in sustained grafts in most cases [56].

In patients with continued poor graft function in the absence of graft rejection, a boost of donor stem cells without additional preparative chemotherapy may improve graft function [57-59]. Nine of 15 (60%) evaluable patients became transfusion-independent within one month after a boost marrow was given [59]. Because boost marrow may induce GVHD, T-cell depletion of the stem cells can prevent GVHD and improve survival in some patients [60].

In patients with fulminant rejection, retransplantation is necessary, using the same or another donor. Conditioning should preferentially differ from that used at the first transplant to avoid unnecessary toxicity. Because of an increased risk of rejection and GVHD with repeated transplants, ATG or Campath may be considered during conditioning. A high nucleated cell dose $>2 \times 10^8$/kg should be aimed for. For immune modulation and to enhance engraftment co-transplantation with mesenchymal stem cells has recently been evaluated in pilot studies [61].

Presently, the mechanism causing graft failure after cord blood transplants is not well defined. If it is mediated mainly by recipientT-cells, it may be overcome by ATG, increasing the cell dose and/or the intensity of the conditioning regimen. In immunized patients, it has been speculated to be caused by antibodies against HLA antigens.

Immune Absorption

In the case of alloimmune patients, HLA-specific antibodies may be modulated by high dose intravenous immunoglobuline [62]. The combination of immune absorption and treatment with anti-B-cell antibodies might be able to remove anti-HLA antibodies [63]. This method has successfully been employed in renal transplant recipients with anti HLA antibodies. Immune absorption to remove anti-HLA antibodies has also been employed before AHCT in a few anecdotal cases.

In one patient with antibodies against donor $CD34^+$/VEGFR-2+ cells we have tried to change the conditioning therapy in order to decrease or remove these antibodies (Mattsson et al. unpublished data). A 2 ½-year-old patient with Hemophagocytic lymphohistiocytosis (HLH) showed increasing recipient chimerism after AHCT. At 1 year the patient showed >95% recipient cells in all cell lineages. Antibodies to CD34+/VEGFR-2+ donor cells were detected. The patient was retransplanted with the same donor since no other donor was available. The conditioning therapy consisted of fludarabine combined with cyclophosphamide and 5 days with plasmapheresis. In microcytotoxicity assay patient sera showed 100% lysis of CD34+/VEGFR-2+ donor cells before plasmapheresis, but no lysis after 5 days of plasmapheresis. After AHCT, antibodies against donor CD34+/VEGFR-2+ cells were detected on day +14. The patient again showed increasing recipient hematopoietic chimerism. At four weeks, a bone marrow aspirate showed 95% recipient cells among CD34+ cells and 80% recipient T cells. Despite this, the patient developed acute grade III GVHD and eventually converted to full donor chimerism in all lineages.

In summary, graft rejection is mainly caused by immunized T-cells, although other mechanisms may also exist. Rejection may be overcome by increasing the cell dose, or by more intense immunosuppression and conditioning prior to transplantation. Because of the wider use of HLA-mismatched grafts and RIC, graft failure is an increasing problem in clinical AHCT. Chimerism studies enables early diagnosis and in some cases intervention with or without immunosuppression and infusion of additional donor cells. In cases of fulminant rejection, retransplantation is necessary.

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