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Review

Impaired Hematopoiesis after Allogeneic Hematopoietic Stem Cell Transplantation: Its Pathogenesis and Potential Treatments

Masahiro Imamura

Department of Hematology, Sapporo Hokuyu Hospital, Sapporo 003-0006, Japan; mimamura@med.hokudai.ac.jp

Abstract: Impaired hematopoiesis is a serious complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Bone marrow aplasia and peripheral cytopenias arise from primary and secondary graft failure or primary and secondary poor graft function. Chimerism analysis is useful to discriminate these conditions. By determining the pathogenesis of impaired hematopoiesis, a timely and appropriate treatment can be performed. Hematopoietic system principally consists of hematopoietic stem cells and bone marrow microenvironment termed niches. Abnormality in hematopoietic stem and progenitor cells and/or abnormality in the relevant niches give rise to hematological diseases. Allo-HSCT is intended to cure each hematological disease, replacing abnormal hematopoietic stem cells and bone marrow niches with hematopoietic stem cells and bone marrow niches derived from normal donors. Therefore, treatment for graft failure and poor graft function after allo-HSCT is required to proceed based on determining the pathogenesis of impaired hematopoiesis. Recent progress in this area suggests promising treatment manipulations for graft failure and poor graft function.

Keywords: allogeneic hematopoietic stem cell transplantation; impaired hematopoiesis; graft failure; poor graft function; graft-versus-host disease; hematopoietic stem cells; bone marrow niches

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an essential therapy to cure many hematological diseases. However, there are several obstacles that should be overcome to obtain better outcome. Although graft-versus-host disease (GVHD) is the most frequently observed complication after allo-HSCT, impaired hematopoiesis should be also controlled along with some other complications such as relapse of the underlying diseases, infections (mostly viral infections), and so on. When no recovery of hematopoiesis (i.e., absolute neutrophil count $\geq$500/µL and/or platelet count $\geq 3 \times 10^4$/µL) until day 28 lasting for at least three consecutive days is seen, urgent decision of appropriate treatment is required to ensure a definite hematopoietic recovery. No or delayed recovery of hematopoiesis (cytopenias) is caused by graft failure and poor graft function.

Graft failure and poor graft function can be primary and secondary, respectively. Graft failure incidence occurs in 5.6% of patients who underwent allo-HSCT [1]. Primary graft failure indicates no initial donor engraftment and no initial hematopoiesis, resulting in hypocellular marrow and peripheral cytopenias under mixed or full recipient chimerism. In contrast, a temporal hematological recovery is seen after initial donor engraftment in secondary graft failure, showing hypocellular marrow and peripheral cytopenias under mixed or full recipient chimerism. Primary graft failure can be induced by the following factors: T-cell depleted hematopoietic stem cell graft, insufficient amount of hematopoietic stem cell graft, reduced immunosuppression, type of GVHD prophylaxis, stem cell source, female donor grafts for male recipients, HLA-mismatched graft, presence of donor-specific anti-HLA antibody, major ABO incompatibility, recipients with myeloproliferative diseases, disease status in patients at transplantation, patient's age, use of myelocytotoxic drugs, presence of septicemia, and presence of viral infections [1,2].

Poor graft function occurs in 5.0–27.0% [3,4] and it is associated with GVHD, viral infections, use of myelocytotoxic drugs, patient's age, unrelated donor status, HLA-mismatched donor, mycophenolate mofetil use, and lower $CD34^{+}$ cell dose [5]. Among those, GVHD is the major risk factor for poor graft function observed in 14% of 171 recipients of an HLA-matched bone marrow transplantation [6]. Primary poor graft function occurs after initial donor engraftment but no initial hematological recovery, resulting in hypocellular marrow and peripheral cytopenias under full donor chimerism. Hypocellular marrow and peripheral cytopenias are seen after initial donor engraftment and initial hematological recovery in secondary poor graft function under full donor chimerism. All four conditions require no evidence of disease relapse. Thus, chimerism analysis is important to choose an appropriate treatment, discriminating graft failure from poor graft function. Here, I will focus on the pathogenesis of impaired hematopoiesis after allo-HSCT and possible therapeutic manipulations.

2. Importance of Chimerism Analysis for Determination of Graft Failure and Poor Graft Function

Chimerism analysis based on polymerase chain reaction amplification of variable number tandem repeat or short tandem repeat allows the detection of imminent graft failure (rejection), poor graft function, or disease recurrence [7,8]. Graft failure can be discriminated from poor graft function by analyzing chimerism status as well as bone marrow and peripheral blood recovery. When cytopenias are present around day 28 after allo-HSCT, it is important to analyze the chimerism status to determine whether impaired hematopoiesis is caused by graft failure or poor graft function. Full recipient or mixed chimerism leads to primary graft failure or secondary graft failure. Mixed chimerism is composed of three different types depending on the extent of residual recipient cells; namely, decreasing, stable, and increasing mixed chimerism [9]. Bader et al. [10] suggest that decreasing mixed chimerism requires weekly follow-up until establishing complete chimerism (>97% to >99% of donor cells). Stable mixed chimerism requires weekly monitoring during engraftment including T-cell and NK-cell chimerism and thereafter bimonthly monitoring to realize late graft rejection. Increasing mixed chimerism requires weekly monitoring during the first 200 days (since most relapses occur during this period in patients with acute leukemia). Pre-emptive immunotherapy in patients with hematological malignant diseases is recommended when recipient cells exceed 5%. On the other hand, it is recommended when recipient cells exceed 30% in patients with non-malignant diseases.

Another frequently observed phenomenon is split chimerism in which donor cells are not detectable in all cell compartments, whereas some cell compartments are completely recipient origin [10]. This split chimerism often occurs in patients with severe combined immunodeficiency or in patients transplanted with reduced intensity conditioning regimens. Therefore, it is important to analyze chimerism not only in whole peripheral blood or bone marrow cells but also in lineage-specific subpopulations. Initially, the importance of chimerism analysis in T cells was indicated by the findings that patients with >90% donor T cells developed more frequently acute GVHD than did patients with <90% donor T cells [11] and patients with <90% donor T cells had rejection and relapse more frequently than did patients with >90% donor T cells [12]. On the contrary, Guimond et al. [13] demonstrated that mixed chimerism in T-cell and NK-cell subpopulations were frequently found in pediatric patients with leukemia relapse, but not in children in remission. In contrast, mixed chimerism in these subpopulations was not found in adult patients with relapse. Pediatric patients with mixed chimerism in T-cell and NK-cell subpopulations on day 28 seemed to be more likely to reject the graft [14]. Bornhäuser et al. [15] demonstrated that patients with NK-cell donor chimerism <75% on days 10–30 after allo-HSCT more often rejected their grafts than those with >75%. Baron et al. [16] demonstrated that T-cell and NK-cell chimerism levels below 50% were significantly associated with higher risk for graft rejection.

We analyzed donor-type chimerism in $CD3^{+}$, $CD14/15^{+}$, and $CD56^{+}$ cells from patients who underwent allo-HSCT with myeloablative or non-myeloablative conditioning

regimens by PCR amplification of four types microsatellites (D3S1359, D6S89, ACTBP2, and HGH) [17]. More frequent mixed chimerism on day 28 was observed in all fractions from patients transplanted with non-myeloablative conditioning regimens and in $CD3^+$ cells from patients transplanted with a non-total body irradiation (TBI) regimen. TBI-containing myeloablative conditioning regimens induced faster engraftment and full donor chimerism in all fractions than did non-TBI containing myeloablative conditioning regimens. Patients who had >50% donor-type chimerism in $CD3^+$ cells on day 14 frequently developed acute GVHD (>grade II), and patients who had donor-type chimerism <50% in $CD56^+$ cells on day 14 had more frequent graft failure. Furthermore, patients <75% donor-type cells in all fractions on day 28 frequently developed graft failure and relapse. Patients transplanted with non-myeloablative regimens and showed >50% donor-type chimerism on day 14 had more frequently acute GVHD (grade II to IV) than those with <50% donor-type chimerism. In mixed chimerism in $CD14/15^+$ and $CD56^+$ cells on days 14 and 28, decreasing mixed chimerism is a favorable marker for better overall survival, while increasing mixed chimerism is not. In patients with increasing mixed chimerism, some additional treatment should be considered. Although tapering and withdrawal of immunosuppressive drugs or donor-lymphocyte infusion (DLI) are occasionally performed, the effect appears to be vague. These results suggest that the extent of donor-type chimerism in lineage-specific cells show an impact on outcome in allo-HSCT. Thus, the chimerism analysis provides important information as to when prompt therapeutic interventions should be made.

Recently, new methods using next-generation sequencing and crystal digital PCR which are more sensitive and accurate than conventional methods for analyzing chimerism status have been developed [18]. Therefore, these methods will be widely used for chimerism analysis in the future.

3. Factors Mediating Graft Failure and Poor Graft Function

3.1. Involvement of T Cells and NK Cells

Graft failure is caused by residual host immunity (i.e., alloreactive immune responses), mainly mediated by T cells and NK cells [19]. T-cell-mediated graft rejection can occur in both HLA-mismatched and HLA-matched settings [20,21]. Although residual host $CD8^+$ T cells are a major effector for graft rejection, residual host $CD4^+$ T cells can reject graft and NK cells also play an important role in graft rejection via defective inhibitory receptor function of NK cells [22–28]. $CD8^+$ and $CD4^+$ T-cell-mediated graft rejection were associated with massive infiltration in the bone marrow of these cells secreting interferon (IFN)-γ [29,30]. Furthermore, $CD8^+$ T-cell-mediated rejection was unable to be induced through perforin, Fas ligand (FasL), tumor necrosis factor receptor (TNFR) 1, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), tumor necrosis factor-like weak inducer of apoptosis, and tumor necrosis factor-like ligand 1A [31,32]. NK-cell-mediated rejection, mainly observed in major histocompatibility complex (MHC)-mismatched transplantations, is the result of a "missing-self recognition," when the inhibitory receptors expressed on donor NK cells, belonging to host Ly49 family in mice and to the killer immunoglobulin-like receptors (KIRs) in humans, fail to recognize their cognate MHC class I molecule on host cells [33]. Graft rejection by host NK cells, at least partially, depends on perforin-mediated cytotoxicity [34,35]. NK cells also express activating receptors such as CD226 [36,37] and natural killer group 2D (NKG2D) [38]. The balance of activating and inhibitory signals determines NK-cell activation against target cells [39]. Accordingly, donor T cells and NK cells facilitate donor hematopoietic stem cell engraftment through inhibiting residual host immunity. However, an opposite finding was reported by demonstrating that rapid expansion of donor T cells suppressed hematopoiesis derived from donor hematopoietic stem cells [40]. This controversial observation appears to be caused by the difference of T-cell dose in infused hematopoietic cells which may correlate to the severity of acute GVHD.

3.2. Involvement of Regulatory T Cells

CD4$^+$CD25$^+$ regulatory T cells (Tregs) are not restricted to their regulatory actions within adaptive and innate immune systems, thus suggesting that the ability of these cells to inhibit progenitor cell activity illustrates the complex interactions between the immune system and hematopoietic compartments. Namely, negative regulation of myeloid progenitors can occur in the presence of Tregs after ablative conditioning and allo-HSCT through transforming growth factor (TGF)-β. Thus, the intentional addition (i.e., donor) and/or deletion (i.e., recipient) of this population may be important to consider within the context of the hematopoietic and immunologic reconstitution of the patient after allo-HSCT [41]. Similarly, TGF-β is also involved in Treg engraftment facilitation as anti-TGF-β monoclonal antibody treatment prior to allo-HSCT led to a significant increase in NK-cell-mediated graft rejection, suggesting that Tregs mediate NK-cell suppression through TGF-β [42]. Accordingly, adoptive transfer of host-type Tregs improved durable engraftment of allogeneic bone marrow grafts [43,44]. High-resolution in vivo imaging showed, marked co-localization of hematopoietic stem cells with host Tregs on the endosteal surface in the calvarial and trabecular bone marrow. However, hematopoietic stem cells were lost by depletion of Tregs, suggesting a direct effect of Tregs in bone marrow niche generation and maintenance [45]. This effect seems to be essentially dependent on interleukin (IL)-10 production by Tregs. Recently, bone marrow Tregs have been reported to mediate stromal cell function and support hematopoiesis via IL-10 [46]. Following Treg depletion, the function and phenotype of both mesenchymal stromal cells (MSCs) and hematopoietic stem cells was impaired. Transplantation also revealed that a Treg-depleted niche has a reduced capacity to support hematopoiesis. Bone marrow Tregs are high producers of IL-10 and Treg-secreted IL-10 has direct effects on MSC function.

Treg-based cellular therapies are still limited because of the difficulties to isolate them from peripheral blood in sufficient amounts. Use of ex vivo expanded third-party Tregs [47] or pharmacological approaches using low-dose IL-2 [48–51], IL-2/anti-IL-2 monoclonal antibody complexes [52] and keratinocyte growth factor (KGF) [53] to induce Treg expansion in vivo may be utilized.

Koreth et al. [48] investigated whether low-dose IL-2 could preferentially enhance Tregs in vivo and suppress clinical manifestations of chronic GVHD, since IL-2 is critical for Treg cell growth, survival, and activity [54]. Daily low-dose IL-2 was safely administered in patients with active chronic GVHD that was refractory to steroid therapy, showing sustained Treg expansion in vivo and amelioration of the manifestations of chronic GVHD. The mechanism of this phenomenon is mediated by selective increase of signal transducer of transcription 5 (STAT5) phosphorylation in Tregs and a decrease of phosphorylated STAT5 in CD4$^+$ T cells, thus restoring the homeostasis of CD4$^+$ T-cell subsets and promotes the reestablishment of immune tolerance [49]. On the contrary, Xhao et al. [50] and Betts et al. [51] suggested that low-dose IL-2 therapy required still caution. Although administration of a complex of IL-2 and anti-IL-2 antibody enhanced donor chimerism early as well as long-term engraftment following non-myeloablative conditioning regimen and MHC-matched allo-HSCT, timing of administration of this complex was crucial: administration of this complex post-HSCT more efficiently facilitated engraftment than pre-HSCT. Importantly, this approach clearly suppressed the emergence of host anti-donor CD8$^+$ T cells by the transient activation and expansion of recipient Tregs [52]. Efficacy of low-dose IL-2 therapy may be expected to some extent; however, more investigation is required to obtain a sufficient and reliable conclusion.

3.3. Involvement of Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs), which can be obtained from bone marrow, umbilical cord, and adipose tissue, have the capacity to differentiate in vitro and in vivo into several mesenchymal tissues, including bone, cartilage, tendon, muscle, adipose tissue, and, possibly, bone marrow stroma [55,56]. MSCs possess the following characteristics [56]. MSCs seem to escape the immune system. Adult MSCs express intermediate levels of

HLA major histocompatibility complex (MHC) class I molecules and do not express HLA class II antigens of the cell surface [57]. MSCs possess multiple effects on immune cells as follows: increase in Tregs and IL-10 production, decreasing IFN-γ production by T helper cell type 1, increasing IL-4 production by T helper cell type [58], inhibition of mixed lymphocyte cultures and subsequent development of cytotoxic T cells by soluble factors [59], production of IL-6, IL-8, stem-cell derived factor 1, and vascular endothelial growth factor, inhibition of T-cell activation by prostaglandin E_2 which induces Tregs [56,58], production of indoleamine 2,3-dioxygenase which is induced by IFN-γ which catalyzes the conversion from tryptophan to kynurenine and inhibits T-cell responses [60], inhibition of T-cell responses by TGF-β [59], hepatocyte growth factor, and IL-2, induction of macrophage differentiation from M1 to M2 [56,61], delayed maturation of antigen presenting cells [62], decreased expression of HLA-DR, suppression of B-cell responses [63], secretion of HLA-G which interacts with inhibitory receptors on NK cells [64], suppressed differentiation of naïve T cells into Th-17 cells [65].

Furthermore, MSCs are key players in the bone marrow stem cell niche [66]. Following the transplantation of mouse bone marrow MSCs under the kidney capsule, the MSCs formed several crucial niche elements such as osteoblasts, adipocytes, and reticular fibroblasts that recruited HSCs and sustained hematopoiesis in the recipient [66]. MSCs contribute to the formation of the bone marrow niche, thus providing an appropriate microenvironment for control of the maturation, differentiation, and survival of blood-born cells [67]. MSCs support hematopoiesis and colocalize with HSCs during ontogeny [68].

Almeida-Porada et al. [69] demonstrated that co-transplantation of human stroma cell progenitors into preimmune fetal sheep resulted in early appearance of human donor cells in circulation and enhanced cell levels in the bone marrow at later time points after transplantation. Lazarus et al. [70] demonstrated that co-transplantation of HLA-identical sibling culture-expanded mesenchymal stem cells and hematopoietic stem cells in patients with hematologic malignancies were feasible and safe, indicating a need for further investigations. In case of patients with higher risk of graft failure and poor graft function, co-transplantation of MSCs may be warranted as shown in several human studies [71–75]. However, efficacy of co-transplantation of MSCs in allo-HSCT is still controversial [76–78] because of the weak study design and small study populations in previous clinical studies [79,80], although it appears that the infusion of MSCs has been shown to be safe and well-tolerated in humans with a slightly positive trend for overall survival [80]. In order to prove the efficacy of co-transplantation of MSCs, well-designed larger clinical studies are required.

MSCs possess immunoregulatory function as wells as engraftment-enhancing function [56]. Therefore, MSCs can be utilized for prevention of acute and chronic GVHD as well as graft failure.

Le Blanc et al. [81] first reported that severe acute GVHD was successfully treated with third party haploidentical MSCs. We have also used bone marrow-derived third party MSCs (JR-031) for steroid-refractory grade III or IV acute GVHD in 25 patients (grade III 22 patients and grade IV, 3 patients), resulting in 24% CR and 36% PR, respectively [82]. MSCs did not seem to inhibit a graft-versus-leukemia effect. Adverse effects commonly associated with MSC infusions were not observed. Furthermore, Kurzuberg et al. [83] reported a similar effect in pediatric patients who had steroid-refractory acute GVHD after allo-HSCT. Among several MSCs, placenta-derived decidua stromal cells appear to be more effective than bone marrow-derived MSCs for treatment of severe acute graft-versus-host disease [84].

3.4. Donor-Specific Anti-HLA Antibody

Humoral immunity is also related to graft rejection and delayed engraftment. Donor-specific HLA antibodies (DSA) can cause primary graft failure in HLA-mismatched and haploidentical transplantations [85–90]. Integrated humoral and cellular immunity against the same alloantigen of the donor can mediate graft rejection in DSA-positive patients

who underwent HLA-mismatched cord blood transplantation [91]. Furthermore, other donor-specific antibody against CD34^{+}/VEGFR-2^{+} endothelial progenitor stem cells causes primary graft rejection [92].

The treatments to desensitize patients with DSA are classified into the following four strategies: 1. Antibody removal by using plasmapheresis or immunoabsorption; 2. inhibition of antibody production by using rituximab, and proteasome inhibitor against alloantibody-producing plasma cells (bortezomib); 3. antibody neutralization using intravenous immunoglobulin, or with donor HLA antigens (platelet transfusions or white blood cell infusion in the form of an irradiated buffy coat); and 4. inhibition of complement cascade [90]. Plasmapheresis is the most common method of desensitization; however, plasmapheresis alone does not effectively prevent graft failure. Therefore, combination therapy is essential. Plasamapheresis plus rituximab or intravenous immunoglobulin, or plasamapheresis plus intravenous immunoglobulin plus tacrolimus are effective desensitization treatments for a strong DSA [85,86,88–90]. Platelet transfusion was the most simple and effective treatment option for class I DSA [86,90].

4. Involvement of Pro-Inflammatory Cytokines in Graft Failure and Poor Graft Function

Among several pro-inflammatory cytokines, IFN-γ and tumor necrosis factor (TNF)-α are critical cytokines that inhibit hematopoiesis through apoptosis of hematopoietic stem and progenitor cells (HSPCs) and/or inhibition of cell proliferation and differentiation.

4.1. Interferon-γ

Mori et al. [93] showed that the Fas expression in both hematopoietic progenitor cells and whole bone marrow cells increased in case of acute GVHD but not chronic GVHD, resulting in apoptosis of hematopoietic cells through Fas in a murine GVHD model. In fact, anti-Fas antibody treatment protected the recipient mice from bone marrow failure. IFN-γ produced by alloreactive T cells may entail a severe GVH reaction and could be responsible for cytopenias that are frequently observed in subjects with GVHD [94]. FasL-dependent apoptosis and decreased donor cell proliferation is responsible for spleen hypoplasia. Blockade of Fas/FasL interaction by the use of anti-FasL blocking antibodies significantly reduced cytopenias and bone marrow aplasia. Antibody-mediated IFN-γ neutralization reversed blood cytopenias [95]. Increased apoptosis of HSPCs through Fas/FasL pathway, caspases, and related proapoptotic genes by increased IFN-γ is frequently observed in murine GVHD models [30,83–86,96–99] and human allo-HSCT [99,100].

Merli et al. [99] showed that anti-IFN-γ monoclonal antibody (emapalumab) treatment promoted donor cell engraftment in 2 out of 3 children with primary hemophagocytic lymphohistiocytosis (HLH) who, after experiencing graft failure, were re-transplanted from the same HLA-haploidentical donor under the compassionate use coverage of emapaulimab, an anti-IFN-γ monoclonal antibody recently approved by the US FDA for treatment of patients with primary HLH. In murine study, anti-IFN-γ monoclonal antibody treatment promoted donor cell engraftment. These results suggested that the IFN-γ pathway played a major role in graft failure occurring after allo-HSCT, and provided the rationale for exploring the therapeutic/preventive role of targeted neutralization of IFN-γ.

Lin et al. [97] studied the kinetics of hematopoiesis and the functions of HSPCs in an acute GVHD model. Although hematopoiesis was progressively suppressed during acute GVHD, the hematopoietic regenerative potential of donor-derived hematopoietic stem cells remains intact. There was a dramatic reduction in primitive hematopoietic cells and a defect in the ability of these cells to generate common myeloid progenitors (CMPs) and megakaryocyte/erythrocyte progenitors (MEPs). These effects were observed along with a concomitant increase in granulocyte/macrophage progenitors, suggesting that differentiation into MEPs is blocked during acute GVHD. The serum levels of Th1 cytokines, including IL-1α, IL-2, and IFN-γ, were significantly higher in the acute GVHD mice than in control mice. Because elevated Th1 cytokine levels are a key indicator of donor T-cell proliferation and differentiation, they investigated whether inhibiting T-cell immunity

could attenuate the hematopoietic suppression associated with acute GVHD. Cyclosporine A was able to partially reverse the hematopoietic suppression as well as the differentiation blockage of CMPs. Chen et al. [98] reported that the activity of IFN-γ on murine hematopoiesis is context dependent. IFN-γ-augmented apoptotic gene (Fas, caspases, and related proapoptotic genes) expression facilitated destruction of HSPCs in the presence of activated cytotoxic T cells, as occurs in human bone marrow failure. Wang et al. [100] reported the polarization of CD4$^+$ and CD8$^+$ T cells toward a type 1 pattern in poor graft function. Dysregulated T-cell responses may contribute to the occurrence of poor graft function after allo HSCT.

Recently, Tucci et al. [101] have reported a case of secondary HLH-related graft failure in the context of HLA-haploidentical HSCT successfully treated with emapalumab in the presence of concomitant life-threatening infections, including disseminated tuberculosis. This seminal case supports emapalumab use for treatment of secondary HLH and prevention of graft failure in patients underwent haploidential HSCT even in the presence of multiple infections.

IFN-γ is a potent negative regulator of HSPCs [102–106]; therefore, increased IFN-γ exerts a non-MHC restricted inhibitory action on HSPCs [94,95]. IFN-γ appears to facilitate apoptosis of HSPCs either directly or through induction of caspase-1, tumor necrosis factor-related apoptosis-inducing ligand, and Fas [106,107]. In addition, IFN-γ inhibits self-renewal of hematopoietic stem cell modulating expression of key cell-cycle genes, such as cyclin D1 [94,108], Myc [94], and p57 [108]. IFN-γ -mediated cyclin D1 suppression appears to affect the immature HSPCs but not mature hematopoietic cells. Furthermore, IFN-γ interferes with thrombopoietin-induced phosphorylation of STAT5 in hematopoietic stem cells through modulation of suppressor of cytokine signaling 1 [108].

4.2. Tumor Necrosis Factor-α

Tumor necrosis factor (TNF)-α is also a pro- inflammatory cytokine that negatively regulates the growth of murine and human hematopoietic progenitors [109–112]. A negative effect of TNF-α on hematopoietic stem cell maintenance by enhancing their differentiation rather than self-renewal has been suggested [113]. The negative effect of TNF-α was not dependent on the Fas/FasL pathway [113], although markedly increased Fas antigen expression on CD34$^+$ hematopoietic stem cells was induced by stimulation with TNF-α and IFN-γ, and anti-Fas antibody rescued bone marrow failure [93,94]. Like many other inflammatory diseases, bone marrow failure is associated with TNF-α overexpression. In murine lymphocyte infusion-induced bone marrow failure models but not allo-HSCT models, treatment with anti-TNF-α monoclonal antibody induced significant prolongation of survival although less impressive than using anti-IFN-γ monoclonal antibody treatment [29]. Furthermore, using mice deficient for either TNF receptor super family 1a (Tnfrsf1a) receptor or Tnfrsf1b receptor or both, a TNF-α-mediated suppression of hematopoietic stem cell activity was shown [114]. In vivo administration of TNF-α targeted cycling rather than quiescent hematopoietic stem cells. In fact, blockade of TNF-α using etanercept, which is a soluble TNF-α receptor 2 and competes for TNF-α binding, early after transplant appears to limit a cytokine-mediated suppressive effect on repopulating cell function, thus facilitating engraftment [115]. TNF-α from host macrophages and TNF-α receptor expressed on donor T cells are critical in the pathogenesis of murine immune-mediated bone marrow failure [115,116]. Aplastic anemia patients have higher frequencies of TNF-α producing CD16$^+$CD68$^+$ macrophages in the bone marrow than healthy controls. In clinical settings, anti-TNF-α antibody treatment or use of TNF-α blockade may be effective for graft failure and poor graft function, but the efficacy was limited even in combination with other immunosuppressive drugs [117,118].

5. Damage of Hematopoietic Stem/Progenitor Cells and Bone Marrow Microenvironment in Graft Failure and Poor Graft Function

Hematopoiesis depends on special bone marrow microenvironment termed niches in which HSCs reside as well as on the functional crosstalk between hematopoietic stem cells

and these niches [119]. Early studies suggested that bone marrow endosteal, perivascular and vascular endothelial cells as well as osteoblasts have a fundamental role in the maintenance of hematopoietic stem cells by providing signals that regulate cell self-renewal, differentiation, and quiescence in mice [120]. However, recent studies showed that the hematopoietic niches are more complex [121]. There are various cell types and niche factors that directly or indirectly regulate hematopoietic stem cell activity [120,121]. Periarteriolar nestin (*Nes*)–green fluorescent protein (GFP)^{high} cells, neural–glial antigen 2-positive cells, myosin heavy chain 11-positive cells, perisinusoidal *Nes*–GFP^{low} cells, CXC-chemokine ligand 12 (CXCL12)-abundant reticular (CAR) cells and leptin receptor-positive cells are key regulators of hematopoietic stem cell maintenance [122–125]. Furthermore, sympathetic nervous system nerves regulate hematopoietic stem cell mobilization, and nonmyelinating Schwann cells may contribute to hematopoietic stem cell quiescence [126,127]. Osteoblasts may have a role in regulating lymphoid progenitors [128]. Adipocytes may negatively affect hematopoietic stem cell maintenance [129]. Hematopoietic cells, such as macrophages, neutrophils, Treg cells and megakaryocytes can contribute to hematopoietic stem cell maintenance or mobilization [120,121]. Regional localization of hematopoietic stem cell subsets has shown that platelet-biased or myeloid-biased von Willebrand (*Vwf*)–GFP$^+$ hematopoietic stem cells and *Vwf*–GFP$^-$hematopoietic stem cells may be located in and regulated by separate bone marrow niches containing megakaryocytes and arterioles, respectively [120,121].

Graft failure and poor graft function can be induced by not only HSPCs but also bone marrow microenvironment (niches) damage.

We showed that donor effector CD4$^+$, and to a lesser extent CD8$^+$, T cells caused early destruction of osteoblasts, and dysfunction of vascular niches and CAR cells (qualitatively, but not quantitatively), leading to bone marrow suppression and severe impairment of B lymphopoiesis with dramatically decreased numbers of B-cell precursors and decreased expression of transcriptional factors essential for B lymphopoiesis, such as E2A and PAX5 in a murine acute GVHD model [130]. Anti-CD4 monoclonal antibody treatment ameliorated bone marrow failure and B lymphopoiesis preserving graft-versus-tumor effect. The most controversial cellular components of the bone marrow niche are osteoblasts, as initial studies pointed toward their regulatory role in hematopoietic maintenance [121]. Since 3D imaging studies have shown that endogenous hematopoietic stem cells are not significantly associated with osteoblasts, mature osteoblasts do not have a direct role in regulating hematopoietic stem cell activity [131,132]. However, osteolineage cells seem to support the maintenance of more committed hematopoietic progenitors, in particular, the lymphoid lineage. Osteoblasts are both necessary and sufficient for murine B-cell commitment and maturation, and thereby constitute the cellular homolog of the avian bursa of Fabricius [133]. There are several reports regarding impaired B lymphopoiesis accompanied with murine GVHD [134] and human GVHD [135,136]. These phenomena appear to be partially related to bone marrow niche damage. In our case, acute GVHD injured osteoblasts and/or other hematopoietic niches including vascular niches and CAR cells, although IL-1, IFN-γ, and TNF-α did not play an important role for exerting impaired hematopoiesis and B lymphopoiesis. The Fas/FasL pathway appears to be partially related to bone marrow suppression and impaired B lymphopoiesis. Similarly, decreased osteoblasts and cytopenias were observed in allo-HSCT patients with chronic GVHD, accompanied with an increasing CD4/CD8 ratio [137].

Other reports on damage of bone marrow niches causing GVHD-associated graft failure or poor graft function are shown in Table 1. Kong Y et al. [138,139] reported that acute and chronic GVHD in patients after allo-HSCT induced injury of osteoblasts, vascular, and perivascular niches as well as HSPCs. The patients with poor graft function showed markedly hypocellular marrow with scattered hematopoietic cells and significantly lower CD34$^+$ cells, endosteal cells, perivascular cells, and endothelial progenitor cells compared with good graft function allo-HSCT recipients. There was no difference between early and late poor graft function regarding damage of bone marrow niches. Yao et al. [140]

showed that sinusoidal endothelial cells (SECs) is a target of acute GVHD in a murine GVHD model. High level of Fas and caspase-3 expression and high rate of apoptosis were identified in SECs, indicating that these were destroyed by acute GVHD. Furthermore, high FasL expression on engrafted donor $CD4^+$, but not $CD8^+$ T cells, and high level of MHC class II but not MHC class I expression on SECs suggested that apoptosis was mediated by $CD4^+$ donor T cells through the Fas/FasL pathway. Medinger M et al. [141] investigated whether acute GVHD might reduce the number of nestin+ perivascular bone marrow stem cell niche (N^+SCN). They examined patients with AML who had undergone allo-HSCT. The number of N^+SCN in bone marrow biopsies was significantly reduced in acute GVHD patients at the time of acute GVHD compared with patients who did not have acute GVHD. Cao et al. [142] reported that reduced and dysfunctional bone marrow endothelial progenitor cells (BM EPC), characterized by decreased migration and angiogenesis capacities and increased levels of reactive oxygen species (ROS) and apoptosis, were found in acute GVHD patients. Furthermore, lower frequency and increased levels of ROS, apoptosis and DNA damage were found in bone marrow $CD34^+$ cells of acute GVHD patients. The severity of acute GVHD and GVHD-mediated cytopenia was associated with BM EPC impairment in acute GVHD patients. In addition, the EPC impairment positively correlated with ROS level. Thus, reduced and dysfunctional BM EPCs may be involved in the pathogenesis of acute GVHD, indicating that improvement of BM EPCs may represent a promising therapeutic approach for acute GVHD patients. Song et al. [143] reported that bone marrow MSCs from patients with poor graft function expanded more slowly and exhibited more apoptosis and senescence than MSCs from patients with good graft function. Increased intracellular ROS, p53, and p21 levels were found in MSCs from patients with poor graft function. Furthermore, the ability of MSCs to sustain hematopoiesis was significantly reduced in patients with poor graft function. This study suggests that improvement of bone marrow MSCs may represent a promising therapeutic approach for patients with poor graft function after allo-HSCT. Zhao et al. [144] reported that activated inflammatory macrophages increased in patients with poor graft function after allo-HSCT but anti-inflammatory macrophages decreased. Furthermore, increased intracellular levels of TNF-α and IL-12 were evident in bone marrow macrophages from patients with poor graft function, while decreased intracellular levels of TGF-β were observed, leading to the occurrence of poor graft function.

For repairing the damage of bone marrow niches, administration of N-acetyl-L-cysteine (NAC) or atorvastatin is recommended as therapeutic manipulations. NAC is a ROS scavenger that can enhance the defective hematopoietic stem cells by repairing the dysfunction of bone marrow microenvironment [145,146]. Atorvastatin can enhance endothelial cell function in patients with poor graft function after allo-HSCT [147]. Atorvastatin downregulated the activated p38 and its downstream transcription factor, cyclic adenosine monophosphate-responsive element-binding protein, thereby repairing the dysfunction of bone marrow endothelial progenitor cells.

Table 1. Damage of bone marrow microenvironment by graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Studied in:	Type of GVHD	Target	References	Reported Year
Murine	Acute	Osteoblasts	[130] Shono Y, et al.	2010
		Vascular niches		
		CAR cells		
Human	Acute/chronic	Endosteal niches	[138] Kong Y, et al.	2013
		Vascular niches		
		Perivascular niches		
		Hematopoietic stem cells		
Human	Chronic	Osteoblasts	[137] Shono Y, et al.	2014

Table 1. *Cont.*

Studied in:	Type of GVHD	Target	References	Reported Year
Murine	Acute	Vascular niches	[140] Yao Y, et al.	2014
Human	Acute	Perivascular niches	[141] Medinger M, et al.	2015
Human	Acute	Endosteal niches	[139] Kong Y, et al.	2016
		Vascular niches		
		Perivascular niches		
		Hematopoietic stem cells		
Human	Acute	Vascular niches	[142] Cao XN, et al.	2018
Human	Acute	Mesenchymal stem cells	[143] Song Y, et al.	2018

6. Other Therapeutic Interventions for Graft Failure and Poor Graft Function

6.1. CD34$^+$-Selected Stem Cell Boost

In previous sections, potential usefulness of MSCs and Tregs as cellular therapies for graft failure and poor graft function were shown. One more promising manipulation is CD34$^+$-selected stem cell boost.

Larocca et al. [148] reported that in patients with poor graft function, a boost of CD34$^+$-selected peripheral blood donor cells is associated with a high chance of trilineage recovery (a rate of 75%) and a low risk of acute GVHD and non-relapse mortality is lower when using peripheral blood cells for the boost. Klyuchnikov et al. [149] reported that hematological improvement was observed in 81% of 32 patients undergoing a CD34$^+$-selected stem cell boost without prior conditioning. The recipients of related grafts responded faster than recipients of unrelated grafts (20 versus 30 days). The cumulative incidence of acute (grade II to IV) and chronic GVHD after CD34$^+$-selected stem cell boost was 17% and 26%, respectively. Patients with acute GVHD received a higher median CD3$^+$ cell dose. The 2-year probability of overall survival was 45%. Minardi et al. [150] reported 50 pediatric patients with poor graft function underwent a CD34$^+$-selected stem cell boost after allo-HSCT. Within 8 weeks, a significant increase in median neutrophil counts and a decrease in red blood cell and platelet transfusion requirement were observed, and 78.8% of patients resolved one or two of their cytopenias. 36.5% had a complete hematological response. The rate of acute GvHD grade I-III was only 6% and resolved completely. No GvHD grade IV or chronic GvHD occurred. Mohty et al. [151] reported that post-transplant CD34$^+$-selected boost could be effective in restoring normal graft function in patients with poor graft function with full donor chimerism after allo-HSCT, including in those patients who received haploidentical stem cell transplant, allowing hematopoietic recovery without increase in GVHD. The complete response rate was 70% and the median time to response was 15 days with all responding patients recovering within the first month after boost. Cuadrago et al. [152] reported the outcome of 62 consecutive patients who had primary or secondary poor graft function who underwent a CD34$^+$-selected stem cell boost from the same donor without further conditioning. Forty-seven of 62 patients showed hematological improvement and became permanently transfusion and growth factor-independent. Recovery was similar in patients with mixed and full donor chimerism. Five-year overall survival was 74.4% in patients demonstrating complete recovery, 16.7% in patients with partial recovery and 22.2% in patients with no response.

6.2. Eltrombopag

Eltrombopag, a thrombopoietin-receptor agonist, which was first used for the treatment of chronic idiopathic thrombocytopenic purpura [153], has been added to first-line immunosuppressive therapy, significantly improving the hematopoietic recovery [154]. Recently, eltrombopag monotherapy has been shown to improve hematopoiesis in patients

with low to intermediate risk-1 myelodysplastic syndrome, indicating that eltrombopag preferentially stimulates normal hematopoietic stem and progenitor cells [155].

In terms of pharmacological therapies for graft failure and poor graft function, anti-IFN-γ antibody appears to be efficacious but larger clinical studies are required. Efficacy of anti-TNF-α antibody treatment or use of TNF-α blockade appears to be limited. In contrast, efficacy of eltrombopag for poor graft function has been increasingly reported and seems to be promising. Although eltrombopag is basically more effective for poor graft function compared with graft failure probably because of its preferential stimulation of normal HSPCs [155], a further study is required to confirm this point.

Marotta et al. [156] reported a retrospective single-center experience with the thrombopoietin-mimetic agent eltrombopag for the treatment of poor graft function. Thirteen patients have received eltrombopag for either poor graft function or primary graft failure. In the 12 poor graft function patients eltrombopag was started at the median time of 79 days after HSCT, due to persistent thrombocytopenia, with concomitant anemia and neutropenia in 7 and 3 patients, respectively. Hematological response was seen in 7 patients, with 6 complete responses. Hematological responses were seen both in patients with evidence of immune-mediated pathophysiology, and with possible infectious/iatrogenic causes. In responding patients, eltrombopag was discontinued in 6 of 7 patients without further relapse. These results suggest that eltrombopag is safe and possibly effective in the setting of the treatment of poor graft function, and pave the way for future prospective studies. Fu et al. [157] reported that 38 patients treated with eltrombopag for refractory thrombocytopenia after haploidentical-HSCT. Eight patients had delayed platelet engraftment, 15 patients had secondary failure of platelet recovery, and 15 patients had poor graft function. The cumulative incidence of platelet recovery to transfusion independence was 63.2% and to $\geq 50 \times 10^9$/L without transfusion support was 52.3%. Neutrophil counts and hemoglobin were also increased in the nine responders with poor graft function. Nineteen (79.2%) of the 24 responders were able to taper off eltrombopag, and the remaining 5 patients were able to begin a taper. The median duration of treatment was 64 (range 14–195) days. The presence of megakaryocyte before initiation was the only independent factor influencing the efficacy of eltrombopag. Yuan et al. [158] reported 13 patients treated with eltrombopag for poor platelet engraftment without evidence of relapse at the time of initiation, including 6 patients with primary platelet engraftment failure and 7 with secondary platelet engraftment failure. The overall response rate was 62%. Of the 6 patients with primary isolated platelet failure, 3 responded, and of the 7 patients with secondary platelet failure, 5 responded. The median time to response was 33 days (range, 11 to 68 days). In addition, no significant differences in platelet recovery were noted in patients with adequate and decreased bone marrow megakaryocytic reserve (60% and 67%, respectively).

7. Future Directions

Hematological diseases were thought to be driven solely by genetic or epigenetic lesions within hematopoietic cells. However, the bone marrow niches that maintain and regulate daily production of blood and immune cells in the distinct interaction of different HSPCs are now increasingly being recognized as having an important role in the pathogenesis and chemoresistance of hematological diseases [159]. Allo-HSCT is a replacement therapy of both recipient hematopoietic stem cells and bone marrow niches by those derived from normal donors. Harmful conditions such as GVHD or persistent inflammation/infection to hematopoietic stem cells and bone marrow niches constructed from normal donor cells should be avoided to ensure a definite engraftment and prompt hematopoietic recovery. Occurrence of graft failure and poor graft function suggests a replacement failure due to damage of hematopoietic stem cells and/or bone marrow niches. Based on delineating the pathogenicity of graft failure and poor graft function, we are required to decide a prompt and appropriate treatment for curing each patient who underwent allo-HSCT.

A recent report showed that donor healthy HSPCs transfer functional mitochondria to the stromal microenvironment, thus improving mitochondria activity in recipient MSCs. Mitochondrial transfer to MSCs is cell-contact dependent and mediated by HSPC connexin-43 (Cx43). Recipient stromal microenvironment recovery and donor HSPC engraftment were augmented after mitochondria transfer. Healthy donor HSPCs not only reconstitute the hematopoietic system after transplantation but also support and induce the metabolic recovery of their damaged microenvironment via mitochondrial transfer [160] and vice versa [161,162]. This exchange of mitochondria results in Cx43-dependent scavenging of ROS from donor HSPCs [163] and the support of the metabolic activity of the recipient MSCs and their regenerative functionality, which further contribute to the success of the hematopoietic engraftment. These findings indicate $CD34^{+}$-selected stem cell boost and administration of MSCs have advantages to facilitate engraftment. $CD34^{+}$-selected stem cell boost appears to play important roles in increasing the number of hematopoietic stem cells as well as repairing stromal cells damaged by GVHD or persistent inflammation/infection. However, since it is still unclear whether the maintenance, differentiation, and proliferation of normal HSPCs can be regularly supported even though mitochondrial transfer from normal HSPCs can "functionally" normalize damaged recipient stromal cells; namely, it is unclear whether dysregulated function of recipient stromal cells can be completely corrected or not in the context of supporting normal hematopoiesis. Furthermore, it is unclear whether normal MSCs can correctly normalize abnormal hematopoietic stem cells. Therefore, recipient hematopoietic stem cells as well as stromal cells should be replaced by normal cells by allo-HSCT.

Possible treatments for graft failure and poor graft function are summarized in Table 2. Only treatment for primary graft failure is second transplant. According to recent clinical findings, treatment order for secondary graft failure appears to be $CD34^{+}$-selected stem cell boost, MSCs, eltrombopag, low dose IL-2, anti-IFN-γ antibody, and second transplant; however, in case of active GVHD and inflammation/infection, MSCs are preferred to be used first. Tapering or withdrawal of immunosuppressive drugs, or DLI may be tried, although the efficacy is limited. Treatment for primary and secondary poor graft function appears to be $CD34^{+}$-selected stem cell boost, eltrombopag, MSCs, low-dose IL-2, anti-IFN-γ antibody, and second transplant. In case of active GVHD and inflammation/infection, MSCs are preferred to be used first, similarly to the order in secondary graft failure. Regarding administration of NAC or atorvastatin, clinical evidence is still lacking; therefore, future clinical studies are awaited. MSCs possess strong immunoregulatory activity as well as hematopoiesis-enhancing activity including bone marrow niche-remodeling capacity; therefore, administration of MSCs is appropriate for the treatment of patients who are suffering from severe GVHD or inflammation/infection, and who have damage of bone marrow niches. Eltrombopag seems to be more effective in the patients with full donor chimerism status than those with mixed chimerism status because of its preferential stimulation to normal HSPCs [155]. In terms of MSCs, $CD34^{+}$-selected stem cell boost, eltrombopag, those efficacies seem to be not so differed; therefore, we should decide the administration order depending on the patient's conditions and other various medical and non-medical factors, considering their advantages and disadvantages. In terms of Tregs administration, this treatment is postponed until the establishment of supplying system of sufficient amount of these cells like MSCs. Alternatively, low-dose IL-2 treatment may be one of the candidates to expand Tregs in vivo. Anti-IFN-γantibody treatment in clinical settings has been just started with favorable responses; however, larger clinical studies are required. Furthermore, although combined treatment with multiple agents may be effective, future clinical trials are warranted.

Table 2. Possible therapeutic manipulations for graft failure and poor graft function.

Impaired Hematopoiesis	Chimerism	Initial engraftment	Initial hematological recovery	Treatments
Primary graft failure	Mixed/full recipient	–	–	Second transplant
Secondary graft failure	Mixed/full recipient	+	+	CD34$^+$ cell boost
				Mesenchymal stem cells *
				Eltrombopag
				Low-dose IL-2
				Anti-IFN-γ antibody
				Second transplant
Primary poor graft function	Full donor	+	–	CD34$^+$ cell boost, Eltrombopag
				Mesenchymal stem cell *
				Low-dose IL-2
				Anti-IFN-γ antibody
				Second transplant
Secondary poor graft function	Full donor	+	+	CD34$^+$ cell boost, Eltrombopag
				Mesenchymal stem cell *
				Low dose IL-2
				Anti-IFN-γ antibody
				Second transplant

* In case of active GVHD and inflammation/infection, mesenchymal stem cells are preferred to be used first.

8. Conclusions

Graft failure and poor graft function after allo-HSCT are serious complications. These conditions are often seen in GVHD and persistent inflammation/infection. Based on chimerism analysis and evaluation of hematological recovery status, we can accurately recognize the situation in transplanted patients who have either graft failure or poor graft function. Although we need further clinical evidence by reliable studies, administration of MSCs, CD34$^+$-selected stem cell boost, and eltrombopag are potential candidates for treating these conditions at the present.

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