



Recent Advancements in Poor Graft Function Following Hematopoietic Stem Cell Transplantation

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Poor graft function (PGF) is a life-threatening complication that occurs after transplantation and has a poor prognosis. With the rapid development of haploidentical hematopoietic stem cell transplantation, the pathogenesis of PGF has become an important issue. Studies of the pathogenesis of PGF have resulted in some success in CD34⁺-selected stem cell boosting. Mesenchymal stem cells, N-acetyl-l-cysteine, and eltrombopag have also been investigated as therapeutic strategies for PGF. However, predicting and preventing PGF remains challenging. Here, we propose that the seed, soil, and insect theories of aplastic anemia also apply to PGF; CD34⁺ cells are compared to seeds; the bone marrow microenvironment to soil; and virus infection, iron overload, and donor-specific anti-human leukocyte antigen antibodies to insects. From this perspective, we summarize the available information on the common risk factors of PGF, focusing on its potential mechanism. In addition, the safety and efficacy of new strategies for treating PGF are discussed to provide a foundation for preventing and treating this complex clinical problem.

Keywords: hematopoietic stem cell transplantation, poor graft function, prognosis, bone marrow microenvironment (BMME), hematopoietic stem cell (HSC)

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is an effective treatment for malignant hematological diseases. However, delayed or incomplete hematopoietic recovery, also known as poor graft function (PGF), limits the success of HSCT. The definition of PGF is currently controversial. The European Society for Blood and Marrow Transplantation (EBMT) defined PGF as two or three episodes of cytopenia lasting for more than 2 weeks, after day +28 in the presence of donor chimerism > 5% (1). Given the chimerism kinetics and potential for confusion with graft failure (GF), most recent studies based on clinical practice proposed that PGF should be defined as the presence of at least two hematopoietic cell count lines that do not meet the engraftment standard (absolute neutrophil count > 1.5 × 10⁹/L, platelet (PLT) count > 30 × 10⁹/L, hemoglobin > 85g/L) lasting for more than two consecutive weeks beyond day +28 post-HSCT, in the presence of full donor chimerism and primary disease in remission without severe graft-versus-

host disease (GVHD) and relapse (2). Secondary poor graft function (sPGF) refers to the loss of donor cells after the initial engraftment. Whereas primary PGF is characterized by no initial donor cell engraftment, it is nearly impossible to recover autologous hematopoiesis; thus, patients with this condition are likely to die of infection and/or other complications and urgently require a secondary transplant.

The cumulative incidence of PGF after allogeneic HSCT (allo-HSCT) varies between 5% and 27% (3–5). Differences in underlying diseases and management strategies affect the incidence of PGF. At Peking University Institute of Hematology, the incidence of primary PGF after unmanipulated haploidentical HSCT (haplo-HSCT) was found to be approximately 5.6% (6, 7), and sPGF developed in 5.7% of patients after allo-HSCT (4). In a prospective study, approximately 15% of patients with severe aplastic anemia (AA) who underwent haplo-SCT developed primary PGF (8). Primary PGF shows a very poor prognosis, with a 1-year overall survival (OS) rate of 25.0% (5) and 2-year OS of 6% in patients without hematopoietic recovery (9). Because of persistent leukocytopenia and thrombocytopenia, PGF is often accompanied by complications such as infection and bleeding, thus increasing the mortality rate. As PGF is a life-threatening complication, new prevention and treatment strategies are urgently needed.

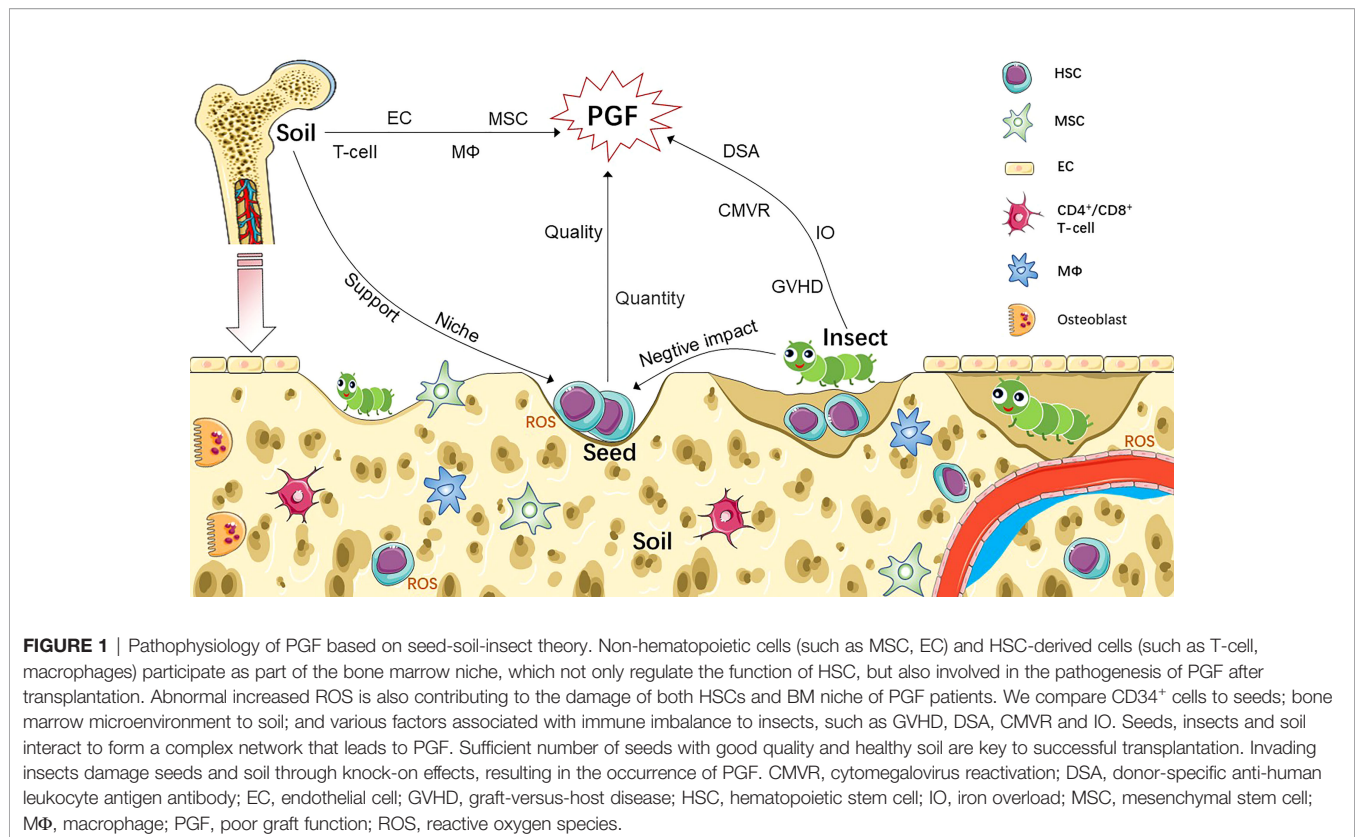
The occurrence of PGF is related to numerous factors such as primary disease, quality and quantity of hematopoietic stem cells (HSCs), damaged bone marrow (BM) microenvironment, donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA), and viral infection. Based on this information, we hypothesized that the seed, soil, and insect theories of AA pathogenesis can be applied to PGF (**Figure 1**). Based on this theory, we review current research progress on the pathogenesis, prevention, and treatment of PGF.

THE SEED

Similar to seeds, HSCs have the potential of self-renewal and multi-differentiation. Sufficient and functional stem cells have historically been considered key to the success of HSCT. Defects in HSCs, including changes in their quality and quantity, can lead to PGF or GF (**Figure 1**). The donor's choice directly determines the seed source. Young people are considered better donors than elders, men are superior to women as donors, and matched sibling donors (MSDs) should be prioritized over haploidentical donors (HIDs). However, an older donor/recipient age, female-to-male transplants, and donor-recipient ABO major-mismatch transplants are major risk factors for transplant-related mortality (10). For patients > 50 years old and with high-risk leukemia, HID-HSCT led to a better prognosis compared to MSD-HSCT, with a reduced relapse rate and/or improved leukemia-free survival and OS (11, 12). Interestingly, HID-HSCT may have a stronger graft-versus-leukemia effect than that of MSD-HSCT (12, 13). Thus, in 2021, the Chinese Society of Hematology recommendations

noted that “HIDs are the preferred donor choice over MSDs for patients with high-risk leukemia or elderly patients with young offspring donors in experienced centers” (14). The peripheral blood (PB) and BM are the predominant sources of stem cells. There is evidence that in haplo-HSCT with post-transplantation cyclophosphamide using a PB graft, compared with a BM graft, increased the risk of acute GVHD (aGVHD), whereas the 2-year OS, chronic GVHD, relapse, or non-relapse mortality (NRM) were comparable (15, 16). However, another study showed that patients receiving BM had significantly higher 2-year relapse rates compared to those in the PB cohort (36% vs. 16%) (17). Before 2019, mixed grafts of BM + PB were preferred over PB alone in HID-HSCT, because they achieved longer disease-free survival (18). A recent study reported that mixed grafts or PB alone did not influence clinical outcomes (19). Except for haploidentical grafts, rapidly accessible cord blood is a suitable alternative for pediatric patients without HLA-matched donors. Interestingly, the lower incidence of GVHD was not correlated with an increase in long-term survival. For example, in T-cell depleted PB stem cell transplantation, because of the delayed recovery of immune function, the incidence and severity of GVHD are low but are accompanied by an increased risk of infection, relapse, PGF, and transplantation-related mortality, particularly following transplantation with purified CD34⁺ cells (20, 21). As a result, different transplant centers have attempted to use transplant protocols without T-cell depleted conditions, suggesting that unmanipulated transplants are an alternative strategy under haploidentical settings (22). Additionally, a study at Peking University showed that haplo-HSCT without T-cell depleted transplantation has a comparable prognosis as MSD-HSCT (23, 24). Currently, the impact of different graft sources on the incidence of PGF is not well-understood.

A high CD34⁺ cell count is favorable for rapid hematopoietic recovery (8). Cell thresholds were devised to guide whether to carry out further apheresis collection. Currently, most centers use $2 \times 10^6/\text{kg}$ CD34⁺ cells as the minimum threshold. CD34⁺ cells $\geq 5 \times 10^6/\text{kg}$ are currently recommended as the optimal dose by the EBMT. Granulocyte colony-stimulating factor, alone or in combination with chemotherapy, is a standard mobilization regimen for collecting larger amounts of CD34⁺ cells. Plerixafor, a recently approved mobilization agent, is a small-molecule antagonist of CXC chemokine receptor 4 that can effectively block the binding between this chemokine and stromal cell-derived factor-1 α , and then release HSCs from the BM to the PB. The combination of granulocyte colony-stimulating factor and plerixafor significantly increased the yield of CD34⁺ cells without causing adverse reactions (25). CD34 molecules were first identified on the surfaces of human hematopoietic stem and progenitor cells (HSPCs). CD34 is also an established marker of other non-hematopoietic cells, including vascular endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and embryonic fibroblasts (26). Thus, the collected “CD34⁺ cells” should not be confused with “CD34⁺ HSPCs.” Introducing new HSPCs markers, such as the signaling lymphocytic activation molecule family (including



CD150, CD48, and CD244) (27), may enrich the purer stem cell population. In a nested case-control study of 830 patients, CD34⁺ cell dose $< 5 \times 10^6/\text{kg}$ was an independent risk factor for primary PGF (5). A low CD34⁺ cell dose ($<$ median, $2.64 \times 10^6/\text{kg}$) was also an independent risk factor for sPGF (4). In recent decades, the use of CD34⁺-selected stem cells boosted without preconditioning has significantly improved the prognosis of patients with PGF. In a small-scale study (28), most patients with PGF who received selected CD34⁺ PB stem cells from matched unrelated or mismatched related donors achieved rapid engraftment; more importantly, the procedure was safe, with a low risk of *de novo* grade I–III aGVHD (6%), which was resolved completely. In a long-term follow-up study, CD34⁺-selected infusion without conditioning was feasible in recipients with full donor chimerism and in those with mixed chimerism, whose recovery was similar; patients showing complete recovery had a longer 5-year OS than those with partial recovery (74.4% vs 16.7%) (29). Active infection was considered as the strongest predictor of the efficacy of CD34⁺-selective infusion (29), possibly because of the impaired immune microenvironment caused by inflammation. Cryopreserved products are viable alternatives when additional fresh stem cells cannot be collected. Although the median selection of CD34⁺ counts per kilogram of recipient weight was relatively low ($1 \times 10^6/\text{kg}$), this method achieved promising results; five of the eight cryopreserved product recipients (63%) exhibited a complete hematologic response (25).

It is essential to maintain high-quality stem cells at each step of the transplantation process. An increasing number of studies have been performed to optimize the cell handling, freezing, and thawing steps to ensure stem cell quality (30). Although methods for improving the viability and recovery rate of thawed stem cells are continuously being developed, the procedures still have a negative effect on the product quality and potency (31). Colony assays are the gold standard for stem cell proliferation and differentiation potency *in vitro*, which are used as an additional quality criterion. Watts et al. (32) demonstrated that if the granulocyte-macrophage colony-forming cell dose exceeded $2 \times 10^5/\text{kg}$ after 14 days in culture, total CD34⁺ cells between 1 and $1.9 \times 10^6/\text{kg}$ were also acceptable. When colony assays cannot be performed, cell doses below the threshold should be declared as inadequate, and remobilization and recollection are necessary. However, few centers routinely perform clonal analysis, as these tests require technical support, laboratory standardization, and higher expenses. A rapid method was recently developed to assess the cord blood unit potency for frozen cord blood based on aldehyde dehydrogenase (33). Further studies are necessary to confirm whether this method can be used as an alternative to clonal analysis. In addition, the detection of blood disease-related mutations in donor stem cells prior to transplantation may be of some significance in ensuring the quality of stem cells.

Accumulating evidence has suggested that excess levels of oxygen species (ROS) are responsible for defective hematopoiesis of HSC in patients with PGF, which may be related to

disruptions in the stem cell cycle caused by elevated ROS. After transplantation, transiently elevated oxygen tension is beneficial for the rapid proliferation of engrafted HSCs, because it promotes the regeneration of hematopoiesis during the “engraftment window” in the BM niche (34). The BM microenvironment gradually returns to conditions of hypoxic homeostasis with increased oxygen consumption after hematopoietic reconstitution. *In vivo* imaging showed that ROS mediated the initial homing and proliferation of HSCs in lethally irradiated mice, but is not indispensable for long-term hematopoietic reconstitution after transplantation (35). More importantly, Cheng et al. (36, 37) found that in transplanted human HSCs, radiation-induced bystander effects increased ROS levels, contributing to HSC damage and a decrease in transplantation efficiency. It has been hypothesized that forkhead homeobox type O transcription factors are key mediators of ROS regulation in HSCs, contributing to stem cell maintenance and the DNA damage repair response (38). As a negative regulator of forkhead homeobox type O transcription factors, the phosphoinositide 3-kinase (PI3K)/AKT pathway is suppressed in HSCs but activated in hematopoietic progenitors. Activated PI3K/AKT signaling induced HSCs re-entry into the cell cycle, and eventually exhaust HSCs through deletion of phosphatase and tensin homologs (39). In BM, elevated ROS levels induce DNA strand breaks and apoptosis, contributing to the exhaustion of CD34⁺ cells through the p53-p21 pathway in patients with PGF following allo-HSCT, even if the CD34⁺ cells are functionally normal before transplantation (40). Thus, activated p53 can induce HSC depletion. However, Hainaut et al. (41) demonstrated that p53 can also function against ROS-induced DNA damage through its intrinsic redox dependence. Therefore, p53 as a regulator of ROS, playing a dual role in stem cell maintenance.

THE SOIL

The BM microenvironment, as the niche for HSC survival, consists of blood vessels, nerves, and a variety of cells that form a complex and precise network to regulate the functional characteristics of HSCs; thus, we compared this microenvironment to soil. In recent years, the mechanisms of various cell and molecular interactions in the BM microenvironment involved in the pathogenesis of PGF have been determined. Huang et al. (42) observed that patients in the sPGF group had marked marrow hypoplasia, and the proportion of CD34⁺ cells, EPCs, CD146⁺ perivascular cells, and endosteal cells were significantly lower than those in the good graft function and healthy control groups. Three years later, they demonstrated that the BM microenvironment was equally damaged in both early and late PGF (43). Recently, a series of translational studies demonstrated that defective autophagy regulated by Beclin-1 (44) or abnormal glycolysis induced by PFKFB3 (45) results in damage to BM endothelial cells (ECs), particularly their decreased hematopoiesis-supporting ability, which is involved in the pathogenesis of PGF post-HSCT. Thus, some transplant events, which may trigger an abnormal increase in ROS

in the BM microenvironment, may be essential factors contributing to damage to the BM niche in patients with PGF. As described above, a dysfunctional BM microenvironment may contribute to PGF pathogenesis (**Figure 1**).

Endothelial Cells

ECs play a crucial role in regulating hematopoiesis by secreting stem cell factor and chemokine ligand 12 in the BM microenvironment (46). An unexpected finding regarding the origin of BM ECs was reported by Plein et al. (47) during early embryogenesis, ECs arise from erythro-myeloid progenitors. Thus, HSCs may provide survival and proliferation signals for EPCs. Accumulating evidence has shown that decreased and dysfunctional BM ECs post-HSCT contribute to the development of PGF (43, 48). Huang et al. (49) provided further evidence that pre-HSCT, BM ECs dysfunction was responsible for the pathogenesis of PGF after haplo-HSCT. BM ECs <0.1% pre-HSCT was an independent risk factor for PGF. Defective hematopoiesis caused by damaged BM ECs is positively correlated with ROS levels (49). Radiation therapy is commonly used in anticancer treatment and myeloablative conditioning regimens before HSCT. Irradiation also severely damages the BM vascular system, particularly sinusoidal ECs, leading to elevated ROS in the BM (35). Notably, elevated ROS levels are observed in ECs and recovering bones in the non-hematopoietic state, even at 2 weeks after sub-lethal irradiation (7 Gy) (50). Huang et al. (48) also showed that the intracellular ROS levels of BM EPCs were elevated after transplantation, and these cells had decreased proliferation and migration capacities. Vasculature reconstruction-mediated hematopoietic engraftment after radiotherapy depends on the expression of vascular cell adhesion molecule 1 on ECs (35), vascular endothelial growth factor receptor 2 signaling in apelin⁺ ECs (51), and vascular endothelial growth factor A provided by transplanted HSPCs (52).

Allogeneic EPCs infusions induced hematopoietic and immune reconstitution in mice, accelerated BM microvascular recovery, and ameliorated GVHD (53, 54). Few studies have reported the infusion of EPCs in humans for clinical treatment, likely because of the limited number of circulating EPCs. In contrast, atorvastatin, a lipid-lowering drug widely used in clinics, was reported to quantitatively improve the impaired function of BM EPCs *in vivo* by downregulating the p38 MAPK pathway in subjects with PGF (48). The antioxidant N-acetyl-L-cysteine can reduce ROS levels both *in vitro* and *in vivo* (49, 55). Prophylactic intervention with oral N-acetyl-L-cysteine not only prevents the occurrence of PGF post-HSCT, but also promotes hematopoietic reconstitution effectively by repairing impaired BM ECs in patients with PGF (49). These results indicate that it is valuable to use antioxidant drugs to improve PGF caused by elevated ROS levels.

Mesenchymal Stem Cells

MSCs are a type of BM stromal cells with multi-directional differentiation potential, immunoregulatory and hematopoietic support capabilities (56). MSCs show potential for use in treating PGF after HSCT. The mechanisms of MSCs in the pathogenesis of PGF are only beginning to be understood. Compared to in patients with good graft function, BM MSCs from patients with

PGF exhibited increased intracellular ROS, higher levels of apoptosis and senescence, and a significantly reduced hematopoiesis-supporting ability *in vitro* (57). Animal experiments and early-phase clinical trials showed that co-infusion of MSCs and HSCs promoted HSC engraftment and improved PGF (58–60). Nevertheless, whether MSCs with immune-suppressive properties increase the incidence of infection and relapse remains controversial. As early as 2007, a clinical study demonstrated that all patients who underwent co-transplantation of *ex vivo* expanded MSC with HLA-disparate CD34⁺ cells showed continuous hematopoietic engraftment, without additional infection compared to in the control group (61). Recently, a systematic review and meta-analysis of children and young individuals showed that MSC co-infusion improved the absolute neutrophil count and PLT engraftment, and greatly reduced the risk of chronic GVHD but had a minimal impact on aGVHD and NRM (59). Similarly, in a systematic review and meta-analysis of haplo-HSCT for severe AA, there was no obvious difference in the 2-year OS, incidence of GVHD and cytomegalovirus (CMV) infection between the MSC co-transplantation group and group not transplanted with MSCs (62). Although the effect of MSCs on PGF was not discussed in the article, co-administration of MSCs with HSCs may not be suitable for patients with severe AA undergoing haplo-HSCT. When infusion of MSCs was performed after transplantation, 17 of 20 patients with primary or secondary PGF experienced hematopoietic recovery when the MSCs were from a third-party donor (60). Moreover, some patients also developed varying degrees of CMV or Epstein-Barr virus infection, acute or chronic GVHD of varying degrees, and even relapse or non-relapse death (60). As summarized above, MSC infusion either before or after transplantation is an effective option for improving PGF, possibly because of their hematopoietic support capabilities. Possible risk factors such as long-term treatment with immunoinhibitors and HLA mismatch may affect the susceptibility to infection. Further studies are needed to determine whether MSCs increase the incidence of infection.

The Insects

Immune-mediated destruction of hematopoiesis is well-established in the pathogenesis of AA, most likely in the form of AA, an immune imbalance in abnormal hematopoiesis post-HSCT may be responsible for PGF. We compare various factors potentially associated with immune dysregulation post-transplantation, such as GVHD and CMV infection, to insects. GVHD is a fatal complication of allo-HSCT and occurs when donor immunoreactive cells recognize and attack recipient tissue. Grade III–IV GVHD is significantly associated with PGF development (9). Various factors that lead to GVHD, such as ongoing immune stimulation, may prevent hematopoietic reconstitution and exhaust hematopoietic precursor cells, eventually resulting in PGF development after transplantation.

Both CD4⁺ and CD8⁺ T cells are dramatically polarized towards the type 1 immune response in patients with PGF after allo-HSCT (63, 64). Thus, dysregulated T cell responses in the BM immune microenvironment may be involved in the pathogenesis of PGF after HSCT. Luo et al. (65) found that M2

macrophages (MΦs) supported and M1 MΦ suppressed HSC self-renewal and expansion *in vitro*. MΦs derived from patients with PGF exhibited significantly increased M1 and decreased M2 relative to those from patients with good graft function and healthy donors (66). Furthermore, the function of MΦs was impaired, characterized by reduced hematopoiesis-supporting ability, resulting in BM CD34⁺ cell dysfunction through p38 MAPK pathway upregulation, and aggravated pancytopenia in patients with PGF (66). Moreover, Zhao et al. (67) confirmed the opposing effects of M1 and M2 MΦs on megakaryocytes: M1 MΦs inhibit whereas M2 MΦs promote MK maturation and platelet formation. MΦs in patients with prolonged isolated thrombocytopenia also polarized towards M1, and unbalanced MΦs polarization impaired the megakaryopoiesis-supporting ability of BM MΦs, which was rescued by activation of the PI3K-AKT pathway. Further studies are needed to determine how these dysfunctional immune cells interact with other cellular elements or directly affect hematopoiesis, which may provide insight into the underlying molecular mechanisms and potential therapeutic strategies for patients with PGF after HSCT.

Thrombocytopenia caused by ongoing immune attacks limits the recovery of PGF. The thrombopoietin (TPO) receptor agonist (TPO-RA), romiplostim and eltrombopag showed promising results for treating immune thrombocytopenia (ITP). Additionally, the combination of eltrombopag with standard immunosuppressive therapy (horse antithymocyte globulin plus cyclosporine) shows great potential for treating severe AA (68), because it improves the rate, rapidity, and strength of hematologic responses in severe AA without causing toxic effects. Moreover, eltrombopag has been successfully used to treat PGF after allo-HSCT (69). Eltrombopag has changed the paradigm of AA treatment, however, some patients do not respond to this treatment. Nakao et al. (70) reported that high-dose romiplostim (20 µg/kg) was highly effective in patients with AA refractory to eltrombopag. Avatrombopag is a second-generation TPO-RA approved for second-line treatment of primary chronic ITP. A multicenter study performed in the United States confirmed that: patients with ITP who previously used other TPO-RAs (eltrombopag or romiplostim) and responded poorly exhibited a high response rate to avatrombopag (71). Thus, TPO-RA may be another option for treating PGF.

Donor-Specific Anti-HLA Antibodies

Antibody-mediated graft rejection is considered to cause GF. Various preformed antibodies are detectable in patients after allo-HSCT (72). DSA refers to specific antibodies corresponding to a mismatched antigen produced in patients after organ/tissue transplantation. Circulating DSA can lead to hyperacute rejection and thus is an important factor affecting HSC engraftment and is related to PGF, particularly primary PGF (7, 73). In a retrospective analysis of 394 patients who underwent haplo-HSCT, DSA with median fluorescence intensity (MFI) ≥1000 was significantly correlated with prolonged isolated thrombocytopenia (hazard ratio 3.262; $P = 0.009$) (74). DSA with MFI ≥ 1000 was also considered associated with the cumulative incidence of neutrophil engraftment for 60 days after single-unit cord blood

transplantation ($P = 0.03$) (75). Ciurea et al. (76) found that patients with high DSA levels (> 5000 MFI) and complement-binding DSA antibodies (C1q-positive) exhibited graft rejection at the time of transplantation, whereas patients whose C1q became negative after desensitization therapy were successfully engrafted by donor cells. In the absence of effective salvage approaches, the mortality rate of patients with GF is close to 100%, particularly after haplo-HSCT. A second early transplant can often successfully salvage GF (77, 78). The absence of DSA was associated with lower NRM and improved OS (79). These studies support the consensus guidelines from the EBMT, suggesting that DSA and C1q levels must be monitored to further assess the risk of allograft in patients with DSAs $\geq 1,000$ MFI (80).

Reducing DSA levels is essential for preventing primary PGF. Plasma exchange, rituximab, PLT transfusions, bortezomib, and immunoglobulin are often used clinically to decrease DSA levels. The rate of granulocyte reconstruction in the DSA-positive group was lower than that in the DSA-negative group after desensitization therapy (81–83). During HLA-mismatched HSCT, a single dose of rituximab was effective for desensitization and prevented the onset of primary PGF in DSA-positive patients, whereas bortezomib and immunoglobulin alone showed a limited ability to rapidly decrease DSA levels (81). Patients were desensitized to a DSA level < 2000 MFI after combination therapy with rituximab and/or plasmapheresis (83). However, DSA may rapidly rebound at any time. In a case report by Hassan et al. (84), during hematopoietic progenitor cell transplantation, DSA unexpectedly rebounded and rapidly increased during desensitization with repeated plasma exchange and immunoglobulin, finally leading to primary PGF. However, the cause of this phenomenon remains unclear. As an IgG-degrading enzyme of *Streptococcus pyogenes*, imlifidase can inhibit complement- and Fc γ R-mediated effector functions by cleaving donor-specific IgG into Fc and F(ab')₂ fragments (85). Endoglycosidase of *S. pyogenes* (EndoS) reduces the affinity of IgG for Fc γ Rs by specifically hydrolyzing glycans of all subclasses of human IgG (86). Both imlifidase and EndoS partially block DSA's function. To further reduce the titer and inhibit the effector functions of residual DSA, Anderson et al. (87) demonstrated that a combination of imlifidase and EndoS can be used to inactivate DSA and inhibit DSA-mediated killing of donor BM cells in allogeneic BM transplantation. Further studies are needed to confirm whether enzyme-mediated DSA blocking prevents antibody rebound.

Cytomegalovirus Infection

CMV and Epstein-Barr virus reactivation are independent risk factors for sPGF within the first 100 days of allo-HSCT (4, 88). CMV and Epstein-Barr virus co-reactivation not only leads to a shorter 1-year OS and leukemia-free survival, but also results in poor regulatory T cell reconstitution at day 30 after allo-HSCT (89). CMV reactivation (CMVR) after HSCT can lead to a variety of common life-threatening infectious complications such as pneumonia, retinitis, or sPGF. The prognosis of CMVR and immune reconstitution of CMV-specific T-cells are closely related (90, 91). In the first year post-transplantation, clonal expansion of CMV-specific effector memory T-cells drives the

reconstitution of CD4⁺ and CD8⁺ T-cells. Furthermore, the heterogeneity and diversity of the remaining T-cell repertoire are impaired in patients who experience reactivation (92, 93).

Previous studies suggested that CMVR after transplantation is strongly associated with aGVHD. Recent evidence demonstrated that mismatches in major or minor histocompatibility antigens promote CMV disease by inducing non-cognate transplantation tolerance, which inhibits the efficient reconstitution of antiviral CD8⁺ T cells, eventually resulting in cytopathogenic tissue infections (90). CMVR was associated with an increased risk of NRM with or without GVHD; however, the interaction between GVHD and CMVR was not significant ($P = 0.326$) (94). Therefore, aGVHD does not appear to be necessary for CMVR. However, the results of different studies varied based on the baseline characteristics. Single-center studies reported that CMVR after allo-HSCT is positively correlated with a decreased risk of relapse in acute myelocytic leukemia but not in other hematological malignancies. This benefit is of little significance considering the increased NMR and overall mortality (95). Another study of the Center for International Blood and Marrow Transplant Research database confirmed CMVR as a risk factor for poor prognosis, but showed no benefit of CMVR on the relapse of hematologic disease (96). CMV peak titers, disease stage, and T-cell depletion with antithymocyte globulin, which are associated with immunity, may modulate the impact of CMVR on leukemia relapse (97, 98).

In the era of PCR-based monitoring, universal prophylaxis or preemptive therapy strategy is typically adopted to prevent and treat CMV infections after HSCT (99). In the 1980s and 1990s, high-dose acyclovir and valacyclovir showed limited efficacy in preventing CMV disease (100). Some agents have been used for decades to control CMV infection and lead to significant toxicity. For example, ganciclovir (101, 102) is hemotoxic and frequently leads to secondary bacterial and fungal infections. Additionally, foscarnet (103) and cidofovir (102) exhibit severe renal toxicity. The introduction of letermovir (LMV) is an important advancement. As a CMV DNA terminase complex inhibitor, LMV can be administered orally and intravenously and has no myelotoxicity or nephrotoxicity (102, 104). Co-administration of cyclosporine increased the bioavailability of LMV from 35% to 85%; thus, lower doses are required in patients taking cyclosporine to prevent GVHD. Increasing evidence has shown that prophylactic LMV treatment effectively prevents the development of refractory or resistant CMV infections and ultimately decreases transplant-related mortality (105–107). In addition, Zamora et al. (108) provided initial evidence that compared with ganciclovir preemption, LMV prophylaxis-associated CMV antigen exposure reduction delays CMV-specific T-cell reconstitution after HSCT.

Virological monitoring of CMV in the blood plasma is routinely performed using quantitative PCR, but there is currently no consensus on the plasma viral load threshold when initiating CMV preemptive treatment. Real-time CMV-specific cell-mediated immunity responses were successfully applied to predict clinical CMV events and guide the early discontinuation of antivirals (109). Future strategies may involve vaccination dependent on functional reconstitution of CD4⁺ T cells and B

cells (91, 110), other novel antiviral agents [maribavir (111), CMX001 (112)], antibodies that block cell-to-cell spread and kill latently infected cells (113, 114), and adoptive cell therapy not limited by GVHD and steroids (115).

Iron Overload

Iron is a raw material for hematopoiesis. Long-term blood transfusion and inflammation are the most common factors leading to iron overload (IO) in patients with hematological malignancies. Studies have shown mixed results regarding the impact of IO pre-transplant on PGF and prognosis, possibly because of differences in marker selection and baseline data of the study population. Serum ferritin (SF) is a biomarker of IO. In two prospective studies by Zhao et al. (5) and Malki et al. (116), SF > 2000 ng/mL before HSCT was identified as an independent risk factor for primary PGF and a strong poor prognostic factor. In a subsequent prospective multicenter study, patients with SF > 1500 ng/mL before the start of conditioning with allo-HSCT had an inferior OS (hazard ratio, 2.5, CI = 1.5-4.1, $P = 0.0005$) and progression-free survival (hazard ratio, 2.4, CI = 1.6-3.8, $P < 0.0001$) (117). In contrast, in a prospective cohort study using liver magnetic resonance imaging to quantify the liver iron content, there was no significant correlation between IO (liver iron content >1.8 mg/g) before allo-HSCT and the cumulative incidence of multiple complications, OS, or NRM after HSCT (118). Interestingly, using SF or the liver iron content as a marker of IO revealed that IO was not related to the occurrence of acute or chronic GVHD (117, 118). Hcpidin expressed by the liver, it modulates iron absorption and release and is overexpressed when IO decreases these processes, and the erythropoiesis demands can eventually not be met (119). The rates of OS and PLT engraftment were significantly lower in the high hepcidin group than in the low hepcidin group (120). Hcpidin may be an alternative marker of IO to predict delayed PLT engraftment after allo-HSCT; however, there is currently no accepted validated method for evaluating hepcidin. Growth differentiation factor 15 belongs to the transforming growth factor-beta superfamily and has been proposed as an erythroid regulator involved in hepcidin suppression (121). Erythroferrone is a new erythroid regulator of hepcidin produced by erythroid precursors in response to stress erythropoiesis *via* the Jak2/Stat5 signaling pathway (122).

Zhao et al. (123) reported that IO damaged the erythroid colony-forming capacity of normal HSPCs and reduced the frequency of abnormal HSPCs in MDS mice. Impaired erythroid HSPCs are, at least in part, related to growth differentiation factor 15-induced ROS (123). In addition, IO contributes to MSC damage through the AMPK/MFF/Drp1 pathway, which displays increased cell apoptosis, decreased cell viability, and extensive autophagy, all of which are ROS-dependent (124). Excess iron levels can compromise BM stromal cells, inhibit erythropoietin and thrombopoietin levels, and disrupt hematopoietic function by increasing oxidative stress (125). Thus, the holistic situation during treatment and the link between IO and ROS should be considered. Currently, deferiprone and deferasirox are the most commonly used iron-chelating agents for removing IO in the clinic (126). Eltrombopag is also a powerful iron chelator with intracellular

iron mobilization characteristics that can reduce iron-induced ROS and stimulate stem cell hematopoiesis independently of the TPO receptor (127, 128). Tang et al. (69) preliminarily verified the feasibility of treating sPGF post-allo-HSCT with eltrombopag in a retrospective analysis. Co-administration of eltrombopag with clinically available chelators, such as deferasirox, may be an effective means for indirect PGF treatment (127). Additionally, upregulation of ferritin (129) and transferrin infusion (130) improve BM hematopoietic function induced by IO in mice; further studies are required to confirm its clinical feasibility.

CONCLUSION

The pathogenesis of PGF involves a complex, interlocking network. Future approaches to address PGF should focus on optimizing seeds, improving soil, and killing insects, emphasizing the importance of early detection and treatment to avoid PGF. With regard to seeds, a certain scale of research has focused on improving the quantity; and quality inspection before infusion should be performed to prevent the occurrence of PGF. Emerging research attempts to describe the relationship between the BM microenvironment and PGF, and improve the understanding of how various stromal cells, related factors, and abnormally activated transduction pathways interact to promote the initiation and development of PGF, these may lead to the development of prevention and treatment strategies. From a superficial perspective, different “insects” have different impacts on PGF through different mechanisms. These insects are products of immunodeficiencies. Therefore, new drugs that kill insects and focus on targeted immune modulation are needed. The quality of donor CD34⁺ cells should be routinely evaluated prior to transplantation. If possible, to predict the incidence of PGF, the content and functional status of donor cells and level of oxidative stress in the recipient’s BM microenvironment should be detected to determine whether to continue transplantation or administer corresponding treatment in advance. These steps may be feasible preventive measures for PGF and require further validation.

AUTHOR CONTRIBUTIONS

YW and TY conceptualized the outline and topic of the article. YM, XY, and ZL participated in collecting literature and draft manuscripts. ZL designed the figure. YM and XY analyzed the literature and made the figure. YW, TY, and YG coordinated the revision. All authors contributed to the article and approved the submitted version.

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