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Reviews

A Review of Growth Factor Support in Bloodless Autologous Hematopoietic Stem Cell Transplant

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A B S T R A C T

Bloodless autologous hematopoietic cell transplantation is associated with risks of severe bleeding and profound anemia. RBC or platelet transfusions are often used to prevent these hematologic complications. However, in patients such as Jehovah's Witnesses who refuse major blood components, the lack of transfusion support is not an absolute contraindication to an autologous hematopoietic cell transplant. Pennsylvania Hospital performed the world's first bloodless hematopoietic cell transplant more than 15 years ago and has gradually improved its technique with a sizable patient population. Erythropoiesis-stimulating agents were successfully employed as part of their pretransplant regimen to prevent severe anemia. Thrombopoietin agonists' potential role in bloodless transplant is also currently being explored. Although there is limited literature, available reports in combination with physiologic reasoning may support the use of these growth factors to promote transplant success. These agents offer potential benefit and may be of utility in minimizing complications of a bloodless transplant. In this review, we summarize the available literature and offer insight into how we may incorporate growth factors to allow bloodless autologous hematopoietic cell transplantation to be an available option to patients who may otherwise be denied.

BACKGROUND

The risk associated with bloodless autologous hematopoietic cell transplantation (aHCT) includes severe bleeding and profound anemia. Support with platelet (PLT) or RBC transfusions is often required to prevent complications associated with temporary marrow aplasia before hematopoietic recovery. Without transfusion support, profound anemia may lead to decreased systemic perfusion and cause multiorgan failure. Similarly, profuse bleeding occurring during severe thrombocytopenia may be detrimental. In either scenario, there are few options for effective rescue. Because of these reasons, patients who refuse blood products are often denied transplantation. However, high-dose chemotherapy (HDC) followed by aHCT may be the best option for long-term disease-free survival in patients with high-risk or relapsed lymphoma or multiple myeloma.

Jehovah's Witnesses refuse blood transfusions based on their religious beliefs that the life of every creature is in its blood. Although other religions also forbid the consumption of blood, the extension of this application to blood transfusions is distinctive to Jehovah's Witnesses. The ban of blood transfusions was established in 1945, and the spiritual and social ramification continues to be present today [1,2]. There are an estimated 8.5 million Jehovah's Witnesses worldwide [3]. Although they deny whole-blood products such as RBCs and PLTs, blood-derived products such as albumin may be allowed based on individual choice [2].

Lack of transfusion support is not an absolute contraindication to HDC-aHCT. Pennsylvania Hospital performed the world's first bloodless hematopoietic cell transplant more than 15 years ago and has gradually improved its technique with a sizable patient population. Ford et al. [4] published the method used at the Pennsylvania Hospital. Erythropoietin-stimulating agents (ESAs) were employed as part of its pretransplant regimen. Before mobilization and collection, patients received ESA 60,000 units weekly to target a hemoglobin (Hb) level of 11 g/dL. Concurrent i.v. iron was also given if patient was iron deficient or believed to have functional iron deficiency. Many

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Table 1
Comparison of ESAs and TPO Agonists Use in Protocols

Transplant Setting	Ford et al. [4]	Joseph et al. [5]	Coltoff et al. [6]	Elemary et al. [7]	Khan et al. [8]	Our Institution
Pretransplant	ESA 60,000 units s.c. weekly with i.v. iron until Hb ≥11 g/dL	ESA 40,000 units s.c. weekly with i.v. iron starting 2 months before transplant until Hb >11 g/dL	ESA 40,000 units s.c. weekly with i.v. iron until Hb 10-11 g/dL	ESA 60,000 units s.c. weekly with i.v. iron until Hb >11 g/dL	None	ESA 40,000 units s.c. weekly with i.v. iron starting 4 weeks before transplant until Hb ≥11 g/dL
ESAs peritransplant	None	None	Restart i.v. iron when Hb <11 g/dL; Restart ESA when Hb <9 g/dL	None	Darbepoetin 200 mcg s.c. every 2 weeks starting D+12 until Hb >10 g/dL	ESA 40,000 units s.c. weekly starting day +6 until Hb > 10 g/dL
TPO agonists peritransplant	None	None	Romiplostim 4 mcg/kg s.c. starting D+2 to D+7, continued until PLTs $>100 \times 10^9$/L	None	None	Romiplostim 4 mcg/kg s.c. weekly starting on day +6 until PLTs $>50 \times 10^9$/L

Abbreviations: ESA = erythropoiesis-stimulating agents; Hb = hemoglobin; IV = intravenous; PLT = platelet; s.c. = subcutaneous.

institutions have since established their own institutional guidelines for bloodless aHCT, incorporating ESAs and/or thrombopoietin (TPO) agonists, compared in Table 1, in addition to standard blood conservation techniques. In this article, feasibility of preventing severe anemia and thrombocytopenia with these growth factors is explored.

ERYTHROPOIESIS-STIMULATING AGENTS

Erythropoietin (EPO) is a hormone naturally secreted by the kidneys into plasma in response to hypoxia. Upon arrival in the bone marrow, EPO binds to EPO-receptors (EPO-Rs) on the surface of erythroid progenitor cells. This triggers the erythroid differentiation cascade, resulting in mature RBCs [9]. The life span of endogenous RBCs (120 days) is long enough to support the patient safely through transplant in the absence of blood loss or other complications. Provided an adequate baseline Hb level to account for cytotoxic effects of HDC, sufficient Hb should be present at nadir to ensure organ perfusion.

The priming method to target a specific baseline Hb is reported in both bloodless aHCT and bloodless surgical procedures. The impact of baseline Hb on transfusion needs has been demonstrated in several studies [10,11]. One study evaluated 11 patients with multiple myeloma who received tandem autologous transplants. Mean Hb before first transplant was 9.5 g/dL. Ten of 11 patients required RBC transfusions, with an undefined transfusion threshold in the report. All patients received ESAs to maintain Hb between 12 and 14 g/dL starting 30 days after the first transplant. Mean Hb before second transplant was 12.5 g/dL. Only 1 of 11 patients required RBC transfusions ($P < .001$) [11]. This study suggests that a higher baseline Hb dramatically decreases the need for transfusion.

When deciding a target level of baseline Hb, the expected Hb decline is considered. Ford et al. [4] targeted a Hb of 11 g/dL. Median Hb at onset of HDC was 11.8 g/dL. The mean Hb nadir was 7 g/dL, with a median duration of grade 3/4 anemia (Hb <8 g/dL) of 9 days. Hemoglobin decreased a median of 4.9 g/dL from baseline to nadir. In a cohort of 125 patients with lymphoma or multiple myeloma, only 1 patient was considered a treatment-related mortality from profound anemia. This patient had a pretransplant Hb of 9 g/dL. The protocol was amended to target a baseline Hb of 11 g/dL thereafter [4]. Similarly, 2 other single-center studies also targeted a baseline Hb of 11 g/dL using ESAs before bloodless aHCT [5,6]. In 1 study of 24 patients with plasma cell dyscrasias undergoing bloodless aHCT, no treatment-related mortality or hematology complications were observed with a median baseline Hb of 10.7 g/dL [5]. Preparing for a Hb decline of 5 to 6 g/dL from baseline, targeting a Hb of 11 g/dL pretransplant is a reasonable goal to prevent profound anemia peritransplant for a bloodless aHCT.

Safety should also be considered when deciding a target baseline Hb. ESAs carry a black box warning of cardiovascular and thromboembolic events, including myocardial infarction, stroke, and venothromboembolism, when targeting Hb >11 g/dL, although this has not been studied in patients with hematopoietic cell transplant or myeloid malignancies [12,13]. Ford et al. [4] had an unexpectedly large proportion of cardiac-related adverse events and mortality reported, although etiology is multifactorial and some incidents were caused by transient IL-11 use. Therefore, a higher Hb goal may have adverse effects. A Hb goal of 11 g/dL may be reasonable to maximize benefit and to minimize potential thromboembolic events.

Ideally, ESAs should be used to prime the Hb to target level without delaying transplant. Reticulocytes increase within 10 days of an ESA dose, and peak Hb effect is seen in 2 to 6 weeks [12]. Therefore, weekly ESA dosing should begin 4 to 6 weeks before HDC, depending on baseline Hb level. To avoid transplant delay, initiation of ESA during chemotherapy treatment may also be considered. In addition, i.v. iron should always be administered with ESAs to increase response, regardless of iron deficiency [14-17]. Studies reveal that the addition of i.v. iron reduces transfusion need and increases Hb levels. Oral iron does not exhibit the same effect [16,17]. Weekly ESA with i.v. iron may be given concomitantly starting 4 to 6 weeks before HDC until a target Hb of 11 g/dL is reached.

Use of ESAs after allogeneic transplantation is well supported, but use of ESAs after autologous transplantation has conflicting data. The few studies available have generally failed to demonstrate benefit [18-20]. In the setting of aHCT, the development of erythropoiesis is limited by the availability of EPO-R-bearing erythroid precursors. After aHCT patients receive HDC, serum EPO rapidly increases to disproportionately elevated levels for 1 to 3 weeks, peaking after 1 week [9,21,22]. Physiologic evidence and limited studies further solidify that the rate of erythropoiesis is determined by marrow proliferative activity rather than diminished EPO stores. Therefore, administration of EPO shortly after HDC is not necessary. However, studies demonstrate ESA efficacy when started approximately 4

weeks after transplant. Darbepoetin and i.v. iron have shown improvement in erythroid reconstitution when initiated 28 days after aHCT [23]. Similarly, recombinant human EPO was proven efficacious when started 30 days after transplant [24]. The use of EPO at 4 weeks post-transplant should be reserved for patients who are persistently anemic and/or symptomatic. If a patient has recovered, additional administration should be avoided.

There are currently no studies to evaluate if a higher level of EPO would translate into faster count recovery. In general, bone marrow engraftment begins 7 to 8 days after stem cell infusion. ESAs may be given weekly starting around engraftment to facilitate erythropoiesis. This could potentially shorten the duration of grade 3/4 anemia. Patients who may benefit from post-transplant ESA include those at risk of engraftment failure due to prior radiation exposure or treatment or inadequate physiologic EPO production in the setting of renal impairment.

THROMBOPOIETIN MIMETICS

TPO is a glycoprotein produced in the liver and binds to TPO-receptor (TPO-R), historically known as myeloproliferative leukemia receptors. TPO-R is located on hematopoietic progenitor cells, megakaryocytes, and PLTs. The interaction between TPO and TPO-R activates the intracellular transcriptional pathways, leading to megakaryocyte differentiation and PLT production. Similar to EPO, TPO requires the presence of healthy precursor cells to demonstrate effect. Unlike EPO, TPO production is not reactionary. Endogenous TPO is produced at a constant rate by the liver. Upon binding, TPO is internalized and degraded, mostly by megakaryocytes and PLTs. Therefore, with low serum PLT levels, TPO level increases due to decreased clearance [25]. Based on the physiology of endogenous TPO, the serum level of endogenous TPO should remain adequate after HDC-aHCT, assuming adequate liver function.

Romiplostim is an Fc-peptide fusion protein that mimics TPO currently approved for immune thrombocytopenia [25]. It is not used to normalize PLT count due to the increased risk of thromboembolic complications. Portal vein thrombosis has also been reported in patients with chronic liver disease [26]. Eltrombopag, lusutrombopag, and avatrombopag are oral, nonpeptide TPO-R agonists. There is currently no evidence to support these agents' use in the aHCT setting.

Oprelvekin is recombinant IL-11, which is a growth factor shown to promote maturation of megakaryocytes, leading to increased production of PLTs [27]. IL-11 was initially used by Ford et al. [4] immediately post-transplant to decrease the duration of thrombocytopenia. However, it was discontinued due to lack of efficacy and the concerns for cardiac toxicity. One retrospective study of 73 patients with lymphoma evaluated IL-11's efficacy in the post-transplant setting and showed similar results. Thirty-five patients received 1.5 mg of IL-11 daily from the fifth day after aHCT until PLTs $>80 \times 10^9$/L, while 38 control patients did not receive IL-11. The PLT nadir was 18.9 and 21.5 ($P = .04$), and time to PLT recovery was 14.3 and 13.2 ($P = .37$) for the IL-11 and control group, respectively [28]. In a phase II study of 80 patients with breast cancer who received myeloablative chemotherapy followed by aHCT, 28 patients received 25 mcg/kg and 26 patients received 50 mcg/kg of oprelvekin. The incidence of PLT transfusion and time to PLT recovery was not statistically significant in either dose group. Furthermore, there were increased incidences of adverse effects, including edema, conjunctival bleeding, hypotension, atrial arrhythmias, and tachycardia [29]. Due to lack of demonstrated benefit and concerns for adverse effects, oprelvekin use is not recommended in the setting of aHCT.

Before considering the addition of TPO mimetics, the risk of bleeding should be assessed in bloodless transplant patients. Ford et al. [4] reported no treatment-related mortality related to thrombocytopenia or bleeding. Only a total of 18 bleeding episodes were observed among 125 patients, and all occurred at PLTs of $<5 \times 10^9$/L [4]. Per American Society of Clinical Oncology practice guidelines, prophylactic transfusion to prevent severe bleeding is recommended only when PLTs fall below 10×10^9/L in allogeneic transplant patients [30]. A Cochrane review showed similar bleeding rates when transfusion is triggered at a PLT level of 20×10^9/L versus 10×10^9/L in hematologic disorders after myelosuppressive chemotherapy or HCT [31]. For autologous transplant patients, the American Society of Clinical Oncology recommends transfusion at the first sign of bleeding rather than prophylactically [28]. Subgroup analysis of 421 aHCT patients in the Trial of Prophylactic Platelets (TOPPS) trial found similar rates of grade 2 to 4 bleeds (45% versus 47%) in patients with and without prophylactic transfusions [32]. Therefore, the incidence of bleeding post-aHCT appears low, with risk highest when PLTs fall below 5 to 10×10^9/L.

Priming with TPO mimetics and the effect of PLT level before HDC have not been evaluated. Theoretically, PLT level before HDC does not affect nadir level post-HDC because the life span of a PLT is 7 to 10 days. PLT engraftment occurs around 13 days [33]. Therefore, PLT nadir is unavoidable as most PLTs existing before transplant will be removed from the bloodstream before new PLTs are formed at engraftment. In the retrospective review of 60 transfusion-supported aHCT patients, the median time to first PLT transfusion was 10 (range, 9 to 13) days, regardless of PLT levels at onset of conditioning (range, 127 to 374) [5]. Because a low nadir is inevitable, romiplostim's place in therapy may be more reasonable in the post-aHCT setting.

There is limited evidence of romiplostim use in the setting of aHCT. One study explored the use of romiplostim in 13 patients who refused blood products and underwent aHCT. Ten of these patients received romiplostim 4 mcg/kg before and/or after transplantation, and 3 patients did not receive any romiplostim. A mean of 2.6 days of grade 4 thrombocytopenia (PLTs $<10 \times 10^9$/L) was reported for all 13 patients. The study suggests the duration of grade 4 thrombocytopenia appears to be reduced compared with results of a historic study of 26 bloodless transplantation patients reporting a median of 4 days [34,35]. However, 3 of 13 patients included in the analysis did not receive any romiplostim, 2 of whom had 0 days of grade 4 thrombocytopenia. Comparatively, Ford et al. [4] reported a median of 3 days of grade 4 thrombocytopenia and a median of 4 days of grade 3 thrombocytopenia (PLTs $<20 \times 10^9$/L) in 125 patients without any romiplostim use. One protocol gave romiplostim 4 mcg/kg weekly starting 2 to 7 days post-transplant, continued until PLTs $>100 \times 10^9$/L. Two patients underwent bloodless aHCT following this protocol and experienced no bleeding events or met indications for transfusions [6]. Because of the small sample size and lack of comparator, it is unknown if romiplostim is responsible for these results. Evidence is not sufficient to support romiplostim use definitively in the post-aHCT setting.

The pharmacokinetics of romiplostim may dissuade its use for transplant patients, but other factors should be considered. In healthy volunteers, PLT count began to increase at day 5 after 1 dose of romiplostim. Peak effect was seen after days 12 to 16, and PLT count returned to normal around day 28 [36].

Based on pharmacokinetics, romiplostim does not exert an immediate effect on PLT recovery in a healthy person with presumed adequate hematopoietic activity. However, there are no studies to show the pharmacokinetics of romiplostim in patients with a lack of normal hematopoietic activity, such as after HDC. Furthermore, exposure to treatment, extent and type of malignant disease, and liver insult from certain chemotherapies should be considered in the aHCT population. It can be difficult to predict the patient's PLT recovery behavior and the chance of bleeding. Therefore, administering romiplostim to overlap with engraftment may be considered to facilitate PLT engraftment and optimize safety and success of aHCT.

DISCUSSION

The possibility of a bloodless transplant is evident in the literature with several published experiences [4-8]. Joseph et al. [5] evaluated 24 bloodless aHCT matched 1:3 with transfusion-supportive aHCT. There was no difference between the 2 groups in length of stay, time to neutrophil or PLT engraftment, bleeding, or thrombosis complications. There was no transplant-related mortality in either group at the 100-day or 1-year mark. Khan et al. [8] also explored 4 bloodless tandem aHCT and concluded that bloodless tandem aHCT may be safely performed if hematopoietic support is optimized with ESAs and blood conservation techniques. Refer to Table 1 for comparison of available protocols regarding ESAs and TPO agonists.

Pathophysiology and available literature can be reasonably used to support the potential use of ESAs and TPO mimetics to decrease complications. ESAs may be used through the priming method to prevent organ hypoxia by optimizing baseline Hb. Both ESAs and TPO agonists may be considered post-aHCT to facilitate engraftment.

Risk versus benefit must be assessed based on individual characteristics and medical history. As previously mentioned, ESAs carry a black box warning of cardiovascular and thromboembolic events. High-risk patients with a history of uncontrolled hypertension, cardiac or cerebrovascular disease, or thrombosis should be closely monitored. In addition, immunomodulator therapies, such as pomalidomide and lenalidomide, used to treat multiple myeloma increase the risk of thromboembolic events and require prophylaxis. Although immunomodulators are usually discontinued a few weeks before transplant, they may overlap with ESA priming therapy. Currently, there is no evidence to assess the efficacy and safety of aspirin or other agents in preventing thromboembolic events when immunomodulators are used concurrently with ESAs. Further studies are needed to identify the most efficient anticoagulation technique.

Despite cardiovascular and thrombotic risk, a target Hb of 11 g/dL may not be adequate depending on the type of conditioning regimen. As reported by Ford et al. [4], patients with lymphoma had a greater drop in Hb compared with patients with multiple myeloma (5.9 versus 4.2). Therefore, patients with lymphoma may require a higher Hb goal, perhaps targeting Hb >12 g/dL. Risk versus benefit of a higher target goal should be considered on an individual basis.

In addition to standard blood conservation techniques and growth factor use, supplements such as folic acid and vitamin B-12 should be used to adequately replenish body stores to support erythropoiesis. Similarly, vitamin K should be administered to ensure optimal serum levels. Many patients experience gastrointestinal side effects, including diarrhea and vomiting, from conditioning regimens such as melphalan for multiple myeloma. These adverse effects cause tremendous loss of vitamin K stores. Although vitamin K does not directly affect thrombopoiesis, it does play a key role in the coagulation cascade and should be repleted to prevent bleeding. Stem cell mobilization should be maximized with granulocyte colony-stimulating factors and plerixafor to ensure adequate $CD34^+$ cells for autograft. Although optimal mobilization techniques and cell count have not been established, studies suggest higher cell numbers may be associated with faster hematopoietic recovery [37]. Further investigation on optimal mobilization techniques and cell count for bloodless aHCT is warranted.

In addition to the aforementioned strategies, artificial blood substitutes are an area in development to alleviate the need for blood products. RBC substitutes derived from perfluorochemicals (PFCs), hemoglobin (bovine or human), and stem cells have been studied [38]. RBC substitutes are of particular interest due to their lack of infectious risk or need for blood type matching, as well as potentially fewer complications from infusion. PFCs are chemicals with oxygen-carrying capacity, and their lack of an animal or a human component makes them appealing to patients unable to receive blood products. However, PFCs have not yet proven great success and may cause a 10% to 15% drop in PLT count [38]. Hb-based RBC substitutes demonstrate greater promise. Several acellular and cellular Hb-based oxygen carriers are under development [38]. Hemopure, an acellular Hb-based oxygen carrier, has demonstrated success in managing anemia for Jehovah's Witness patients in need of emergent blood product [39]. While research continues, no artificial blood substitutes are approved by the US Food and Drug Administration to date. A product of this nature would be beneficial for all.

It is important to understand and respect the beliefs of Jehovah's Witnesses and to properly address the ethical and legal concerns surrounding a bloodless transplant. The acceptability of certain minor blood fractions and related components is dependent on individual choice, whereas recombinant protein products such as EPO are usually accepted but should be identified and reviewed with their religious leaders if the patients so choose. When setting up a bloodless transplant program, accurate classification of available products should be clearly defined to avoid confusion and accidental breach of religious sanction. During informed consent, these treatment modalities should be addressed carefully and explained in uncomplicated language to ensure patient comfort and establish trust in their treatment team. An ethical quandary may arise when a provider's moral and professional obligations are in conflict with the patient's wishes for medical treatment. In addition to informed consent, detailed health care advanced directives should be discussed and documented to protect both the physician and the patient's wishes.

CONCLUSION

Current literature supporting the use of ESAs and TPO agonists in the bloodless aHCT setting is limited. However, available published single-center experiences in combination with physiologic reasoning may be used to develop strategies to maximize transplant success. These agents offer potential benefit and may be of utility in minimizing complications of a bloodless autologous transplant. The goal is to make available the option of transplant to patients who may otherwise be denied. Further studies would be needed to validate the use of ESAs and TPO agonists in the bloodless aHCT setting.

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