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The Source of Cells for Allografting

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ABSTRACT

Peripheral blood is used almost exclusively as the source of hematopoietic cells for autografting, but the best source of cells for allografting is the subject of considerable discussion and debate. Randomized studies comparing unstimulated bone marrow with G-CSF–mobilized peripheral blood in the sibling allogeneic setting have indicated a trend to more chronic graft-versus-host disease in peripheral blood recipients. However, whether the use of G-CSF–mobilized peripheral blood cells leads to more acute graft-versus-host disease is uncertain. Adults undergoing sibling allografting appear to benefit in terms of improved disease-free survival or improved overall survival with the use of G-CSF–mobilized peripheral blood. It is not clear, however, whether these benefits also extend to children or those undergoing matched unrelated transplantation.
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KEY WORDS

Bone marrow transplantation • Peripheral blood transplantation • Allogeneic

INTRODUCTION

The preferred source of progenitor cells for high-dose therapy and hematopoietic stem cell transplantation has changed in the last 2 decades. Traditionally, cells harvested directly from bone marrow in the iliac crests were used for both autologous and allogeneic transplantation.

Progenitor cells capable of re-establishing hematopoiesis after myeloablative therapy are present in low concentrations in blood, but the number of apheresis procedures required for a satisfactory graft makes collection from unstimulated blood impractical. However, the concentration of peripheral blood progenitor cells increases after the administration of recombinant growth factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor alone or after chemotherapy, allowing collection of an adequate graft with only 1 apheresis procedure or a few apheresis procedures. Autologous peripheral blood harvesting by apheresis has permitted the collection of large numbers of progenitor cells, and phase II studies and randomized trials [1,2] have demonstrated faster hematologic recovery compared with marrow autografting. Peripheral blood autografting has also facilitated graft manipulations such as $CD34^+$ cell selection and tumor cell purging, which had been difficult with the smaller number of progenitor cells collected by autologous marrow harvesting. For these reasons, peripheral blood has almost completely replaced marrow in autologous transplantation, and marrow is used only for patients in whom mobilization is poor or those who cannot tolerate apheresis.

ALLOGENEIC PERIPHERAL BLOOD TRANSPLANTATION

Peripheral blood as a source of progenitor cells for allografting was initially overlooked for 2 major reasons. First, compared with marrow, peripheral blood contains approximately 10-fold more T lymphocytes, which are the principal mediators of graft-versus-host disease (GVHD). In marrow allografting, T-cell depletion studies had shown a correlation between the number of T lymphocytes in the allograft and the extent and severity of GVHD. Second, there were concerns about the risks to healthy donors of both administering recombinant growth factors and apheresis, including uncertainty about whether central venous catheters would be required.

In 1995, 3 pivotal studies [3-5] demonstrated the safety and feasibility of using G-CSF–mobilized peripheral blood allografts. Patients experienced prompt hematologic recovery with an incidence of GVHD similar to that described in marrow recipients. In addition, no serious short-term complications of G-CSF–mobilized peripheral blood harvesting were noted among the healthy donors.

A retrospective study of HLA-identical sibling donor transplants that compared outcome in recipients of either peripheral blood (n = 288) or marrow (n = 536) allografts [6] demonstrated more rapid neutrophil and platelet recovery among those who received peripheral blood. Although there was no difference in the incidence of grade II to IV acute GVHD, chronic GVHD was more common in peripheral blood recipients (65% versus 53%; $P = .02$). Treatment-related mortality was lower and disease-free survival higher among peripheral blood recipients who had more advanced disease; no difference was shown in those with early disease.

RANDOMIZED TRIALS OF ALLOGENEIC PERIPHERAL BLOOD TRANSPLANTATION

Direct comparisons of peripheral blood and marrow in allogeneic sibling donor transplantation have been reported in at least 8 randomized trials [7-14]. The results from the 4 largest trials [9,12-14], which included 829 evaluable patients, may be summarized as follows.

Hematologic Recovery

Neutrophil and platelet recovery was faster among peripheral blood allograft recipients. In some trials, fewer red blood cell and platelet transfusions and shorter hospitalizations were also reported.

Acute GVHD

Three [9,12,13] of the 4 trials found no difference in the incidence or severity of acute GVHD among peripheral blood and marrow recipients. In contrast, the largest trial [14] described a statistically significantly higher incidence of grade II to IV acute GVHD in peripheral blood recipients (52% versus 39%; $P = .01$). Patients in this study did not receive day 11 methotrexate, whereas those in 2 of the other 3 studies did, which may account for this difference.

Chronic GVHD

An increase (statistically significant or a trend) in the incidence of overall and extensive chronic GVHD was demonstrated in recipients of peripheral blood allografts. A meta-analysis of published reports [15] that included randomized trials, registry data, and case series has confirmed this observation. However, although more chronic GVHD with peripheral blood allografting seems certain, the magnitude of this observation and its effect on relapse, survival, and recipients' quality of life are less clear. Furthermore, chronic GVHD after peripheral blood allografting may be qualitatively different from that after marrow allografting, and further studies that include long-term follow-up of patients in the randomized trials will be important.

Survival

Only 1 trial [13] demonstrated a benefit in overall survival among peripheral blood recipients (68% versus 60% at 30 months; $P = .04$). Bensinger et al. [12] reported a trend toward better overall survival of similar magnitude among peripheral blood recipients (66% versus 54% at 24 months; $P = .06$), whereas the 2 European studies [9,14] noted no difference.

Improved overall survival in the Canadian trial [13] was due to lower treatment-related mortality in peripheral blood recipients. It is interesting to note that this benefit was realized early (before day 30) and continued beyond day 100. It seems likely that faster hematologic recovery and more rapid and complete early [16] and later [17,18] immunologic reconstitution contribute to lower treatment-related mortality of peripheral blood recipients.

Although subgroup analyses of randomized studies are problematic because of power limitations and imbalances of prognostic factors between groups, both North American studies [12,13] demonstrated a survival benefit of peripheral blood allografting only in patients with advanced disease (acute myelogenous leukemia beyond first remission, chronic myelogenous leukemia beyond the first chronic phase, and myelodysplastic syndrome with excess blasts). Such patients may derive greater benefit from the faster hematologic and immunologic recovery afforded by peripheral blood transplantation. Alternatively, peripheral blood allografts may exert a more potent antitumor effect, thus benefiting patients with advanced disease, although this hypothesis remains unsubstantiated. Both European studies [9,14] included predominantly patients with early disease, possibly accounting for the absence of a survival benefit of peripheral blood allografting.

COLLECTION PROTOCOLS

The dose of G-CSF administered to donors differed significantly in the 4 trials (Table 1). G-CSF increases the number of $CD34^+$ progenitor cells in the peripheral blood but also affects T lymphocytes, dendritic cells, and natural killer cells, as well as other cellular constituents of the allograft. G-CSF–mobilized peripheral blood allografts contain substantially

Table 1. *Collection Protocols, Target CD34$^+$ Cell Dose, and CD34$^+$ Cell and T-Lymphocyte Content (per Kilogram of Recipient's Weight) of Peripheral Blood (PB) Allografts in 4 Randomized Comparisons of Allogeneic Marrow and Peripheral Blood*

Study	G-CSF Dose (μg/kg/d)	Days of G-CSF	Number of Aphereses, Median (Range)	Target PB CD34$^+$ Cell Dose	Actual PB CD34$^+$ Cell Dose, Median (Range)	Actual PB T-Cell Dose, Median (Range)
Schmitz et al. [14]	10	4	1 (1-3)	4×10^6	5.8×10^6 (1.5-68.3)	300×10^6 (16-2123)
Couban et al. [13]	5	4	2 (1-2)*	2.5×10^6	6.4×10^6 (0.7-32)	370×10^6 (120-3080)
Bensinger et al. [12]	16	5	1 (1-4)	5×10^6	7.3×10^6 (1.0-29.8)	279×10^6 (143-788)
Blaise et al. [9]	10	5	2 (1-3)	4×10^6	6.6×10^6 (1.5-19.2)	356×10^6 (131-754)

*If the target CD34$^+$ cell dose was not achieved after 2 aphereses, the protocol called for a marrow harvest to supplement the PB collection.

more monocytes, natural killer cells, and dendritic cells than marrow [17,19,20], and G-CSF directs T lymphocytes to a T-helper type 2 phenotype that secretes interleukin-4 and interleukin-10 [21]. Differences in the methodology of progenitor cell mobilization with G-CSF and peripheral blood collection may lead to substantial quantitative and qualitative differences in the peripheral blood allograft between studies that is not accounted for solely by CD34$^+$ cell and T-lymphocyte quantitation. For example, the 3- to 4-fold variation in G-CSF dose administered to donors may have affected the extent of polarization of T-helper cells in the allograft. Similarly, an allograft collected in 1 day would necessarily be different from an allograft collected over 2 days, even if both contained a similar number of CD34$^+$ cells. More sophisticated characterization of the allograft with comparison of different collection strategies and further study of immune recovery after transplantation may lead to improved outcomes after peripheral blood allografting.

UNRELATED DONOR ALLOGENEIC TRANSPLANTATION

The safety and feasibility of peripheral blood allografting with sibling donors has led to interest in its application in the unrelated donor setting. Because GVHD is the major cause of morbidity and mortality in unrelated allogeneic transplantation, the observations of more acute GVHD disease in the European Bone Marrow Transplantation Group study [14] and more chronic GVHD in all randomized trials have raised concerns about unrelated donor transplantation with peripheral blood allografts. However, matched cohort comparisons of unrelated marrow and peripheral blood transplantation [22,23] reported faster hematologic recovery among peripheral blood recipients, with no difference in either acute or chronic GVHD or survival.

While results of randomized trials have been pending, the use of peripheral blood allografts in unrelated transplantation has varied among transplant centers and countries. Some have advocated unrelated peripheral blood allografts for diseases in which the risk of relapse is high and marrow allografts in diseases such as chronic-phase chromic myelogenous leukemia, in which the risk of relapse is relatively low. However, the benefit of chronic GVHD in reducing the risk of relapse has yet to be demonstrated in peripheral blood transplantation, and prospective confirmation of this treatment strategy is required.

Some registries of unrelated marrow donors have permitted the collection of allografts from the peripheral blood, whereas others have not. Transplant centers may request a peripheral blood or marrow allograft, but the collection center and wishes of the volunteer donor also determine which product is ultimately collected. Despite the absence of definitive data comparing unrelated marrow and peripheral blood transplantation, the use of peripheral blood allografts for unrelated transplantation is increasing in Europe and North America, and the window of opportunity within which to complete a randomized trial may be closing.

DONOR CONSIDERATIONS

Marrow harvesting from healthy donors is generally safe and well tolerated, and serious risks are limited mainly to the complications of general anesthesia. Peripheral blood donors must receive a recombinant growth factor for several days followed by 1 or more apheresis procedures. Administration of growth factors such as G-CSF to donors was initially a major safety concern in peripheral blood allografting. G-CSF causes donors to experience bone pain, myalgias, arthralgias, and malaise [24]. It also leads to leukocytosis, thrombocytopenia, and increases of alkaline phosphatase, lactate dehydrogenase, uric acid, alanine aminotransferase, γ-glutamyl transpeptidase, prothrombin, thrombin/antithrombin complexes, and D-dimer [25]. Although these common effects are usually transient, rare but more serious medical events, including myocardial infarction and stroke [26,27], have been reported. There have also been cases of spontaneous splenic rupture requiring emergency splenectomy after G-CSF administration to healthy donors [28,29]. Careful follow-up of donors who receive G-CSF is essential to determine whether there are serious long-term effects of this practice.

ALLOGENEIC G-CSF–STIMULATED MARROW TRANSPLANTATION

The use of autologous and allogeneic progenitor cells collected from peripheral blood leads to faster hematologic recovery because more $CD34^+$ cells are obtained. This approach also leads to the collection of 10-fold more T lymphocytes, which may explain the higher incidence of chronic GVHD after peripheral blood allografting. It is possible that treatment of a donor with G-CSF before marrow harvest may also allow collection of more $CD34^+$ progenitor cells compared with unstimulated marrow without the large number of T lymphocytes that accompany peripheral blood collection. Several investigators have demonstrated the safety and feasibility of this strategy [30-32]. A randomized comparison of G-CSF–mobilized peripheral blood and G-CSF–stimulated marrow allografts closed early because more overall (90% versus 47%; $P < .02$) and extensive (80% versus 22%; $P < .02$) chronic GVHD was seen in peripheral blood compared with G-CSF–stimulated marrow recipients [33]. No difference in overall survival was observed among the 57 evaluable patients, and further studies of this approach are warranted.

CONCLUSIONS

The use of G-CSF–mobilized peripheral blood allografts is a safe and feasible alternative to unstimulated marrow. In matched sibling donor allogeneic transplantation, peripheral blood allografts lead to faster hematologic recovery and may result in less blood product use and shorter hospitalizations. Despite no apparent increase in acute GVHD, peripheral blood allografting is associated with more chronic GVHD, and the effect of this on survival, relapse, and the recipients' quality of life remains to be determined.

In the absence of evidence from randomized trials, bone marrow remains the standard allograft for unrelated transplantation, although peripheral blood may be a reasonable alternative. Further studies of the long-term outcome of allogeneic peripheral blood transplantation are needed to define the consequences of increased chronic GVHD. In addition, randomized trials of mobilized blood allografts in unrelated transplantation and in children, as well as further evaluation of stimulated marrow allografts, are required. Finally, as the components of the allograft are better characterized and understood, it should be possible to define optimal mobilization, stimulation, and collection strategies.

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