Risk assessment in haematopoietic stem cell transplantation: Stem cell source

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Bone marrow (BM) has been used for many years as the unique source of progenitor cells for allogeneic transplantation. However, two other sources of progenitor cells, peripheral blood (PB) and umbilical cord (UC), are being increasingly used. The type of graft is one of the most important factors in determining the speed and robustness of the reconstitution after the transplant of monocytes, T lymphocytes, B lymphocytes, NK cells, and dendritic cells. This fact is of especial relevance since the most important reactions after allogeneic transplants — e.g. graft-versus-host disease (GVHD), graft-versus-leukaemia effect (GvL), achievement of full donor chimerism, and fight against infections — are strongly influenced by a rapid and robust reconstitution of these cells. For this reason, the choice of the type of graft for allogeneic transplantation will influence the clinical outcome.

Key words: stem cells; G-CSF; cord blood; allogeneic; transplantation.

Bone marrow (BM) has been used for many years as the unique source of progenitor cells for allogeneic transplantation. However, two other sources of progenitor cells, peripheral blood (PB) and umbilical cord (UC), are being increasingly used. There are many differential characteristics among the three sources of progenitor cells, including anatomical and biological differences and the administration of granulocyte-specific colony-stimulating factor (G-CSF) for mobilizing progenitor cells. However, the most important difference influencing the clinical results is the absolute number of progenitor cells and of accessory cells present in the inoculum. The proportion of CD34+ cells in the inoculum is very similar in UC, BM, and PB (G-CSF), ranging between 0.6 and 1% of the mononuclear cells. However, there is a huge difference in the volume of harvest among the three sources of progenitor cells: 0.1, 1.5, and 10–20 L when UC, BM, and PB are used, respectively. The different volumes of harvest result in an important difference in the number of progenitor cells and accessory cells infused with the graft,

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and subsequently in the myeloid and lymphoid reconstitution. This determines the important differences in the initiation of the allogeneic reactions.

The main characteristics of these three sources of haematopoietic progenitor cells (HPCs) will be discussed in this chapter with respect to: (1) the evolution in their use in Europe; (2) donor risk and donor aspects; and (3) the graft composition and its implication in clinical results.

**CURRENT USE OF BONE MARROW, PERIPHERAL BLOOD AND UMBILICAL CORD FOR ALLOGENEIC TRANSPLANTATION IN EUROPE**

The immense majority of autologous transplants in Europe are currently performed using PB progenitor cells (PBPCs). In the period between 1990 and 1994 there was a dramatic change from BM to PB, and since then more than 95% of autologous transplant patients receive haematopoietic progenitor cells from PB after G-CSF mobilization (PB/G-CSF). The main reason for this change is the higher number of progenitor cells collected from PB/G-CSF, the rapidity of neutrophil and platelet recovery, and the preference of the patient. Starting in 1994, the incorporation of PB/G-CSF as a source of progenitor cells for allogeneic transplantation has been slower, but currently this source is used for as much as the 70% of the total of allogeneic transplants, both in the HLA-identical sibling and unrelated settings (Figure 1). The continuous increment in the use of PB/G-CSF for allotransplants is due in part to the popularity of allogeneic transplants conditioned with reduced-intensity regimens (allo-RIC), which now represents around one third of the total of allotransplants performed in Europe (Figure 2). Whereas for conventional myeloablative allogeneic transplants some stem-cell transplant centres choose BM and others prefer PB/G-CSF, there is an overall agreement for the preferential use of PBPC over BM for RIC transplants; the reason for choosing PB/G-CSF for allo-RIC is the large quantity of progenitor cells and T cells in PB/G-CSF grafts, which facilitates engraftment and achievement of full T-cell donor chimerism after allo-RIC. In 2004 281

![Figure 1. Percentage of autologous (auto-PBT) and allogeneic (allo-PBT) transplantation using peripheral blood as the source of progenitor cells in Europe (European Group for Blood and Marrow Transplantation activity survey).](image-url)
allogeneic transplants using UC blood units were performed in Europe\(^6\), representing only 3% of the total of allogeneic transplants and 7% of the unrelated allo-SCT. However, these figures should not lead to underestimation of the great possibilities of UC transplant for allotransplants in the future. Thus, the Spanish Registry of Bone Marrow Donors (REDMO) has reported that the proportion of UCT in the unrelated setting is sharply increasing in Spain, representing last year 40% of the total of unrelated allo-transplants, as compared to 35% for PB and 25% for BM.

**DONOR RISKS AND DONOR ASPECTS**

The procedure for collecting HPCs is associated with considerable side-effects for the donors, which differ in severity depending on the source. This aspect has greatly influenced the decrease in the use of BM as a source of progenitor cells for allo-transplants. Harvesting HPCs from BM requires 100–200 punctures in iliac crests under general anaesthesia in the operating room. BM donation is associated with acute side-effects, like intense pain (20–85% of donations), fever, bleeding or local infection (<20% of donations), or prolonged hospitalization due to abscess or bacteraemias (1% of donations).\(^{12–14}\) A few reports of life-threatening or incapacitating complications after BM donation have been reported, the rate of death being estimated at 1/10,000 donations.\(^{12–14}\)

The procedure for collecting HPCs from PB is less aggressive. Collection is by leukapheresis through peripheral-vein access, and the procedure takes approximately 3–4 hours. Serious side-effects associated with PBPC collection are much less frequent than after BM donations.\(^{15–23}\) Thus, the hospitalization rate due to complications associated with the apheresis procedure or to severe thrombocytopenia is <0.6%.\(^{18–23}\) However, for PBPC collection the donor is not only submitted to the procedure of leukapheresis but also receives G-CSF, which is associated with other risks. Thus, after G-CSF administration the spleen enlarges temporarily by 10% of its size in most of the donors, with an estimated risk of splenic rupture of 1/10,000–1/5000 of the cases. Other rarely severe adverse events associated with
G-CSF administration are cardiovascular accidents — the German registry reported two strokes and one myocardial infarction in 3286 PBPC donations — and flares of underlying autoimmune disorders. An aspect that raises important concerns is the possibility that G-CSF might induce leukaemia in healthy donors. Recent data show that G-CSF does dramatically change the expression of many genes, but that the normal situation is restored in <2 months. Moreover, it has been shown that G-CSF in normal volunteer donors generates epigenetic and genetic alterations in lymphocytes (for instance temporary alterations in replication timing and DNA stability) which can result in chromosomal alterations and aneuploidy. Although these changes might potentially favour the origin of leukaemia, no single piece of evidence for such an association has been reported to date. If it exists, such an association will not be easy to identify, since it has been estimated that to demonstrate an increase of 10% in the probability of developing leukaemia after G-CSF administration, at least 10,000 donors should be followed for at least 10 years. Most of the registries are performing such a long follow-up of the donors, and a few attempts have been made to clarify this concern. Thus, a recent European Group for Blood and Marrow Transplantation (EBMT) study conducted by Alois Grawthol reported, with the limitations of a retrospective study, that the frequency of leukemia after PB/G-CSF donation was identical to that observed after BM harvests (A. Grawthol, personal communication). Thus, of 28,134 marrow donors assessed, nine developed a haematological malignancy after donation for an overall reported rate of 0.032%. Those receiving G-CSF for collection of PBPCs had a similar reported rate of haematological cancers (5/16,431; 0.03%). This apparent lack of a deleterious severe effect of G-CSF on haematopoietic progenitor cells is not surprising taking into consideration that the serum level of G-CSF in healthy donors is very similar to those achieved in patients with sepsis (488 pg/mL and 599 pg/mL, respectively).

Several groups are investigating the clinical use of other agents which have a safer profile than G-CSF and are also capable of mobilizing progenitor cells by detachment of stem cells from the marrow stroma. The effect of G-CSF on haematopoietic progenitor cell mobilization is mediated by a double mechanism. The pool of progenitor cells in bone marrow is increased after 2 days of G-CSF administration, and this is followed by a decrease 5 days after G-CSF administration, which coincides with an increase in progenitor cells in peripheral blood. Thus, G-CSF induces first a proliferation of the number of progenitor cells in bone marrow and afterwards their mobilization to peripheral blood. In bone marrow, homing and mobilization of progenitor cells depends on the interaction of several molecules present on the surface of haematopoietic progenitor cells and on stromal cells. Recently, the importance has been recognized of the interaction between the chemokine receptor CXCR4, present in the haematopoietic progenitor cells, and the stroma-derived factor (SDF), present in the marrow stromal cells. This interaction is important for homing of stem cells in BM. G-CSF induces mobilization by breaking the interaction between CXCR4 and SDF by down-regulating SDF and by inducing the proliferation of the pool of neutrophils in bone marrow, with a maximum after 5 days of administration. Neutrophils release proteolytic enzymes such as metalloproteases, cathepsin G and elastases (Figure 3), which split CXCR4, releasing the haematopoietic progenitor cells and permitting the egress of the haematopoietic progenitor cells to PB. Interestingly, CXCR4 serves as a co-receptor for the entry of HIV into host cells, and several molecules blocking CXCR4 have been investigated for treating HIV-positive patients. One of these molecules is AMD3100, which has been found to be a specific antagonist of CXCR4. Several groups have observed that AMD3100 mobilizes...
stems cells by interrupting the interaction between SDF and CXCR4 (Figure 3).33,35,40

Very recently, the Seattle group has shown that one single subcutaneous injection of AMD3100 to healthy donors mobilizes enough haematopoietic progenitor cells for allo-transplantation 9 hours after administration.40 Compared to G-CSF, the potential benefits of AMD3100 for CD34⁺ mobilization are a safer profile, a synergistic effect with G-SCF, possibly a faster platelet recovery in patients transplanted with CD34⁺ cells that express higher levels of CXCR4,42 and better stem-cell homing.43 These last two advantages are due to the fact that AMD3100, in contrast to G-CSF, does not split CXCR4.

Figure 3. (a) Granulocyte-specific colony-stimulating factor (G-CSF) induces both proliferation and mobilization of stem cells. G-CSF mobilizes stem cells by breaking the interaction of CXRC4 with stroma-derived factor (SDF) by down-regulating SDF and by inducing the release of proteolytic enzymes which split CXRC4.34 (b) AMD3100 mobilizes stem cells by interrupting the interaction between SDF and CXCR4. HPC, haematopoietic progenitor cell.33,35,40
The advantages of using UC blood units for allo-transplantation compared to BM and PB are, among others, that it is easy to collect without risk for the donor, can be simply stored for years in liquid nitrogen, has less restrictive HLA compatibility, and may be provided quickly for unrelated transplantation.\textsuperscript{44–54} On the other hand, disadvantages are the impossibility of obtaining HPCs or lymphocytes after the transplant in case of need for treatment of graft failure or relapse, respectively, and the low number of hematopoietic progenitor cells in a cord-blood unit. This limits the proportion of adults that can benefit from this type of transplantation if we want to administer an adequate number of hematopoietic progenitor cells to the recipients. Thus, it has been estimated that with the UC units available worldwide, <20% of adults might be transplanted with the recommended dose of \(>2.5 \times 10^7\) nucleated cells per kilogram.\textsuperscript{55,56} For this reason, overcoming the cell dose barrier in UC transplant is a very active field of research. Several groups have proposed different approaches for solving this limitation, such as double cord blood transplants\textsuperscript{57,58}, co-infusion of cord blood and haploidentical hematopoietic progenitor cells from a third party\textsuperscript{59,60}, ex vivo expansion of cord blood cells\textsuperscript{61,62}, or co-infusion of cord blood cells together with third-party mesenchymal stroma cells.\textsuperscript{63}

An aspect that deserves special consideration is the increasing donor age, which is due to the increasing patient age in the allogeneic setting. This fact favours the potential of transmitting diseases from donor to recipient, including not only infections but also congenital disorders, autoimmune diseases or malignancies. Crucial points for such individual decisions are the infectious status of the recipient, the lack of an alternative compatible donor, a limited life expectancy of the recipient, and full donor and recipient informed consent.\textsuperscript{64}

**GRAFT COMPOSITION AND ITS IMPLICATIONS IN CLINICAL RESULTS**

The clinical impact of the cell composition of the graft differs greatly depending on whether the type of transplant is autologous or allogeneic. Thus, in the autologous setting the clinical importance of the cell subsets contained in the inoculum relies mainly on the number of progenitor cells administered to the patient and their effect on the kinetics of neutrophil and platelet recovery. Infusion of a large quantity of progenitor cells is associated with a rapid hematopoietic recovery and with a very low probability of graft failure and poor engraftment.\textsuperscript{65} There is a threshold CD34\textsuperscript{+} cell dose below which engraftment is delayed and the positive linear correlation of the number of CD34 cells and kinetics of engraftment reaches a limit, above which an increase in the number of progenitor cells does not provide any additional benefit.\textsuperscript{66} It is not surprising that autologous transplants using PB/G-CSF grafts, which contain three or four times more CD34\textsuperscript{+} cells than BM harvests, are associated with more rapid engraftment and less probability of graft failure than those using BM. The absolute quantity of accessory cells in the graft — such as T cells, NK cells or dendritic cells — is of relative clinical importance in autologous transplantation. In the allogeneic setting, the number of progenitor cells influences the kinetics of recovery, but other factors intervene, such as the degree of HLA compatibility between donor and recipient, the intensity of the conditioning regimen, and the number of T cells in the graft.\textsuperscript{57} More importantly, in the allogeneic setting accessory cells infused with the graft participate in key reactions after the transplant. Thus, infusing either a small or a large quantity of T cells, NK cells, dendritic cells, or mesenchymal cells in allo-SCT influences the incidence of graft failure,
graft-versus-host disease, graft-versus-leukaemia effect, and the speed of immune reconstitution. Of note, there are important quantitative and qualitative differences in the cell composition of PB/G-CSF and BM allografts. As shown by several groups, the total numbers of T cells, B cells, monocytes, and NK cells contained in a PB/G-CSF allograft are 5–10 times higher than those in a BM allograft.\(^{68,69}\) In general terms, the higher the number of accessory cells in the graft, the stronger the allogeneic reactions post-transplant. For this reason, allo-SCT using PB/G-CSF is associated with a higher capacity of engraftment, higher incidence of GVHD, and quicker immune reconstitution than allo-BMT and allo-UCT; in its turn, allo-BMT is associated with stronger alloreactions than allo-UCT.

UC, BM, and PB/G-CSF grafts contain on average a quantity of 0.3, 3, and \(5 \times 10^6\) CD34\(^{+}\) cells per kilogram of recipient weight, respectively. These differences are of special importance, taking into consideration the strong correlation between the number of progenitor cells and clinical outcome. UC transplantation is a clear example of the positive effect of the cell dose on survival, as was apparent from the first reports from the St Louis group on the beneficial effect of transplanting UC blood units rich in mononuclear cells to low-weight patients. In a recent report from the University of Minnesota\(^{48}\), the ratio of the number of CD34\(^{+}\) cells in the UC unit per kilogram of recipient was directly associated with the transplant-related mortality rate. As previously suggested by other groups, their results also indicate that a higher CD34 cell dose partially overcomes the negative impact of HLA for each level of HLA disparity. In Cox regression analyses, CD34 cell dose was the one factor consistently identified as significantly associated with rate of engraftment, transplant-related mortality, and survival. The number of CD34\(^{+}\) cells in UC transplants in adults also positively influences disease-free survival.\(^{70}\)

The quantity of progenitor cells administered to the patients is also of relevance for the clinical outcome in the allogeneic BMT setting. Results from the Genova Group shows the beneficial effect of infusing a high cell dose in allo-BMT in lowering the transplant-related mortality and in increasing the overall survival.\(^{71}\) Similarly, Sierra et al reported the Seattle experience for unrelated BMT, demonstrating that clinical outcome was improved for patients receiving a high marrow cell dose.\(^{72}\) These results have been confirmed by the Hôpital St Louis group\(^{73}\) and by the EBMT in a randomized study of bone marrow versus peripheral blood\(^{74}\), in which the number of CD34\(^{+}\) cells contained in a bone-marrow graft was a very strong prognostic factor for survival. This association of the number of CD34\(^{+}\) cells and survival in allo-BMT has been attributed to shorter neutropenia, faster immunological recovery, and enhanced graft versus leukaemia effect. The Hôpital St Louis group has shown less severe fungal infections in the group of patients receiving a higher number of CD34\(^{+}\) cells.\(^{73}\)

Is this positive correlation of the number of CD34\(^{+}\) cells with survival reported in allo-UCT and allo-BMT also observed in the context of allo-PBT, in which the starting number of CD34\(^{+}\) cells is double that of BM? It could happen that beyond a certain CD34\(^{+}\) cell dose the results in allogeneic transplants do not improve, or it might be even the case that results deteriorate. Until recently, we weren’t able to answer this question. However, allo-PBT allows us to infuse very high numbers of progenitor cells — three times, or perhaps more, the quantity of CD34\(^{+}\) cells usually obtained from a BM harvest. In this regard, results obtained in the EBMT randomized study of transplantation of mobilized peripheral blood cells to HLA-identical siblings with standard-risk leukaemia are revealing.\(^{74}\) In this study, 350 adult patients diagnosed with acute leukaemia in first complete remission or chronic myeloid
leukaemia in first chronic phase were randomized to receive either allo-BMT or allo-PBT. Allo-BMT was performed in 166 cases (median of CD34+ cells: $2.7 \times 10^6$/kg), and allo-PBT in 163 cases (median CD34+ cells: $5.8 \times 10^6$/kg). It was found that in the overall group, the fact of infusing higher CD34+ cell numbers had a borderline positive correlation with survival. Of note, the correlation of survival with CD34+ number was significant in the BM group ($P = 0.022$), but appeared non-existent in the PB group. Furthermore, there are results to suggest that a very high CD34+ cell dose not only does not improve the clinical results, it might actually have a deleterious effect, at least in the context of the HLA-identical sibling. Thus, Przepiorka et al. from the MD Anderson, in a series of unmanipulated allo-PBTs, have suggested an increased rate of chronic GVHD in patients receiving more than $8 \times 10^6$/kg CD34+ cells. This was attributed to a rapidly expanding myeloid cell population, which could have released cytokines that exacerbate GVHD. Three months later, the Seattle group reported a correlation between high numbers of CD34+ cells and the incidence of chronic GVHD in adult patients given unmodified peripheral-blood stem-cell grafts from HLA-identical siblings. Similar results have also been reported by other groups, using T-cell-depleted and unmodified grafts, using standard or reduced-intensity conditioning regimens. This is of especial concern, since chronic GVHD is one of the most important causes of late death after allogeneic transplants. On the other hand, chronic GVHD has been associated with a potent anti-leukaemia effect after allo-BMT. Curiously, this association of chronic GVHD with reduced relapse rate has not been found in some of the most important series of allo-PBT. It might be, then, that a high dose of CD34+ cells increases both the incidences of chronic GVHD and of transplant-related mortality, without the beneficial effect of reducing the relapse rate. In a French randomized study of allo-BMT versus allo-PBT, in the peripheral blood arm, patients surviving more than 100 days and receiving a large quantity of CD34+ cells had a higher probability of chronic GVHD and worse survival than patients surviving more than 100 days and receiving a small quantity of CD34+ cells.

It is not known whether these different results found in allo-PBT as compared to those found in allo-BMT are due to the source or to the dose. It is possible that the clinical relevance of the number of nucleated cells from bone marrow is different from that of the number of nucleated cells from PB/G-CSF, since CD34+ cell and accessory cell function and cytokine patterns from the two sources are different. Alternatively, development of GVHD might not be directly correlated to the CD34+ cell dose. Grafts containing a large amount of CD34+ cells might also contain a correspondingly high number of accessory cells. Thus, an association of the number of donor dendritic cell progenitors with impaired outcome after allogeneic transplantation has been reported. In this study, a high content in the graft of donor DC2 cells was associated with decreased incidence of chronic GVHD and increased rate of relapse. We still need to define the role of the dose of other cell subpopulations important in allogeneic reactions, such as mesenchymal cells, T cells, or monocytes.

The discussed association of the number of CD34+ cells with the clinical outcome in conventional myeloablative allo-PBT might be different in allo-RIC transplants. As a matter of fact, recent data from the Seattle group show that administration of a large number of CD34+ cells decreases the risk of graft failure and improves overall survival after a non-myeloablative conditioning regimen. Of interest, the same group has reported an association of a high dose of B cells with a high incidence of chronic GVHD, less relapse, and better overall survival. The authors attributed this clinical correlation to the role of B cells in presenting antigens.
Several randomized studies have shown important clinical differences between allo-BMT and allo-PBT for patients with haematological malignancies in early and advanced stages. The most important difference between these two modalities of allogeneic transplantation is the kinetics of recovery after the transplant of neutrophils and platelets. Thus, achievement of 500 and 1000 neutrophils/μL and of 20,000 and 50,000 platelets/μL is much quicker with the use of PB/G-CSF than with those obtained from BM. This fact has been attributed not only to the higher number of haematopoietic progenitor cells infused in the allo-PBT setting, but also to the biological characteristics of G-CSF-mobilized progenitor cells. The incidence of acute GVHD is slightly higher in allo-PBT with respect to allo-BMT, but this difference did not reach statistical significance in most of the series. The only randomized study showing a significantly higher frequency of acute GVHD in allo-PBT with respect to allo-BMT is the EBMT clinical trial. Many retrospective and prospective clinical studies have reported that allo-PBT is associated with a high incidence of extensive chronic GVHD. Moreover, this complication seems to be more protracted and more resistant to the treatment than in allo-BMT cases. This complication is associated with a prolonged poor quality of life and it is a very important aetiology of long-term complications. When comparing allo-PBT versus allo-BMT, the overall survival and disease-free survival results are different depending on the phase of the patient’s disease. Thus, results obtained with allo-PBT for patients with diseases in advanced phase favour allo-PBT, and in patients with early-phase disease results seem to be very similar to those obtained with allo-BMT. However, a recent update of the IBMTR study seems to indicate that for patients with advanced-phase disease allo-PBT gives very similar results to those obtained with allo-BMT, and that for chronic myelogenous leukaemia (CML) patients in the first chronic phase results with allo-BMT are slightly better than with allo-PBT. The main reason for a worsening of the results after longer follow-up with allo-PBT is the mentioned higher incidence of chronic GVHD. During the last 10 years several groups have performed allogeneic transplants using progenitor cells from BM after the donor received 2–5 days of G-CSF (BM/G-CSF). This modality of allogeneic transplantation combines the rapid haematopoietic recovery observed after allo-PBT, without its high incidence of extensive chronic GVHD. The compiled experience of the groups using BM/G-CSF has been reviewed recently. BM/G-CSF is associated with kinetics of neutrophil and platelet recovery similar to those of allo-PBT, with an incidence of acute GVHD and chronic GVHD similar to, or even lower that, in allo-BMT. A comparison of the main clinical outcomes and selection of UC, BM, and PB/G-CSF as the source of progenitor cells for allogeneic transplant is summarized in Tables 1 and 2.

Table 1. Comparison of the main clinical outcomes using umbilical cord (UC), bone marrow (BM), and peripheral blood after G-CSF administration (PB/G-CSF) as the source of progenitor cells for allogeneic transplant.

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<th>aGVHD</th>
<th>cGVHD</th>
<th>Relapse</th>
<th>Chimerism</th>
<th>Fight against infections</th>
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<tr>
<td>UC</td>
<td>±</td>
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<td>BM</td>
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<td>PB/G-CSF</td>
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aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.
Practice points

- PB/G-CSF represents the source of progenitor cells for 70% of allogeneic transplants in Europe, both in sibling and unrelated settings.
- G-CSF induces mobilization of progenitor cells by breaking the interaction between CXRC4 and SDF.
- AMD3100 is a specific antagonist of CXCR4; AMD3100 mobilizes enough haematopoietic progenitor cells for allo-transplantation.
- UC, BM, and PB/G-CSF grafts contain on average 0.3, 3, and $5 \times 10^6$ CD34$^+$ cells per kilogram of recipient weight, respectively.
- There is a positive correlation between the number of CD34$^+$ cells and better survival in allo-UCT and allo-BMT; this correlation appears non-existent in allo-PBT.
- Administration of a large number of CD34$^+$ cells might decrease the risk of graft failure and improve overall survival after a non-myeloablative conditioning regimen.
- Allo-PBT is associated with a high incidence of extensive chronic GVHD.
- Allo-PBT seems to offer better results than allo-BMT for patients with advanced-phase diseases; allo-PBT and allo-BMT give similar results in patients with early-phase disease, but longer follow-up is necessary to confirm these findings.
- Allogeneic transplantation of BM/G-CSF is associated with kinetics of neutrophil and platelet recovery similar to that in allo-PBT, with an incidence of acute GVHD and chronic GVHD similar to, or even lower than, that in allo-BMT.

Research agenda

- The use of AMD3100 for mobilizing haematopoietic progenitor cells for allogeneic transplantation.
- Adjusting the dose of CD34$^+$ cells and of accessory cells in the graft.
- Defining the place of BM, PB, and of BM/G-CSF in allogeneic transplantation.
- Overcoming the cell dose barrier in UC transplant.

Table 2. Selection of the source of haematopoietic progenitor cells for allogeneic transplants.

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<tr>
<th></th>
<th>Malignant disease</th>
<th>Non-malignant disease</th>
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<tr>
<td></td>
<td>Early stage</td>
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<tr>
<td>PB/G-CSF</td>
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UC, umbilical cord; BM, bone marrow; PB/G-CSF, peripheral blood progenitor mobilized with granulocyte-specific colony-stimulating factor; RIC, reduced-intensity transplants.
REFERENCES


67. Urbano-Ispizua A, Rozman C, Pimentel P et al. The number of donor CD3+ cells is the most important factor for graft failure after allogeneic transplantation of CD34+ selected cells from peripheral blood from HLA-identical siblings. Blood 2001; 97: 383–387.


85. Walter EK, Rosenthal H, Jones TW et al. Larger numbers of CD4^{bright} dendritic cells in donor bone marrow are associated with increased relapse after allogeneic bone marrow transplantation. *Blood* 2001; **97**: 2948—2956.


95. Elmaagcli AH, Beelen DW, Opalka B et al. The risk of residual molecular and cytogenetic disease in patients with Philadelphia-chromosome positive first chronic phase chronic myelogenous leukemia is reduced after transplantation of allogeneic peripheral blood stem cells compared with bone marrow. *Blood* 1999; **94**: 384—389.


