Peripheral Blood Stem Cells for Allografting

By John Goldman

FOR SOME YEARS NOW, the pendulum has been swinging gently towards peripheral blood stem cells in place of marrow stem cells for clinical practice. We have known since the 1970s that stem cells with engraftment potential were present in the blood of some animals and of patients with chronic myeloid leukemia. By the early 1980s, it was clear that such stem cells were present also in the blood of other patients, such as those with leukemia or lymphoma in remission, during the period of recovery after high-dose chemotherapy. Since then, autografting with peripheral blood-derived stem cells, or more strictly with peripheral blood progenitor cells (PBPCs), has become almost routine in the management of selected patients with leukemia, lymphoma, myeloma, and some solid tumors. Might they also have a use in allografting?

Last year, two seminal reports suggested that the answer might be yes. Dreger et al showed that blood-derived stem cells could be used to reverse graft failure in a patient who had previously received a marrow allograft for leukemia. Russell et al treated a patient whose donor was unsuitable for marrow harvesting with blood-derived stem cells and demonstrated rapid engraftment. It is worth noting that Kesinger et al were probably the first to show the capacity of blood-derived progenitor cells to engraft in the allogeneic situation. However, in 1989, multiple leukapheresis procedures were required and the original observation that engraftment was rapid was not immediately pursued. This issue of Blood contains three very similar reports, two from the United States and one from Europe, that seem to confirm that allografting with blood-derived stem cells does work and can be now considered as a realistic alternative to marrow cells. A total of 25 patients received blood stem cell allografts from sibling donors and all engrafted. In most cases, engraftment of neutrophils and platelets appeared to be more rapid than would have been expected with comparable marrow-derived stem cells. Severe graft-versus-host disease (GVHD; grade III or higher) was seen in only 2 cases and 20 (80%) patients were alive at the time of the reports, 1 for more than 1 year. Thus, allografting with blood-derived stem cells seems clinically feasible.

Why did it take so long to reach this conclusion? There is one important technical reason. All three studies involved treating the normal donor with a recombinant hematopoietic growth factor, namely granulocyte colony-stimulating factor (G-CSF; filgrastim) to mobilize stem cells into the circulation. Without G-CSF, collecting enough stem cells for an allograft would not be a practical proposition. G-CSF only became generally available about 5 years ago and clinicians rightly awaited some experience with its use in the autograft and syngeneic settings before administering the agent to normal sibling donors. Even now, the optimal dosage for stem cell mobilization is not well defined. G-CSF may cause fever and often bone pain at the time of administration but seems to have no other important side effects in the short-term. The possible long-term sequelae of administering a synthetic molecule made by recombinant DNA techniques are unknown. It is at least possible that even short-term exposure to an agent that stimulates supraphysiologic myelopoiesis might set the scene for disordered hematopoiesis many years later.

Two other theoretical notions argued against the use of blood-derived stem cells to replace marrow cells. First, the number of T lymphocytes in a typical blood stem cell harvest greatly exceeds, perhaps by one order of magnitude, the number present in a conventional marrow harvest. This finding automatically raised the possibility that GVHD after blood stem cell allografts would occur with greater frequency and with greater severity than after marrow allografts. This fear can probably now be dispelled. The preliminary data in these three reports contain no suggestion that GVHD is worse with blood than marrow stem cells—indeed, it might even be less. The data instead support the intuitively probable hypothesis that severity of GVHD is based much more on genetic disparities between donor and recipient than on T-cell numbers, although in murine model systems the number of T cells transferred may indeed correlate with severity of GVHD. Second, might blood-derived stem cells support only short-term engraftment? Data from murine studies suggest that stem cells mobilized into the peripheral blood with G-CSF or cyclophosphamide can maintain hematopoiesis for long periods. In the clinic, current autograft studies do not help to answer this question.

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0006-4971/95/8506-0040$3.00/0

because no current cytoreductive protocol is indisputably myeloablative in the longer term, although future studies with genetically marked progenitor cells may be informative. Formally, the three reports in this issue of Blood contribute little to this question, but the observation that no surviving patient experienced late graft failure and one at least has at risk for more than 1 year implies that blood stem cells may not differ from marrow stem cells in engraftment potential.

What then are the possible advantages of using blood stem cells? These should be evaluated separately for donor and recipient. Many donors will appreciate the option to avoid general anesthesia and leukapheresis may be safer than anesthesia in a normal person. Conversely, some donors will still prefer to donate marrow rather than blood and some will be reluctant to receive treatment with G-CSF. In a minority of donors leukapheresis may be impossible without the insertion of a central venous line, a procedure that is uncomfortable and not without risk of complications. Thus, for the donor the possible advantages of leukapheresis do not clearly outweigh those of marrow donation.

The situation is a little clearer for the patient. In all three reports, recovery of leukocyte numbers after allografting was equivalent or faster than in comparable control patients who received marrow stem cells. Similarly, platelet recovery was faster in all three reports. It is easy to imagine that this could translate into less risk of infection and hemorrhage, reduced need for blood product support, and, possibly, earlier discharge from the hospital. One may speculate also that the higher numbers of T cells in the leukapheresis product would offer a greater graft-versus-leukemia (GVL) effect, but this may be just wishful thinking, especially in view of the fact that GVHD seems not to be exacerbated. What seems more probable is that high T-cell numbers will reduce the risk of graft failure, especially where there is some degree of HLA disparity.

If blood-derived stem cells can be used effectively in sibling allografts, can they be used also in transplants involving unrelated donors? The problem here harks back to the possible late sequelae of G-CSF. Should we try to protect unrelated donors to a greater extent than we would sibling donors? Probably yes. Moreover, we should be absolutely sure that blood stem cell usage is not associated with increased risk of GVHD before using blood stem cells from phenotypically HLA-matched donors. The compromise is to wait a little longer before clearing recombinant G-CSF for general use in any member of the community. Institutional Review Boards or Research Ethics Committees should certainly be involved.

What then of the future? Will the use of blood stem cells entirely displace marrow stem cells for allografting? Probably not. It seems more likely that possible differences between blood and marrow-derived stem cells will be characterized and the precise indications for preferring blood to marrow as source of stem cells will be accurately defined. Thus, we still need more detailed answers to questions relating to G-CSF dosage, optimal PBPC numbers, and the speed and durability of engraftment and immunologic reconstitution. There are, for example, a variety of techniques for assessing the function and numbers of the primitive progenitor cells induced to enter the circulation, including assay of long-term culture-initiating cells,\(^\text{28}\) of plastic-adherent pre-CFU-GM,\(^\text{29}\) and of clonogenic CFU-GM and quantitation of CD34\(^+\) cells; the clinical relevance of each needs to be addressed. Clinical studies must compare the incidence and severity of GVHD in equivalent patients and quantitate so far as is possible the GVL effect. For some transplants, use of blood may be clearly be preferable to marrow; in other cases, the choice may be left to the donor. The European Group for Blood and Marrow Transplantation (EBMT) is about to initiate a study comparing blood and marrow stem cells for sibling allografts; hopefully some of the answers will not be too long in coming.

REFERENCES


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