EDITORIAL

The Evolving Role of Autologous Peripheral Stem Cell Transplantation Following High-Dose Therapy for Malignancies

OVER THE LAST DECADE, transplantation of circulating autologous hematopoietic stem cells to facilitate the recovery of bone marrow (BM) function following administration of marrow ablative anti-cancer therapy has been used with increasing frequency. During that time, a number of indications for peripheral stem cell transplantation (PSCT) emerged.

Investigators have used peripheral stem cells preferentially to autologous BM to achieve a more rapid restoration of marrow function following transplant. However, this time advantage is attained only if the stem cells are collected while their circulating numbers are deliberately expanded. Several methods to mobilize stem cells from their extravascular locations into the circulation have been described, but to date only two methods have been applied clinically. Chemotherapy-induced mobilization, the first method, occurs following administration of robust doses of marrow-toxic drug(s). For a variable number but not many days during the recovery period following such therapy, the number of granulocyte-macrophage colony forming units (CFU-GM) that can be assayed in the mononuclear cell fraction of peripheral blood may increase as much as 100-fold above baseline values. Transplantation of an adequate number of these “mobilized” progenitors results in recovery of marrow function approximately a week earlier than would be expected with autologous BM transplantation (ABMT). A major problem with any mobilizing technique is the difficulty determining the optimum time to begin stem cell collections. Criteria that have been used, among others, include the point at which a specific number of neutrophils returned to the circulation, or the platelet count began to increase, or the percentage of monocytes in the neutrophil fraction reached a certain value, but no indicator has been universally reliable. Because stem cell assays require 2 weeks to complete, knowledge that sufficient cells were collected or that the patient exhibited adequate mobilization or that the investigator “guessed right” on the timing of collections are realized long after the mobilization effect has ended. Other frustrating difficulties associated with chemotherapy-induced mobilization sometimes occur. The robust doses necessary to induce mobilization have been associated with morbidity (neutropenic fever, infection) and even mortality. In addition, not every patient exhibits mobilization with this approach. Patients who have received extensive prior therapy for their malignancies and patients who have histopathologic evidence of BM involvement with tumor may not manifest circulating stem cell expansion following chemotherapy mobilization attempts, along with some patients with no apparent “risk factors.”

Most mobilized peripheral stem cell collections consist of more than three daily apheresis procedures. The necessity for apheresis availability during weekends can be annoying, because the duration of meaningful mobilization may be only a few days and a 2-day delay could prevent an adequate total collection. With experience, timing the chemotherapy administration for mobilization may lessen the need for weekend apheresis. The definition of an adequate mobilized peripheral stem cell transfusion product, ie, one which produces rapid marrow recovery, is another unresolved problem. While, traditionally, a set number of CFU-GM in the product is used to indicate an adequate collection of mobilized stem cells, that number is necessarily different at each transplant center because CFU-GM culture methods are not standardized. An earlier concern that mobilization techniques might expand committed progenitors without mobilizing pluripotent stem cells was apparently unfounded. Transplantation of a product rich in committed progenitors and wanting in pluripotent stem cells could lead to a timely recovery of marrow function, followed by marrow aplasia. Methods to detect mobilization of pluripotent stem cells are not available, but clinical trials have shown that late aplasia does not occur with mobilized PSCs, although temporary and incomplete engraftment has been reported.

More recently, mobilization has been accomplished with administration of the recombinant human growth factor GM-colony stimulating factor (rhGM-CSF). This technique has undergone fewer clinical trials than chemotherapy-induced mobilization, but initial studies suggest transplantation of rhGM-CSF-mobilized peripheral stem cells can result in rapid marrow recovery and sustained hematopoiesis. To supply an adequate dose of pluripotent stem cells and an expanded dose of committed progenitors at the time of transplantation to assure both early marrow function recovery and sustained engraftment, some investigators have added rhGM-CSF–mobilized peripheral stem cells to ABM. Less information is available regarding the predictability of mobilization using rhGM-CSF than chemotherapy, and this technique may or may not abrogate the difficulties seen with attempted chemotherapy mobilization in heavily pretreated patients or patients with BM involve-
ment. Using both mobilization methods at one time (chemotherapy followed by rhGM-CSF) seems to expand the number of circulating progenitors to a greater extent than either technique alone. The issue of whether specific growth factors used for mobilization will inadvertently accelerate specific malignancies (interleukin-6 and multiple myeloma for example) needs study.

The work published by Siena et al in this issue of Blood may resolve some of the current difficulties involved with collection and transplantation of mobilized peripheral stem cells. The ability to detect a meaningful expansion of the circulating stem cell population on the day of occurrence rather than 2 weeks later offers a distinct advantage, because not only can the successful mobilization attempt be identified, thus avoiding undesirable collections, but the most effective time to initiate the apheresis procedure becomes obvious as well. The definition of an adequate collection of mobilized peripheral stem cells may also become clear if, as Siena et al suggest, collection of a specific number of CD34+ cells indicates an effective transplant product has been procured. In addition, their method of detecting CD34+ cells may be more reproducible between laboratories than progenitor culture assays.

PSCT has been used by other investigators for patients who are candidates for high-dose therapy but have neither a suitable ABM donor nor a BM suitable for transplantation. These patients have received prior radiation therapy to traditional BM harvest sites or have histopathologically detectable malignant cells in the BM. Occasional patients who have received prior chemotherapy have hypoplastic marrow that cannot be used for ABMT, and others have apparently normal BM encased in bone that is involved with metastatic disease, creating a concern about possibly contaminating the marrow with malignant cells during the harvest procedure. In these clinical situations, earlier marrow function recovery is not the goal of PSCT, but rather, PSCT provides the opportunity to administer high-dose therapy. Mobilization techniques are not attempted for a number of reasons, including the high proportion of patients who have risk factors for mobilization failure (heavily pretreated and/or marrow involvement). These nonmobilized PSCTs generally have resulted in marrow recovery rates equivalent to those seen with patients who receive ABMT. Follow-up of patients with BM metastases who received nonmobilized PSCT shows that long-term event-free survival is at least as likely to occur for them as it is for patients with no marrow involvement who receive ABMT. Until CD34+ cells can be detected in nonmobilized peripheral stem cell collections, the definition of an adequate collection for nonmobilized PSCT products must continue to consider either the CFU-GM content, or the more traditional mononuclear cell content, or both. Perhaps as technologies evolve detection of small numbers of CD34+ cells will become possible and this assay can then be applied to nonmobilized peripheral stem cell collections.

What role might PSCT play in the future? Conceivably a combination of growth factors administered sequentially or concomitantly will mobilize a sufficient number of the appropriate cells to permit the collection of a transplant product with a single apheresis procedure, and that product will restore marrow function so rapidly that these transplants can be done in the outpatient setting. Possibly PSCT will be proven an appropriate alternative to BM purging for patients with malignant involvement of the marrow. Perhaps PSCTs, because of the large number of immunocompetent cells in the product, will be shown to have therapeutic as well as restorative powers. However, one hopes that autologous stem cell transplants in general will become unnecessary as our ability to prevent, diagnose, and treat malignancies improves.

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REFERENCES


10. Gianni AM, Bregni M, Siena S, Tarella C, Orazi A, Stern A, Bonadonna G: Very rapid and complete hematopoietic reconstitution following combined transplantation of autologous bone mar-
row and GM-CSF–exposed stem cells. Bone Marrow Transplant 4:78, 1989 (suppl 2)


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