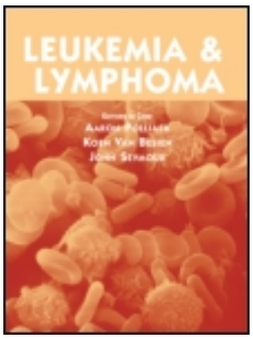

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COMMENTARY

Is autologous progenitor cell mobilization getting any easier?

MARK R. LITZOW

Division of Hematology, Mayo Clinic College of Medicine, Rochester, MN, USA

In the 1990s, randomized trials confirmed the benefit of autologous bone marrow transplant for improving survival in patients with non-Hodgkin lymphoma and multiple myeloma [1,2]. Since the 1990s, the use of peripheral blood stem cells (PBSC) for autologous transplant (AT) has become standard therapy because of the more rapid recovery of hematopoiesis compared to unstimulated bone marrow. With this practice has come the recognition that some patients do not adequately mobilize PBSC and these patients have been variously described in the literature as ''difficult'' or ''hard to mobilize'' or as ''poor mobilizers.''

Risk factors for difficult mobilization have been defined and include disease type (patients with breast cancer and non-Hodgkin lymphoma tending to mobilize less well than patients with leukemia, Hodgkin's disease, and ovarian cancer); older age; bone marrow involvement by tumor; prior radiotherapy to marrow sites and extensive prior chemotherapy [3].

To characterize these difficult mobilizers further, Sugrue et al. [4], in a publication in this journal in 2000, defined such a group as those in whom $\geq 1 \times 10^6$ CD34+ cells/kg could not be obtained after two consecutive large volume aphereses. Of 44 consecutive lymphoma patients who underwent AT, 21 patients met the definition of being difficult to mobilize. Of these 21, seven were unable to achieve this target even after a second mobilization attempt and/or a bone marrow harvest. Predictors of poor mobilization were ≥ 2 prior treatment regimens and a white count $< 25 \times 10^9$/L on the first day of apheresis. Outcome analysis demonstrated that 6 of 19 patients in the poor mobilization group died of relapse within a year of AT compared to only 2 of 23 in the good mobilizer group. There were no treatment-related deaths in either group, and the authors suggested that poor mobilizers had a worse outcome after AT.

Various strategies to improve mobilization in these patients have been described [3]. The standard approach to initial mobilization is to use hematopoietic growth factors such as filgrastim. A number of studies have suggested that combining chemotherapy and growth factors may stimulate greater mobilization of PBSC and have a cytoreductive effect against the patient's malignancy. A retrospective study at our center, however, did not show that cyclophosphamide mobilization improved outcome in patients receiving AT for multiple myeloma [5]. Nevertheless, the use of chemotherapy plus growth factors is a standard mobilization technique at many centers.

Many different combinations of chemotherapy have been utilized for mobilization. In this issue of the journal, such an approach is described by McKibben and colleagues [6]. Based on prior literature supporting the use of paclitaxel for PBSC mobilization in breast cancer patients, the authors previously reported successful utilization of a combination of this drug and filgrastim in patients with hematologic malignancies and solid tumors. In the study described here, this experience was extended to a series of 26 patients with hematologic malignancies who had failed an initial mobilization with filgrastim alone or a combination of other chemotherapy regimens and filgrastim. The patients' initial mobilization was used as the comparator to the efficacy of combining paclitaxel at a dose of 250 mg/m^2 intravenously as a single dose followed by filgrastim at doses of 10 – 16 mcg/kg per day. A median of 1.53×10^6 CD34+ cells/kg were able to be collected

Correspondence: Mark R. Litzow, Division of Hematology, Mayo Clinic College of Medicine, 200 First St. S.W., Rochester, MN 55905, USA. Tel: +507-284-5362. Fax: +507-266-4972. E-mail: litzow.mark@mayo.edu

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following the paclitaxel-based regimen as compared to 0.79×10^6 CD34+/kg after the patients' initial mobilization regimens. The main toxicities of this regimen related to the cytopenias induced by the chemotherapy. Three patients required hospitalization for neutropenic fever. Two of these three recovered, but unfortunately one patient with multiple myeloma became septic with *E. coli* and expired because of multiorgan failure prior to initiation of leukapheresis. Overall, 20 of the 26 patients were able to proceed with AT with a median CD34+ cell dose infused of 2.25×10^6 CD34+ cells/kg (range, 1.43–5.61) [6].

Thus, this approach is a reasonable one to consider in patients who have failed prior mobilization. Whether it is superior to other approaches is not clear. The main benefit of the use of paclitaxel appears to relate to its myelosuppressive abilities rather than to any other unique effect of the drug on the bone marrow. However, it definitely represents one additional alternative to mobilize such patients.

Another exciting option for these patients is the new cytokine, AMD3100. This agent is an inhibitor of SDF1 binding to CXCR4 and appears to promote mobilization of CD34+ cells into the circulation. The use of this AMD3100 in combination with filgrastim in patients unable to collect adequate CD34+ cells with filgrastim alone was reported earlier this year in 280 patients with lymphoma and multiple myeloma. Success was defined as a collection of $\geq 2 \times 10^6$ CD34+ cells/kg with this regimen. Filgrastim was given at a dose of 10 mcg/kg per day and AMD3100 was started at 240 mcg/kg on day 4 of mobilization. Between 60% and 76% of patients in the different disease groups were able to be mobilized with this regimen and engraftment was satisfactory. No graft failures were reported. The AMD3100 was well tolerated [7]. Randomized trials comparing AMD3100 with filgrastim to filgrastim alone in multiple myeloma and non-Hodgkin lymphoma have been recently completed and publication of the results is eagerly awaited.

The options for collecting PBSC from difficult-to-mobilize patients are increasing. These developments should give more patients the opportunity to proceed to life-extending AT and are exciting for those of us who deal with these patients on a regular basis.

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