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Poor Mobilization of Hematopoietic Stem Cells—Definitions, Incidence, Risk Factors, and Impact on Outcome of Autologous Transplantation

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As more efficient agents for stem cell mobilization are being developed, there is an urgent need to define which patient population might benefit from these novel drugs. For a precise and prospective definition of "poor mobilization" (PM), we have analyzed the efficiency of mobilization in patients intended to receive autologous transplantation at our center in the past 6 years. Between January 2003, and December 2008, 840 patients with the following diagnoses were scheduled to undergo leukapheresis: multiple myeloma (MM, n = 602) and non-Hodgkin lymphoma (NHL, n= 238). Most patients mobilized readily: close to 85% of the patients had a level of 20/μL to >500/μL of $CD34^+$ cells at the peak of stimulation. Of the 840 patients, 129 (15.3%) were considered to be PMs, defined as patients who had a peak concentration of <20/μL of $CD34^+$ cells upon stimulation with granulocyte-colony stimulating factor (G-CSF) subsequent to induction chemotherapy appropriate for the respective disease. Among them, 38 (4.5%) patients had $CD34^+$ levels between 11 and 19/μL at maximum stimulation, defined as "borderline" PM, 49 (5.8%) patients had $CD34^+$ levels between 6 and 10/μL, defined as "relative" PM, and 42 patients (5%) with levels of <5/μL, defined as "absolute" PM. There was no difference in the incidence of PM between patients with MM versus those with NHL. Sex, age, body weight (b.w.) and previous irradiation therapy did not make any significant difference. Only the total number of cycles of previous chemotherapy ($P = .0034$), and previous treatment with melphalan (Mel; $P = .0078$) had a significant impact on the ability to mobilize. For the good mobilizers, the median time to recovery of the white blood cells (WBCs) to 1.0/nL or more was 13 days with a range of 7 to 22 days, whereas for the PM group it was 14 days with a range of 8 to 37 days. This difference was statistically not significant. The median time to recovery of the platelets counts to an unmaintained level of >20/nL was 11 days with a range of 6 to 17 days for the good mobilizers, whereas for the PM it was 11 days with a range of 7 to 32 days. Again, this difference was not significant. The majority of the patients today intended for autologous transplantations were able to mobilize readily. As long as $\geq 2.0 \times 10^6$ of $CD34^+$ cells/kg b.w. have been collected, PM was not associated with inferior engraftment.

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INTRODUCTION

Peripheral blood stem cells (PBSCs) have largely replaced bone marrow (BM) cells in autologous transplantations, and have become the source of stem cells in the majority of allogeneic transplantations. In the mid-1980s several institutions demonstrated that PBSCs could represent viable alternatives to BM cells as a source of hematopoietic stem and progenitor cells for autologous transplantation [1-5]. PBSCs offer several advantages such as harvest of cells without general anesthesia, elimination of pain after multiple aspirations from the BM, and above all, they are associated with more rapid engraftment [6-8].

In the meantime, autologous PBSC transplantation is the treatment of choice within the primary treatment strategy for multiple myeloma (MM) [9-12], and is also the preferred treatment option for relapsed/refractory B cell non-Hodgkin lymphoma (NHL) [13-17]. The main disadvantage of PBSCs is that they exist in the circulation in very small numbers. Less than 0.06% of white blood cells (WBCs) are

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$CD34^+$, which is a cell surface protein that is expressed on hematopoietic stem (HSCs) and progenitor cells and represents a reliable surrogate marker for hematopoietic progenitor cells [18-20].

HSCs and progenitor cells reside in the BM and they have to be mobilized into the circulation prior to being collected by apheresis. The number of apheresis procedures needed and the success of transplantation are determined by the efficiency of stem cell mobilization ([21,22], review in [23]). Stem cells adhere to their BM niche by interactions between SDF1α, which is produced by BM stromal cells, and CXCR4, which is expressed on $CD34^+$ cells [24,25]. Granulocyte colony-stimulating factor (G-CSF), which has been in clinical use for more than 2 decades, mobilizes stem cells from the BM niche by secretion of neutrophil-associated extracellular proteases, such as MMP-9, which subsequently releases HSC from their niche [26]. In contrast, Plerixafor (formerly known as AMD3100) is a novel mobilization agent that directly inhibits the CXCR4-SDF1α cell-cell interaction [27,28].

Several stem cell mobilization strategies have been employed since development of PBSC transplantations. In the early days of transplantation, stem cell mobilization was achieved with chemotherapeutic drugs because the use of chemotherapy causes a significant increase in the number of PBSCs at the time of recovery [1,3,5]. However, many patients failed to mobilize sufficient PBSCs for transplantation in response to chemotherapy. In the late 1980s, hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF have been made available [29-33]. Their administration subsequent to chemotherapy has been shown to mobilize PBSCs efficiently [34]. G-CSF and GM-CSF were approved for use as HSC mobilizing agents, but G-CSF (in combination with chemotherapy or alone) has become standard (review in [23]). Unfortunately, some patients fail to mobilize sufficient numbers of PBSCs for transplantation in response to G-CSF with or without chemotherapy [22,30,35-39]. There is thus far no consensus on the definition of poor mobilizers (PM).

Based on this retrospective analysis of 840 patients who were mobilized with chemotherapy and growth factors with the intent of autologous transplantation at a single center, we have provided a more precise definition of "poor" mobilization, and have evaluated the incidence, risk factors, and impact on transplantation outcome in a modern setting.

PATIENTS AND METHODS

Patients

We analyzed data from 602 patients with MM and 238 patients with NHL, who were scheduled to receive autologous PBSC transplantation (PBSCT) between 2003 and 2008 at the Department of Internal Medicine V in Heidelberg. Retrospective data analysis was approved by the Ethics Committee of the Medical Faculty of Heidelberg. The median age was 59 years, with a range from 12 to 75 years (MM: 60 years, range: 27-75 years; NHL: 54 years, range: 12-74 years). PBSCs were mobilized with chemotherapy (CT) followed by G-CSF. The appropriate regimen as CT was used to reduce the tumor burden and to facilitate PBSC harvesting.

Mobilization Regimens

For patients with MM, the following chemotherapy regimens were used for remission induction and for mobilization. CAD (cyclophosphamide [Cy] 1,000 mg/m^2/d day 1, doxorubicin 15 mg/m^2/d days 1-4, dexamethasone 40 mg/day orally days 1-4), TCED (thalidomide 400 mg/day orally, etoposide 40 mg/m^2/d days 1-4, Cy 400 mg/m^2/d days 1-4, dexamethasone 40 mg/day orally days 1-4), HD-Cy (Cy 2000 mg/m^2/day days 1-2) or lenalidomide/dexamethasone (lenalidomide 25 mg/day orally days 1-21, dexamethasone 20 mg/day orally days 1-4, 9-12 and 17-20).

For patients with NHL, the following regimens were used for remission induction and, in case chemosensitivity is demonstrated, the same regimen will be used for mobilization: Dexa-BEAM (dexamethasone 3 × 8 mg/day days 1-10, carmustine 60 mg/m^2/day day 2, melphalan [Mel] 30 mg/m^2/day day 2, cytarabine 2 × 100 mg/m^2/day days 3-6, etoposide 75 mg/m^2/day days 3-6), R-Dexa-BEAM (rituximab 375 mg/m^2/day day 0, Dexa-BEAM), CHOP (Cy 750 mg/m^2/day day 1, doxorubicin 50 mg/m^2/day day 1, vincristine 1.4 mg/m^2/day [max. 2.0 mg] day 1, prednisone 100 mg/day days 1 -5), CHOEP (CHOP plus etoposide 100 mg/m^2/day days 1-3), R-CHOP (rituximab 375 mg/m^2/day day 0, CHOP), R-CHOEP (rituximab 375 mg/m^2/day day 0, CHOP plus etoposide 100 mg/m^2/day days 1-3), DHAP (dexamethasone 40 mg/day days 1-4, cisplatin 100 mg/m^2/day day 1, cytarabine 2 × 2000 mg/m^2/day day 2), R-DHAP (rituximab 375 mg/m^2/day day 0, DHAP) or HD-Cy (Cy 2000 mg/m^2/day days 1-2).

All patients received G-CSF starting 4 to 5 days after completion of chemotherapy in dosages of 5-10 μg/kg/day subcutaneously (s.c.) until the end of the collection period.

If the patients failed to reach target collections, they could have a second or third attempt to mobilize an adequate amount of stem cells for transplantation. The following options were adopted: (1) another attempt to mobilize with chemotherapy and G-CSF; (2) G-CSF alone after a "rest" period of at least 21 days without chemotherapy; (3) BM harvest as an