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Mobilized Peripheral Blood Stem Cells Compared with Bone Marrow as the Stem Cell Source for Unrelated Donor Allogeneic Transplantation with Reduced-Intensity Conditioning in Patients with Acute Myeloid Leukemia in Complete Remission: An Analysis from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

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Reduced-intensity conditioning allogeneic stem cell transplant (RIC-alloSCT) is being increasingly used for patients with acute myelogenous leukemia (AML) with comorbidities. Few published data are currently available regarding for the use of peripheral blood stem cells (PBSCs) compared to bone marrow (BM) in the RIC-alloSCT using unrelated donors (URDs). This retrospective report compared the outcomes of PBSC versus BM RIC-alloSCT. Between 2000 and 2007, 602 patients with AML in complete remission (CR) underwent RIC-alloSCT from URDs with PBSC (508) or BM (94) grafts. Recipient's age was higher in the PBSC versus BM groups 57 (range, 17-77 years) and 51 (range, 17-76 years), respectively ($P < .0001$). Leukemia features and disease status at RIC-alloSCT were also comparable between the PBSC versus BM groups. Engraftment was achieved in 97% and 96% with BM versus peripheral blood (PB), respectively. Acute graft-versus-host disease (aGVHD) grade >II was significantly higher in the PBSC group: 27% versus 12% in the BM group ($P < .002$). Similarly, chronic graft-versus-host disease (cGVHD; at 2 years) was somewhat higher in the PBSC group with 43% $\pm$ 3% versus 35% $\pm$ 6% in the BM group, respectively ($P = .04$). The 2-year probabilities of leukemia-free survival (LFS) were 46% $\pm$ 3% for the PBSC group in comparison to 43% $\pm$ 6% for the BM transplant group ($P =$ NS), whereas relapse incidence was significantly higher in the BM versus the PB transplant group: 46% $\pm$ 6% versus 32% $\pm$ 3%, respectively ($P = .014$). Non-relapse mortality (NRM) was significantly higher for the PBSC versus the BM group: 28% $\pm$ 2%

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versus 13% ± 4%, respectively ($P = .004$). In multivariate analysis, after adjustment for differences between both groups, the PBSC group was associated with a higher incidence of aGVHD (grade II-IV; hazard ratio [HR] = 2.33; $P = .06$), higher NRM (HR = 2.3; $P = .015$), and a decreased relapse incidence (HR, 0.61; $P = .02$) with no statistical difference of LFS between the 2 groups ($P = .88$). In conclusion, our results indicate significantly higher incidence of aGVHD and NRM and a lower incidence of relapse but not statistically different LFS comparing unrelated PBSC to BM grafts after RIC-alloSCT.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplant (alloSCT) is a potentially curative treatment for advanced or high-risk acute myeloid leukemia (AML) [1]. However, myeloablative conditioning may be associated with unacceptably increased toxicity in elderly, medically unfit, or heavily pretreated patients. The introduction of alloSCT with reduced-intensity conditioning (RIC) allowed extension of alloSCT to a much wider patient population by reducing the toxicity and exploiting the graft-versus-lymphoma (GVL) effect as the primary curative approach [2-5]. As engraftment post-alloSCT has been shown to correlate with dose intensity, the engraftment post-RIC is mainly based on strong, but transient immunosuppression and high cell dose [6-9]. Indeed, most of the RIC alloSCTs are performed with mobilized peripheral blood stem cell (PBSC) grafts rather than bone marrow (BM) grafts [10], as PBSCs have been demonstrated to contain significantly higher numbers of CD34+ hematopoietic stem cells compared with BM grafts [11-15]. However, the stem cell source and type of graft may have different implications on transplantation outcome in the RIC setting compared to the myeloablative setting. In the myeloablative setting with BM grafts, the infusion of high doses of progenitor cells has a favorable impact on transplantation outcome, due to faster hematopoietic and immune recovery [16]. In contrast, when using granulocyte colony-stimulating factor (G-CSF)-mobilized PBSCs in the context of myeloablative alloSCT, the infusion of a high number of CD34+ cells increased the incidence of extensive chronic graft-versus-host disease (cGVHD), which adversely affected outcome due to higher transplant-related mortality (TRM) [17-19].

In contrast to the availability of extensive literature comparing mobilized PBSC grafts to BM grafts in sibling myeloablative alloSCT [13,17-22], data in the unrelated setting is still sparse [23]. In the study by Eapen et al. [24], the authors compared the outcome after 331 PBSC and 586 transplants in adults with leukemia and myelodysplastic syndrome. Rates of acute graft-versus-host disease (aGVHD) and cGVHD were significantly higher with PBSC than with BM transplants [13,17-22], whereas TRM, relapse, leukemia-free survival (LFS), and overall survival were similar [23]. Similar results were also observed recently in another analysis from the Center for International Blood and Marrow Transplant Research that compared the effect of graft source in unrelated donor (URD) hematopoietic stem cell transplant in adults with acute leukemia [24]. In both analyses, patients were conditioned with myeloablative preparative regimens [23,24]. With this background, and given the increased usage of both URDs and RIC alloSCT in patients with acute leukemia [25,26], this report aimed to compare outcomes of PBSC versus BM in the setting of RIC alloSCT in patients with AML in remission undergoing alloSCT from matched unrelated donors (MUDs).

PATIENTS AND METHODS

Study Design and Data Collection

This was a retrospective multicenter analysis. Data of adult patients with AML receiving RIC alloSCT using PBSC or BM from an MUD were provided by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT) group. The EBMT registry is a voluntary working group of more than 500 transplantation centers, participants of which are required once a year to report all consecutive stem cell transplants and follow-up. The Acute Leukemia Working Party of the EBMT group approved this study.

Selection Criteria

The study included patients with AML receiving first RIC alloSCT in complete remission (CR) from an MUD using PBSCs or BM, who: (1) were age ≥16 years at time of transplantation; (2) were transplanted between the years 2000 and 2007; (3) had received an RIC regimen defined as the use of fludarabine associated with low-dose total body irradiation (TBI; ≤6 Gy) or busulfan (total dose ≤8 mg/kg) or other immunosuppressive or cytotoxic drugs such as melphalan or cyclophosphamide as defined by the