CORRESPONDENCE

Impact of stem cell source in HLA-matched hematopoietic stem cell transplant for acute lymphoblastic leukemia in first complete remission: a study from the GRAALL and the SFGM-TC

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TO THE EDITOR:

In myeloablative HLA-matched hematopoietic stem cell transplantation (HSCT) peripheral blood stem cells (PBSC) increase the risk of chronic graft-versus-host disease (cGVHD) compared to bone marrow (BM) [1, 2]. While cGVHD is associated with substantial morbidity, it may also augment graft-versus-leukemia activity. An advantage of PBSC over BM in reducing the risk of relapse has been reported in some trials [1, 3]; however, this superiority has not been consistently demonstrated across all studies [1, 2, 4]. This discrepancy likely stems from heterogeneous study populations in term of malignancies, prognosis factors and donor types, making it difficult to isolate the true impact of stem cell source on relapse.

Historically, HSCT was considered the standard of care for treatment of acute lymphoblastic leukemia (ALL), in first complete remission (CR1). Over the past two decades, pediatric-inspired chemotherapy regimens have significantly improved outcomes in adult ALL patients [5–7], leading to a redefinition of the place of HSCT. In the GRAALL-2003 and GRAALL-2005 trials, HSCT in CR1 was offered only to adult ALL patients with high-risk (HR) features. This analysis re-evaluates the impact of PBSC versus BM in HR adults transplanted in CR1, focusing on whether PBSC offers an advantage over BM in reducing relapse risk in both matched related and matched unrelated transplants.

The GRAALL-2003 and GRAALL-2005 trials, conducted from November 2003 to March 2014 in 70 centers, offered HSCT to patients ≤55 years with Ph-negative ALL and at least one HR ALL factor (Supplementary Data) [5, 6, 8]. Conditioning was myeloablative up to 50 years, and BM was the recommended stem cell source. For this analysis, only patients receiving a myeloablative matched sibling donor (MSD) or matched unrelated donor (MUD) transplant with BM or PBSC were included; The cohort comprised 275 patients (184 with B-cell and 91 with T-cell ALL), with follow-up updated to November 2023. Patient characteristics and HSCT modalities are summarized in Supplementary Tables 1, 2. Median age at transplant was 32 years (IQR, 23–43), and 60% were male. Most patients ($n = 259$, 94%) received a total body irradiation (TBI)–based conditioning regimen. Donors were MSD in 154 transplants (56%; 118 BM and 36 PBSC) and MUD in 121 transplants (44%; 67 BM and 54 PBSC). Anti-thymocyte globulin (ATG) was administered to 37 patients, mainly in the MUD group (34/121, 28%; 16 BM and 18 PBSC), while only 3 MSD recipients received ATG. Outcomes for the entire cohort are described in the Supplemental results. Briefly, the median follow-up was of 10.5 years [95% CI, 10.1–11.1], 10-year estimated cumulative incidence of relapse (CIR) was 19% [15–25], 10-year disease-free survival (DFS) and overall survival (OS) were 63% [95% CI, 57–69] and 66% [60–71], respectively. In multivariate analysis, including stem cell source (PBSC versus BM), type of donor (MUD versus MSD), age (≥45 years versus <45 years), use of TBI, and use of ATG, PBSC was not associated with a lower relapse risk but with an increased incidence of any-grade and extensive cGVHD (Supplementary Table 3). Transplantation from a MUD was also associated with a higher incidence of cGVHD. For subsequent analyses, the impact of stem cell source was evaluated separately in MSD and MUD transplant populations.

We first assessed the risk of relapse according to stem cell source in patients undergoing MSD and MUD transplant. In MSD transplant, the 10-year CIR was 17% [95% CI, 8–34] with PBSC versus 24% [17–33] with BM (SHR 0.69 [0.29–1.66], $p = 0.41$; Fig. 1a). In MUD transplants, the 10-year CIR was 11% [5–23] with PBSC versus 19% [12–31] with BM (SHR 0.54 [0.21–1.43], $p = 0.25$; Fig. 1b). The absence of a PBSC benefit on relapse risk in both MSD and MUD transplants was confirmed in multivariate analysis (Supplementary Table 4).

Another objective of the study was to assess the impact of stem cell source in MSD and MUD transplant on additional post-transplant outcomes, particularly cGVHD. PBSC use significantly increased the risk of any-grade cGVHD across both donor types. In MSD transplants, the 10-year incidence of cGVHD was 54% [95% CI, 39–71] after PBSC versus 29% [22–39] after BM (SHR 2.17 [1.25–3.76], $p = 0.006$). In MUD transplants, the 10-year incidence of cGVHD was 64% [51–77] after PBSC versus 40% [29–53] after BM (SHR 1.92 [1.14–3.22], $p = 0.01$; Fig. 1c, d). Compared to BM, PBSC was associated with an increased risk of extensive cGVHD in MUD transplants (32% [20–47] versus 8% [3–18]; SHR 4.92 [1.80–13.47], $p = 0.002$), but not in MSD transplants (SHR 1.87 [0.79–4.40], $p = 0.15$) (Fig. 1e, f). These incidences of cGVHD are lower than those reported in previous BM versus PBSC comparisons [1, 2], possibly due to the younger age of our cohort and to the use of ATG in some MUD transplants [2, 4, 9]. Multivariate analysis confirmed PBSC as an independent risk factor for any-grade cGVHD in both MSD (SHR 1.98 [1.18–3.33], $p = 0.01$) and MUD transplants (SHR 2.06 [1.18–3.60], $p = 0.01$), and for extensive cGVHD in MUD transplants (SHR 5.42 [1.97–14.93], $p = 0.001$). Moreover, in MUD transplants, PBSC use was associated with a higher risk of grade III–IV aGVHD (SHR 4.47 [1.62–12.34], $p = 0.004$), unlike in MSD transplants (Supplementary Table 4). The higher incidence of extensive cGVHD and grade III–IV aGVHD translated into higher NRM and poorer GRFS in the MUD PBSC setting compared with BM (SHR 2.88 [1.24–6.70], $p = 0.014$ for NRM and SHR 2.45 [1.46–4.09], $p < 0.001$ for GRFS) (Fig. 1g, h), whereas no significant differences in NRM or GRFS were observed in MSD transplants according to stem cell source (Fig. 1i, j). Stem cell source did not significantly impact OS or DFS (Fig. 1k, l).

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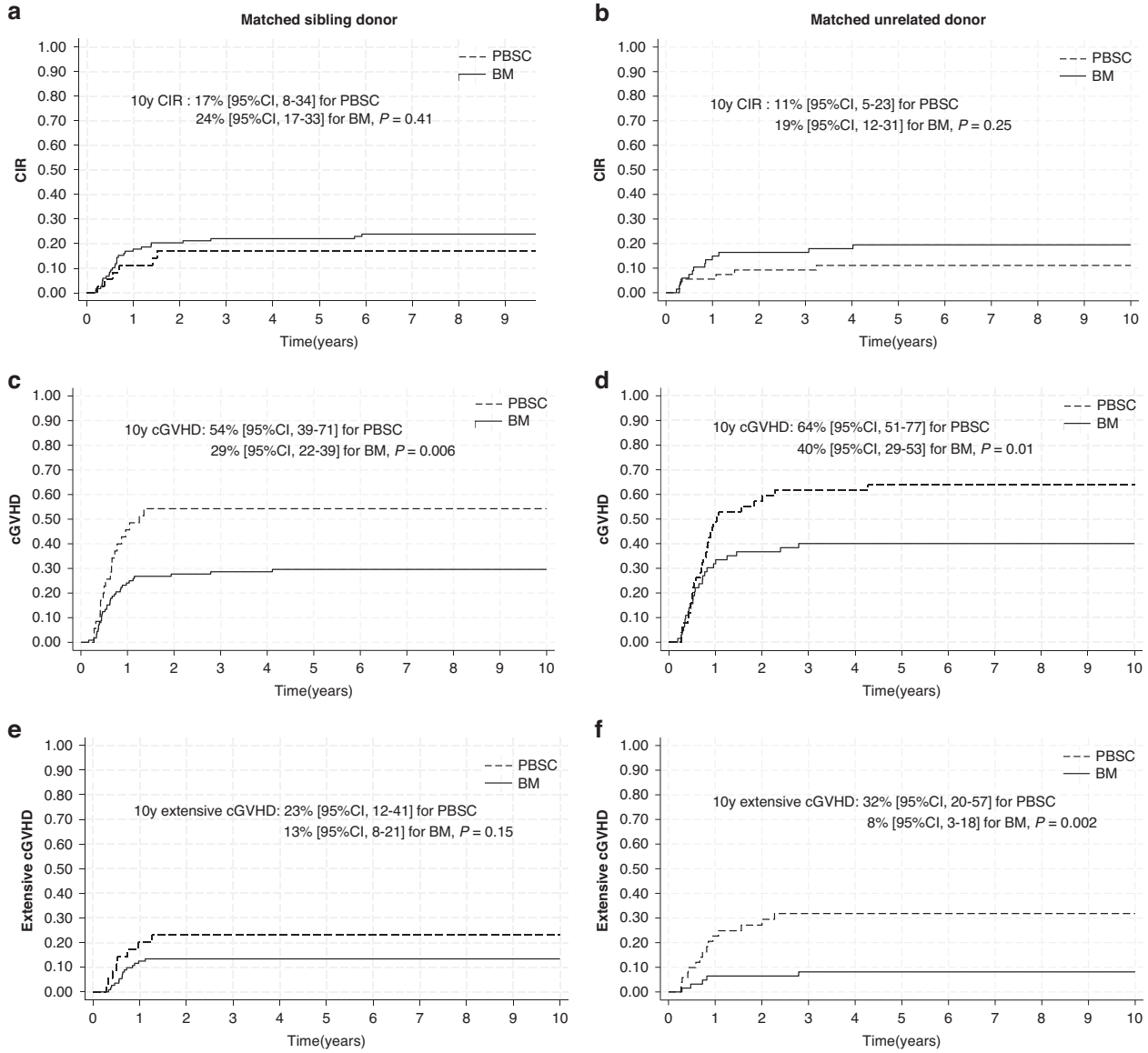

Fig. 1 Impact of stem cell source (PBSC versus BM) by donor type on outcomes. Panels **a**, **b** cumulative incidence of relapse (CIR); **c**, **d** cumulative incidence of any-grade chronic graft-versus-host disease (cGVHD); **e**, **f** cumulative incidence of extensive cGVHD; **g**, **h** non-relapse mortality (NRM); **i**, **j** grade III–IV aGVHD and/or extensive cGVHD-free, relapse-free survival (GRFS); **k**, **l** disease-free survival (DFS). Matched sibling donor (MSD) transplants are shown on the left, 10/10 HLA-matched unrelated donor (MUD) transplants on the right. Dashed lines represent peripheral blood stem cells (PBSC); solid lines represent bone marrow (BM). HR hazard ratio, IC confidence interval.

To our knowledge, this study is the first to specifically evaluate the impact of stem cell source in HR ALL adults transplanted in CR1. In this population, no benefit of PBSC over BM was observed in terms of relapse risk, whereas previous studies suggesting a relapse-protective effect of PBSC included only a minority of patients with ALL transplanted in CR1 [1, 3]. In the MSD setting, both BM and PBSC appear acceptable, as no significant differences were observed in extensive cGVHD, NRM, or relapse. However, in the MUD setting, BM may be preferred due to the higher incidence of extensive cGVHD and increased NRM associated with PBSC, without any corresponding benefit in relapse reduction. Our population is particular in that the majority of patients received BM stem cells in accordance with protocol recommendations, and only a minority received ATG. This practice is no longer standard, as current recommendations support the use of ATG in the MUD setting and with PBSC [10, 11]. While ATG effectively reduces the incidence of GVHD, this beneficial effect may be counterbalanced by an increased risk of infections and a potential reduction in the graft-versus-leukemia effect [12].

Although BM is no longer the stem cell source currently prioritized, partly for logistical reasons, our study allows a re-evaluation of its place in MUD transplantation for patients with ALL in CR1. This study also highlights the importance of reassessing stem cell source in light of individual disease characteristics and relapse risk. These findings warrant confirmation in other cohorts, particularly those incorporating ATG and the now widely used post-transplant cyclophosphamide for GVHD prophylaxis.

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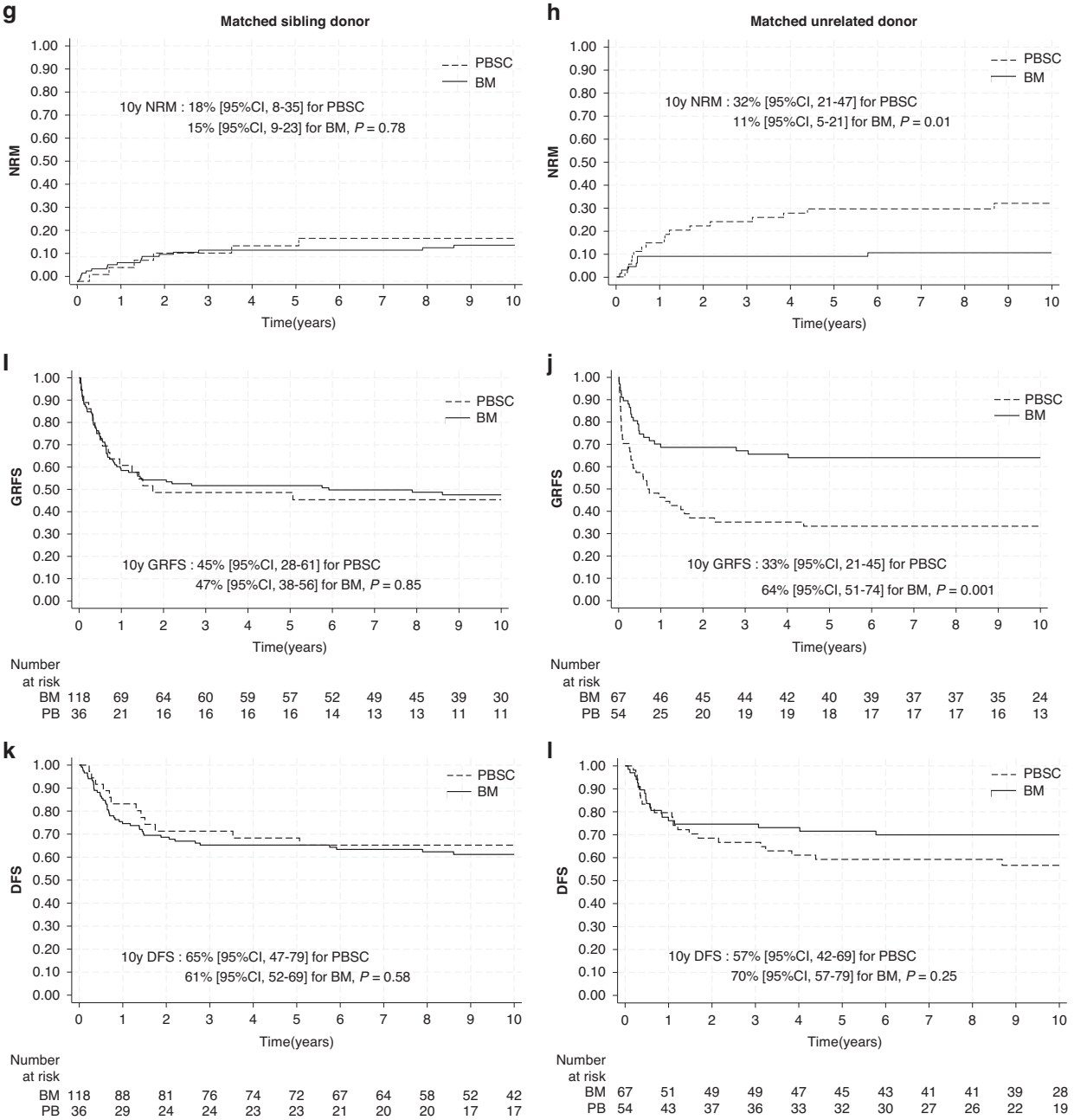

Fig. 1 Continue

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AUTHOR CONTRIBUTIONS

MJ analyzed data, draw the figures and wrote the paper. MR and VL collected clinical and biological annotations on patients. NB performed statistical analysis. NB and ND conceived the study and critically reviewed the article. SM, AH, EF, MS, CCL, JBM, SC, DS, JP, MA, CEB, JC, ML, JVM, EB, PT, XP, AV, ED, YC, KB, GG, JOB, CL, NM, RD, MTR, FP, SF, PC, HLW, SN and ND included patients. All authors revised and approved the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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