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LETTER TO THE EDITOR

More chronic GvHD and non-relapse mortality after peripheral blood stem cell compared with bone marrow in hematopoietic transplantation for paediatric acute lymphoblastic leukemia: a retrospective study on behalf of the EBMT Paediatric Diseases Working Party

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Appropriate donor selection and stem-cell source are crucial issues of the allograft strategy. For many years and for historical reasons, bone marrow stem cells (BM) were the most common source used in the allograft setting. However, the use of peripheral blood stem cells (PB) became more frequent over the years.[1,2] In adults, many studies reported PB efficacy and safety regarding their use as an alternative to BM in hematopoietic stem-cell transplantation (HSCT).[3,4] Data regarding the association between HSCT outcome and stem-cell source from both pediatric donors and patients are limited,[5] therefore, the role of PB as a stem-cell source is still debated in pediatrics. Allografts from PB, according to the Pediatric Blood and Marrow Transplant Consortium Experience (PBMTC) and the European Society for Blood and Marrow Transplantation (EBMT), are increasingly reported in children, with 30% in 2010 vs 10% few years earlier.[6,7] In pediatric patients, only one large study published in 2004 by Eapen *et al.*[5] specifically addressed the question of clinical outcomes after either BM or PB HSCT from HLA-identical sibling donors in children with ALL. This study reported a higher risk of chronic GvHD in the PB group with no positive impact on relapse rate and survival. Therefore, we conducted a retrospective analysis comparing HSCT outcomes after either BM or PB allografts in children, and adolescents below 18 years transplanted for ALL in first or subsequent CR among EBMT centers. We excluded patients with ALL transplanted from cord blood or *ex vivo* T cell-depleted transplants, and patients who received second or subsequent HSCT.

Data of children undergoing PB or BM transplantation between 1 January 2003 and 31 December 2012 were obtained from the Statistical Center of the EBMT. Full description of the statistical approach can be found in the Supplementary Materials. Out of 2584 pediatric patients transplanted for ALL within EBMT centers, 69% were grafted with BM and 31% with PB. Patients characteristics are presented in Table 1 divided in two groups according to the stem-cell source. All aspects of the transplant regimen, including stem-cell source, were at the discretion of each transplant center or according to ALL-BFM 2003 protocol for enrolled patients as described elsewhere.[8] HLA compatibility data were available for 825/1435 (57%) of the patients transplanted from unrelated donor. Among the 498 with 10/10 HLA-unrelated donor, 327 (65%) received BM and 171 (35%) received PB. Among the 327 with 9/10 HLA-compatible donor, 199 (60%) received BM and 128 (40%) received PB. The distribution of 10/10 and 9/10 between BM and PB was not statistically different ($P = 0.16$). GvHD prophylaxis was transplant centers' choice and appeared as adapted to the risk: first, the PB group received more often two drugs (mainly cyclosporin-A and short course methotrexate) than the BM group (73% vs 56%; $P < 0.0001$) and second the PB group received more often *in vivo* T depletion with antibodies as well (82% vs 72%; $P < 0.0001$). Complete engraftment rate was higher in the BM group (98.8% vs 97.3%; $P < 0.006$), whereas neutrophil recovery was faster in the PB group (16 vs 19 days; $P < 0.001$). There were not enough data in the EBMT database to describe platelet recovery. Three-year probability of overall survival (OS) was significantly higher after BM vs PB transplantation (67%; 95% confidence interval (CI): 66–68% vs 62%; 95% CI:

Table 1. Patients' characteristics

Variable	*Bone marrow transplantation*		*Peripheral blood stem cell transplantation*		
	N	%	N	%	P-*value*
Total number	1793		791		
Patient age, years					
Median	9.1		11.5		< 0.001
Range	0.4–17.9		0.6–17.9		
Donor age, years					
Median	20.9		30.7		< 0.001
Range	0.1–58		2.7–51.7		
Patient sex, male	1192	66.6	509	64.5	NS
Disease status					
1st CR	837	46.7	333	42.1	
2nd CR	805	44.9	377	47.7	
3rd CR	151	8.4	81	10.2	NS
TBI for conditioning	1429	79.9	518	65.7	< 0.001
Donor type					
Sibling donor	877	48.9	272	34.4	
Unrelated donor	916	51.1	519	65.6	< 0.001
Donor sex, male	1074	60.7	475	60.9	NS
Female D to male R	448	25.4	184	23.7	NS
CMV seropositivity					
Recipient	833	55.4	332	59.4	NS
Donor	687	45.5	272	47.2	NS
Engraftment	1746	98.8	762	97.2	0.003
Days to neutrophil > 500 per μl					
Median	19 days		16 days		
Range	3–68		2–45		< 0.001

Abbreviations: CsA = Cyclosporine; D = donor; MTX = methotrexate; R = recipient.

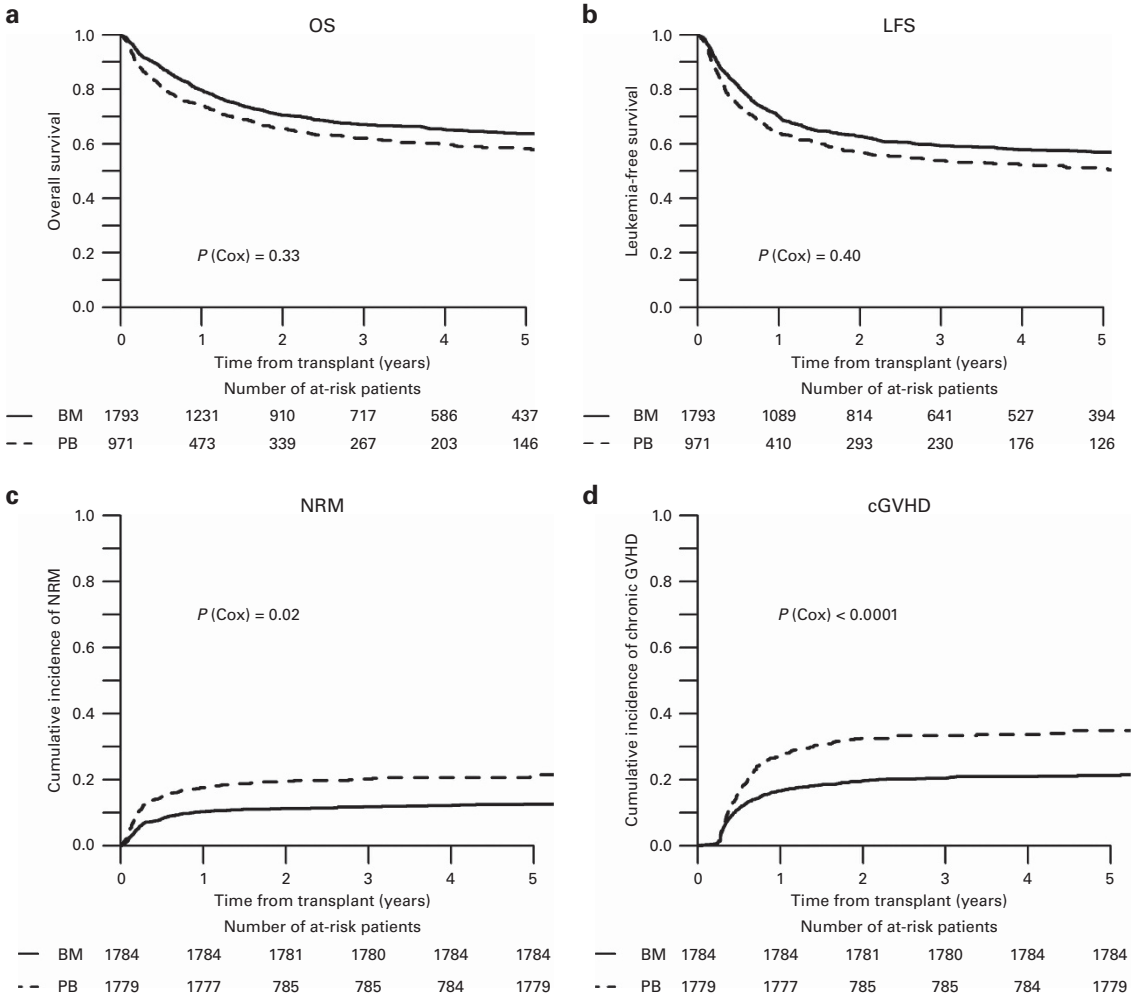

Figure 1. Survival curves. Bone marrow was represented by bold line and peripheral. Blood stem cells as doted line. (**a**) Three-year OS estimated by Kaplan–Meier method was 67% ((95% CI: 66–68%) vs 62% (95% CI: 60–64%); $P = 0.0004$) after BM and PB transplantation, respectively. (**b**) Three-year LFS estimated by Kaplan–Meier method was 59% ((95% CI: 58–60%) vs 54% (95% CI: 53–55%); $P = 0.0007$) after BM and PB transplantation, respectively. (**c**) Cumulative incidence of NRM at 3 years was 12% ((95% CI: 11–13%) vs 20% (95% CI: 19–21%); $P = 0.002$) after BM and PB transplantation, respectively. (**d**) Cumulative incidence of cGvHD at 3 years was 20% ((95% CI: 19–21%) and 33% (95% CI: 31–35%); $P < 0.001$) after BM and PB transplantation, respectively.

60–64%; $P = 0.0004$). The 3-year OS adjusted for other significant factors was similar in the two groups (Figure 1a). Three-year probability of leukemia-free survival (LFS) was significantly higher after BM transplantation (59%; 95% CI: 58–60%) than after PB transplantation (54%; 95% CI: 53–55%; $P = 0.0007$). The 3-year LFS adjusted for other significant factors was similar in the two groups (Figure 1b). Cumulative incidence of non-relapse mortality (NRM) at 3 years was 12% (95% CI: 11–13%) and 20% (95% CI: 19–21%) after BM and PB transplantation, respectively ($P = 0.002$). In multivariate analysis, NRM was significantly higher after PB transplantation (hazard ratio (HR) 1.38; 95% CI: 1.04–1.83; $P = 0.02$) (Figure 1c). Cumulative incidence of relapse at 3 years was similar between the two groups: 29% (95% CI: 28–30%) and 26% (95% CI: 24–28%) after BM and PB transplantation, respectively ($P = 0.29$). In multivariate analysis, chronic GvHD was significantly higher after PB transplantation (HR 1.91; 95% CI: 1.51–2.40; $P < 0.001$) (Figure 1d). Incidence of grade II–IV acute GvHD was similar between the two groups (odd ratio (OR) 1.07; 95% CI: 0.85–1.63; $P = 0.55$). Within the HLA-identical donor subgroup, in the PB group cGvHD (44% vs 21%; $P < 0.0001$), and NRM were higher (19% vs 8%; $P < 0.0001$), being incidence of relapse similar (34% vs 32%; $P = 0.3$) and OS and LFS lower in the BM geno-identical subgroup (69% vs 57%; $P < 0.0001$ and 60% vs 47%; $P < 0.0001$ respectively) in the univariate analysis. Within the unrelated-donor subgroup, cGvHD (28% vs 20%; $P = 0.001$) and NRM were higher (21% vs 15%; $P = 0.01$) in the PB group.

We report here the EBMT experience demonstrating the inferiority of PB HSCT for children with ALL, due to higher incidence of cGvHD and higher risk of NRM without improvement of relapse risk. A faster neutrophil engraftment was the only benefit of PB vs BM graft that could be identified. In adults, several studies provided consistent and relevant data concerning efficacy and safety of PB as an alternative hematopoietic stem-cell source for HSCT. Some clinical trials in adults comparing PB vs BM have reported a survival benefit in some population, in particular a decreased risk of disease relapse. In a meta-analysis published by the Stem Cell Trialists Collaborative Group in 2005, PB grafts were associated with a decreased risk of relapse (21% vs 27% at 3 years; $P = 0.01$). However, PB appeared also as a risk factor for GvHD (68% vs 52% at 3 years; $P < 0.001$).[9] In 2012, a phase-III multicenter randomized trial comparing PB vs BM transplantation from unrelated donors found an incidence of chronic GvHD at 2 years in the PB group of 53% compared with 41% in the bone marrow group ($P = 0.01$).[4] Causes of the higher risk of cGvHD are still debated. For some authors the higher T-cell numbers in mobilized PB[10,11] may have a relevant role, for others, the donor sensitivity to

granulocyte-colony stimulating factor (G-CSF) and his/her ability to mobilize stem cells is associated with the risk of cGvHD, regardless of CD3+ T cell or CD34+ cell number.[12] On the basis of these adult studies, despite the lack of pediatric data, some pediatricians may decide to use PB in pediatric HSCT. But the choice of the allograft source is mainly up to the donor center or the donor himself, at least in the unrelated setting.

More recently, Peters *et al.*[8] performed a prospective study within the multinational Berlin–Frankfurt–Muenster study-group trial to assess the influence of donor type on outcome after HSCT for ALL in children in remission. Patients transplanted from matched sibling donor (MSD) were compared with those transplanted from a 9/10 or 10/10 HLA-matched donor, either related or unrelated (matched unrelated donor (MD)). The recommended stem-cell source was BM from both MSD and MD, but recipients of unrelated grafts received BM or PB according to donor (and donor center) choice. Interestingly, no difference in patients outcomes were found between patients receiving BM or PB, whichever was the end-point considered, that is, OS, LFS, NRM and cGvHD.

Results reported by Eapen *et al.*[5] were confirmed in our series, as the PB source emerged as a risk factor for cGvHD after adjusting for other relevant factors, in a particular type of donor (geno-identical vs matched donor). Moreover, PB as the stem cell source also increased the risk of NRM, which was not counter-balanced by any positive impact on relapse. BM transplantation yielded better LFS and OS in our series compared with PB transplantation, but these differences disappeared after adjusting for the other significant factors. As expected, we confirm that PB lead to more rapid neutrophil engraftment in children. In our study, unrelated donor (UD) were statistically more frequent in PB group than in BM group. It could be explained by the preference of donor centers where pediatricians prefer to harvest bone marrow by themselves from related minor donors. Finally, our results demonstrated an increased risk of GvHD, especially extended cGvHD, a devastating disease for young patients, heavily influencing not only their physical performance but also their physical development and quality of life.

Then, contrary to practices widespread in adult transplantation, we think that PB shouldn't be considered as an equivalent alternative to BM in the pediatric population transplanted for ALL in any remission status. PB stem cells should be reserved for particular situations in which it's not possible to get BM, from either related or unrelated donors including those countries where the stimulation with G-CSF for minor donors is allowed. A clinical trial may identify which peculiar clinical or biological situation might benefit from PB.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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