



The Impact of Donor Type on Long-Term Health Status and Quality of Life after Allogeneic Hematopoietic Stem Cell Transplantation for Childhood Acute Leukemia: A Leucemie de l'Enfant et de L'Adolescent Study

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Sandrine Visentin, Pascal Auquier, Yves Bertrand, André Baruchel, Marie-Dominique Tabone, et al.. The Impact of Donor Type on Long-Term Health Status and Quality of Life after Allogeneic Hematopoietic Stem Cell Transplantation for Childhood Acute Leukemia: A Leucemie de l'Enfant et de L'Adolescent Study. *Biology of Blood and Marrow Transplantation*, 2016, 22 (11), pp.2003–2010. 10.1016/j.bbmt.2016.08.004 . hal-01415935

HAL Id: hal-01415935

<https://univ-rennes.hal.science/hal-01415935>

Submitted on 28 Mar 2018

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The impact of donor type on long-term health status and quality of life after allogeneic hematopoietic stem cell transplantation for childhood acute leukemia: An L.E.A. study.

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Short title: Long-term impact of donor type after childhood SCT

Funding/Support: See Acknowledgements

Conflict of interest: The authors declare no potential conflict of interest.

HIGHLIGHTS

- Donor type has little impact on long-term health status after childhood HSCT.
- Adults reported similar long-term quality of life regardless of donor type.
- The quality of life of adults in the L.E.A. cohort was lower than French norms.

SUMMARY

We compared the long-term impact of donor type (sibling donor (SD) versus matched unrelated donor (MUD) or umbilical cord blood (UCB)) on late side effects and quality of life (QoL) in childhood acute leukemia survivors treated with hematopoietic stem cell transplantation. We included 314 patients transplanted from 1997 to 2012 and enrolled in the multicenter French L.E.A. cohort. More than one third of the patients were adults at last visit; mean follow-up duration was 6.2 years. At least one late effect was observed in 284/314 patients (90.4%). The average number of adverse late effects was 2.1 ± 0.1 , 2.4 ± 0.2 and 2.4 ± 0.2 , after SD, MUD and UCB transplantation, respectively. In a multivariate analysis, considering the SD group as the reference, we did not detect an impact of donor type for most sequelae, with the exception of increased risk of major growth failure after MUD transplantation (OR=2.42) and elevated risk of osteonecrosis following UCB transplantation (OR=4.15). The adults and children's parents reported comparable QoL among the three groups. Adult patient QoL scores were lower than age- and sex-matched French reference scores for almost all dimensions. We conclude that although these patients are heavily burdened by long-term complications, donor type had a very limited impact on their long-term health status and QoL.

Keywords: hematopoietic stem cell transplantation, late effects, quality of life, childhood leukemia, cord blood transplantation

25

26 **INTRODUCTION**

27 Hematopoietic stem cell transplantation (HSCT) has been successfully used to treat
28 children with high-risk or relapsed acute leukemia. Many children and adolescents who
29 undergo HSCT become long-term survivors and may develop long-term complications, such
30 as endocrinopathies, musculoskeletal disorders, cardiopulmonary compromise and subsequent
31 malignancies (1-4).

32 When available, an HLA-matched sibling donor (SD) remains the donor of choice for
33 children who require HSCT. However, only approximately 25% of candidates eligible for
34 allogeneic HSCT have an HLA-matched SD. In the absence of a SD, an HLA-matched
35 unrelated volunteer donor (MUD) or unrelated umbilical cord blood (UCB) are alternative
36 transplant sources. In fact, despite the establishment of bone marrow donor registries with
37 more than 25 million volunteers worldwide, finding a MUD remains a problem for many
38 patients. Thus, the use of UCB as an alternative source for HSCT has increased substantially
39 in the last decade, especially for children (5). Currently, it is estimated that several thousand
40 UCB transplantations have been performed. The short-term outcome of children transplanted
41 with UCB (e.g., hematopoietic recovery, acute and chronic graft versus host disease (GvHD),
42 treatment-related mortality, survival and causes of death) have been well described (6-10).
43 Although overall survival is comparable, it has been clearly established that the course of the
44 early post-transplant period and principal complications differ with respect to the transplant
45 cell source. The risk of GvHD and related complications is intrinsically higher after MUD
46 transplantation compared with sibling transplantation, even if a recent extensive pediatric
47 study has shown that this risk can be overcome by using intensive prophylaxis with
48 cyclosporine, methotrexate and anti-thymocyte globulin (11). UCB transplant induces GvHD
49 to a lesser degree than MUD transplantation, although UCB hematopoietic recovery is slower,

thereby resulting in an extended duration of the aplastic phase and subsequent increased risk of severe infection (12, 13).

In contrast, very few studies have assessed long-term post-transplant health status with regard to donor type in a multivariate analysis (14-18), and to our knowledge, no studies have compared childhood leukemia survivors who received UCB with those who underwent SD or MUD HSCT.

Using the data extracted from the French cohort of childhood leukemia survivors (L.E.A., “Leucémie de l’Enfant et de L’Adolescent”), our primary objective was to describe the long-term health status and quality of life (QoL) after HSCT for childhood leukemia survivors with respect to donor type (SD, MUD or UCB transplantation). Because the patients were transplanted between May 1997 and June 2012 and transplantations involving an HLA haplo-identical family donor were rare in France during this time period, the few patients who underwent such transplantation were not included in this study.

METHODS

Patients

All patients described here were included in the L.E.A. program. This French multicenter program was established in 2003 to prospectively evaluate the long-term health status, QoL and socioeconomic status of childhood leukemia survivors. Patients were included in L.E.A. program if they met the following criteria: treated for acute leukemia after 1980 in one of the participating centers, were younger than 18 years of age at the time of diagnosis, and agreed (or their parents/legal guardians) to participate in the study. The present L.E.A. study focused on patients who received allogeneic HSCT with HLA-identical SD, MUD or UCB stem cells after a total body irradiation (TBI)- or busulfan-based myeloablative conditioning regimen before June 2012. To avoid potential bias due to different treatment periods and follow-up durations, we only included HSCTs performed after May 1997, the

date of the first UCB transplant reported in the L.E.A. cohort. Patients were excluded from the study if they underwent more than one HSCT, if they were treated before May 1997, if they were conditioned with a non-myeloablative regimen, or if they received autologous or HLA mismatched related transplantation. All patients (or their parents) provided written informed consent to participate in the program. The French National Program for Clinical Research and the French National Cancer Institute approved this study.

Evaluation of physical health status

Medical visits were conducted to detect the occurrence of late effects based on clinical examinations and laboratory tests when required. Clinical follow-up commenced one year after HSCT; these examinations were repeated every two years until the age of 20 and for at least ten years of complete remission; patients were then examined every four years thereafter.

Height, weight and body mass index (BMI) were measured at transplantation, study inclusion, and each subsequent medical examination. The measurements were then converted to standard deviation scores (SDS) based on the normal values for the French population (19). Growth failure (stunted height) was defined by a cumulative SDS change equal to or lower than -1 (minor failure for a value between -1.0 and -1.9, and major failure for a value equal to or lower than -2). Overweight was defined as a BMI of 25 kg/m² or more for adults (minor: BMI of 25.0-29.9, major: BMI of 30 or more) and a cumulative SDS change of +1 or more for children under 18 (minor: between 1.0 and 1.9, major: equal to or higher than 2). Low weight was defined as a BMI lower than 18.5 kg/m² in adults and a cumulative loss in SDS of -1.0 or more in children under 18. Children were not assessed for gonadal function if they were under 15 years of age and had not experienced menarche (girls) or did not have any pubertal signs (boys). Patients were diagnosed with gonadal dysfunction if they showed signs of precocious puberty or hypergonadotropic hypogonadism (low estradiol levels with high

follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels in women; low testosterone with high FSH and LH levels in men). Hypothyroidism was defined as a non-transient increase in thyroid stimulating hormone levels. All second tumors (including basal cell carcinoma) were taken into consideration for this analysis. Cardiac function was considered impaired when any one of the following three conditions was present: the echocardiographic shortening fraction was inferior to 28%, the left ventricular ejection fraction was inferior to 55% or specific treatments were required. Femoral neck and lumbar bone mineral density were measured using dual energy X-ray absorptiometry for all adults. Patients were considered to have low bone mineral density when the Z-score was inferior or equal to -2 in at least one of the two sites examined. Metabolic syndrome was defined according to the NCEP-ATPIII revised in 2005 (metabolic syndrome patients had at least three of the five criteria: (1) increased waist circumference (≥ 102 cm in men, ≥ 88 cm in women); (2) elevated blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or treatment necessitated); (3) reduced high-density lipoprotein cholesterol (≤ 40 mg/dL in men, ≤ 50 mg/dL in women); (4) elevated fasting glucose (≥ 1 g/L or drug treatment needed for elevated glucose levels); and (5) elevated triglycerides (≥ 150 mg/dL or drug treatment required for elevated triglycerides))(20). Iron overload was indicated by hyperferritinemia (a serum ferritin dosage ≥ 350 ng/ml at least one year after HSCT) in the absence of concomitant high erythrocyte sedimentation rates. Other late effects (cataracts, alopecia, osteonecrosis, diabetes and central nervous system complications) were systematically screened during every medical visit.

Evaluation of quality of life (QoL)

The VSPAe (Vécu et Santé Perçue de l'Enfant) and VSPA (Vécu et Santé Perçue de l'Adolescent) questionnaires are generic health-related QoL questionnaires specifically designed to evaluate self-reported QoL in 8- to 10-year-old children and 11- to 17-year-old

adolescents. VSP-Ap questionnaires (Vécu et Santé Perçue de l'Enfant et de l'Adolescent rapportés par les parents) are used to assess the parental point of view of their child's or adolescent's QoL. These questionnaire responses consider nine dimensions: psychological well-being, body image, vitality, physical well-being, leisure activities, relationship with friends, relationship with parents, relationship with teachers and school work. In addition to specific scores for each subscale, a global health-related QoL score is computed (21-23).

The SF-36 (the Medical Outcome Study Short Form 36 Health Survey) is a widely used QoL measure that provides a non-disease-specific assessment of adult functioning and well-being, which enables comparison with a broad range of age-matched norm groups (24, 25). The SF-36 is a generic QoL scale for adults consisting of 36 items describing eight dimensions: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional health, mental health, vitality, bodily pain and general health. Two summary scores are also calculated from the subscales: a physical component score and a mental component score. This is a reliable instrument to assess self-perceived health status in adult survivors of childhood cancer. The French version is well validated.

All scores range between 0 and 100, with higher scores indicating better QoL.

Statistical analysis

Chi-squared, Fisher's exact and ANOVA tests were used to compare demographic and clinical variables between the SD, MUD and UCB transplant groups. ANOVA was used to compare the mean number of late effects experienced per patient in each donor type group. Each of the following complications (as defined above) were considered as one late effect: height growth failure (minor or major), overweight (minor or major), low weight, gonadal dysfunction, hypothyroidism, second tumors, cataracts, alopecia, impaired cardiac function,

osteonecrosis, low BMD, diabetes, metabolic syndrome, iron overload and central nervous system complications.

To determine the link between each assessed adverse effect and donor type (i.e., SD, MUD or UCB), adjusted logistic regression models were performed. The six following covariates were included in the models: gender, age at diagnosis, age at last visit, history of relapse, conditioning regimen (TBI- versus busulfan-based), and leukemia type (acute myeloid leukemia (AML) versus acute lymphoblastic leukemia (ALL)). GvHD was considered as a potential intervening variable, i.e., a variable that is on the causal pathway between the transplant source and health status. Consequently, GvHD was not included in the model (26). Adjusted odds ratio (OR) and risk of having one type of late effect (including 95% confidence intervals) were estimated. Adjusted multiple linear regression models were generated to explore the link between the long-term QoL scores and donor type with the same covariates. Each model is presented with its standardized β coefficient, which measures the strength of the effect of graft type on the QoL dimension score.

The SF-36 mean scores reported by adult patients were compared with those obtained from age- and sex-matched French control subjects, using the paired Student's t-test (27).

Statistical significance was defined as $p < 0.05$.

RESULTS

Patient characteristics

A total of 314 patients fulfilled all selection criteria and were included in the analysis. The patient characteristics are summarized in Table 1. One hundred twenty-seven patients had received stem cells from a SD (40.5%), 99 from a MUD (31.5%) and 88 from unrelated UCB (28.0%). The mean follow-up duration from diagnosis and HSCT to last L.E.A. visit were 7.7 ± 0.2 and 6.2 ± 0.2 years, respectively. The mean age at acute leukemia diagnosis was 7.5 ± 0.3 years; UCB recipients were significantly younger at diagnosis ($p = 0.02$). As expected,

the percentage of patients who relapsed before HSCT was significantly higher in the MUD and UCB groups than in the SD group ($p=0.001$). More patients in the SD group (66.1%) were in first hematologic complete remission at the time of transplantation, compared with MUD (51.5 %) and UCB (40.9%); whereas in RC2 or more advance hematologic status, patients more often received an alternative donor type (MUD or UCB) ($p=0.009$). The incidence of significant GvHD (grade II-IV aGvHD or extensive cGvHD) was lower among UCB recipients (27.3% versus 43.3% for SD; and 62.6% for MUD, $p<10^{-3}$). A greater proportion of patients in the UCB and MUD groups had received post-transplant corticosteroids ($p=0.02$); this high percentage in spite of the low GvHD incidence in the UCB group can be explained by the fact that steroids were included in the GvHD prophylaxis regimen of most UCB recipients. The three groups were similar with regard to gender, previous irradiation, age at HSCT, leukemia type, conditioning regimen (TBI- or busulfan-based) and follow-up duration from diagnosis and HSCT to last visit. The patients of the UCB group were younger at last L.E.A. evaluation compared with the other groups, although this difference was not statistically significant ($p=0.11$).

Long-term late effects

Overall, 284 of 314 patients (90.4%) were found to have at least one late effect, without any apparent difference between the three groups. Among the SD survivors, 92.1% suffered from at least one late effect compared with the MUD (92.9%) and UCB (85.2%) survivors ($p=0.14$). The average number of adverse late effects was 2.1 ± 0.1 , 2.4 ± 0.2 and 2.4 ± 0.2 , respectively (non-significant). Twenty-two percent of the transplanted patients had one late effect, 31% had two late effects and 37% had three or more late effects. As shown in Figure 1, no significant difference was found between the donor cell sources ($p=0.52$).

The occurrence of each side effect for each group is outlined in Table 2. The patients treated using SD transplant were considered the reference group for all comparisons. The

multivariate analysis indicated that donor type did not have an impact on most sequelae. The only two significant differences were higher risk of major height growth failure after MUD transplantation (OR[95%CI]=2.42[1.06-5.56], $p=0.04$) and osteonecrosis following UCB transplantation (OR[95%CI]=4.15[1.23-14.04], $p=0.02$). None of the other comparisons revealed significant differences in the multivariate models.

Quality of life

Adults

Adults of the three groups reported very similar QoL (Table 3). The physical composite scores were 52.1 ± 1.6 for the SD group, 50.4 ± 1.8 for the MUD group and 50.3 ± 2.2 for the UCB group ($p=0.72$). The mental composite scores were 43.4 ± 1.4 for the SD group versus 47.3 ± 1.7 for the MUD group and 43.3 ± 2.6 for the UCB group ($p=0.28$). Considering SD as the reference group, multivariate linear regression analysis did not show any difference between the donor sources for each dimension.

Parents' point of view

The QoL of children and adolescents was reported by 204 parents (Table 4). The summary scores were 68.4 ± 1.7 for the SD group, 68.8 ± 2.0 for the MUD group and 69.8 ± 1.9 for the UCB group ($p=0.87$). Parent-reported scoring of the nine dimensions did not indicate that donor type had an impact on the QoL of children and adolescents.

Children and Adolescents

The mean scores reported by children ($n=35$) were comparable for all VSPAe subscales (Table 5). The summary scores were 72.4 ± 3.4 , 74.4 ± 3.7 and 70.3 ± 4.2 for the SD, MUD and UCB groups, respectively ($p=0.78$).

Regarding adolescent QoL (Table 6), no significant difference was found between the three groups, with the exception of 'relationship with parents' and 'school work'. In fact, adolescents of the SD group reported a significantly better 'school work' mean score than

those of the MUD group ($p=0.05$) and a lower 'relationship with parents' mean score compared with the UCB group ($p=0.03$). The summary scores were 64.1 ± 1.7 , 67.6 ± 2.0 and 69.2 ± 2.0 for the SD, MUD and UCB groups, respectively ($p=0.15$).

Comparison to French norms

The QoL assessed in 84 adults of this cohort was compared to age- and sex-matched French reference scores (Figure 2). Almost all subscales were significantly lower in the L.E.A. cohort. The physical composite (51.2 ± 1.1 versus 55.2 ± 0.1 , $p<0.001$) and mental composite scores (44.3 ± 1.1 versus 47.9 ± 0.3 , $p=0.001$) were both lower in the L.E.A. group.

DISCUSSION

The main objective of this study was to assess the long-term health status and QoL of a French cohort of childhood leukemia survivors who had received HSCT from three different donor types. HLA-identical sibling transplanted patients were chosen as the reference group and compared with MUD and UCB transplantations. During the immediate post-transplant phase, MUD transplantation patients are at increased risk of GvHD, while UCB transplants are associated with a slower hematologic recovery (6, 12, 28). We aimed to determine whether donor type also had an impact on long-term health status and QoL. With a 6.2-year post-transplant follow-up, this study showed that regardless of the donor type, the development of adverse health outcomes and QoL in long-term survivors were markedly similar. The mean number of late effects experienced per patient was a little more than two for each group; 90.4% of HSCT survivors in this study developed at least one adverse effect.

Although the occurrence of late effects in patients transplanted during childhood has been described, the impact of donor type on side effects was seldom taken in consideration. In the study by Bresters *et al.*, among 162 survivors of HSCT, 93.2% had sequelae after a median follow-up time of 7.2 years. Donor type was not found to be a risk factor for increased burden of late effects in a multivariate analysis, although only two patients had received UCB

transplantation (1.2%) (14). Armenian *et al.* have found at least one chronic health condition in 79.3% of childhood HSCT survivors (n=145) after a median follow-up time of 12 years. In a multivariate analysis, compared with conventionally treated cancer survivors, HSCT survivors had a significantly elevated risk of adverse health-related outcomes, and unrelated HSCT recipients were at greatest risk (15). Another study involving a cohort of 463 adults and children has reported a significantly higher cumulative incidence of extensive GvHD, cataracts and bone necrosis at 12 years after MUD, compared with SD transplants (16). To our knowledge, the health status of long-term survivors after UCB transplant has never been described. A few studies have reported late complications after HSCT during childhood, in which some patients had received UCB transplantation. However, no comparison between the donor source was performed, and the cohorts included a very limited proportion of UCB recipients: between 1.2% (14) and 5% (29).

The absolute number of late effects per patient is not a sufficient data point to comprehensively describe health status, as the burden of each late effect may markedly vary. Consequently, in this study we described the risks of specific late effects with respect to stem cell sources. Only two late effects were significantly associated with donor type: osteonecrosis was more frequent in the UCB group and major growth failure occurred more often following MUD transplant. Steroids have been shown to play a role in the pathophysiology of post-transplant osteonecrosis; other well-described risk factors include older age, female gender and GvHD (30-33). In the current study, although GvHD risk was lower following UCB transplant compared with MUD and SD transplant, the use of post-transplant steroids was very common as steroids were included in the GvHD prophylaxis regimen of most UCB recipients. Additionally, the higher proportion of patients with a history of pre-transplant leukemia relapse and ALL in the UCB and MUD groups may have played a role by increasing the pre-transplant cumulative steroid dose. Several studies have reported

the impact of TBI conditioning regimens on post-transplant growth (34, 35). In the present study, the risk of major growth failure was higher in patients who had received MUD, whereas the proportion of patients treated with TBI as a pre-transplant conditioning regimen was not significantly greater. Poor post-transplant growth may be due to many other factors, including GvHD and its treatments (36, 37). Significant GvHD occurred more frequently following MUD transplantation compared with the two other groups. However, our data do not support this explanation as we were unable to demonstrate a significant effect of GvHD on major growth failure in our cohort (data not shown).

To evaluate QoL, we used self-reported questionnaires for adults, children and adolescents as well as parent-reported questionnaires for patients less than 18 years of age. We found comparable results among the three study groups for all composite scores. This observation suggests that even if the immediate post-transplant period and burden of early complications experienced by transplanted children may differ with respect to the donor type, this does not explain the QoL reported many years after HSCT. In contrast, the adult QoL scores were significantly lower than sex- and age-matched French norms. Previous L.E.A. reports studying QoL have found similar results regardless of treatment or health condition, thus suggesting that suffering from acute leukemia may also play a role (27, 38). We acknowledge that the observed differences in the physical and mental composite scores, albeit statistically significant, were relatively small and their clinical relevance must be thus interpreted with caution. Others studies showed that cGvHD is the major contributor to reduced QoL after HSCT (6, 39). In our study, significant GvHD incidence was statistically higher among recipients of MUD grafts although QoL was similar. This is perhaps due to the fact that QoL scores reported in our study are the most recent measure for each patient and that survivors with resolved cGvHD may have a comparable long-term QoL to those never diagnosed with cGvHD (39, 40). Data concerning the impact of donor type on QoL are very

scarce. Lof *et al.* did not identify any difference between patients with a related or unrelated donor (41). Very little is known regarding QoL among long-term survivors following UCB transplant. Routine evaluation of health-related QoL should be an integral part of patient follow-up after childhood leukemia, especially when patients are treated by HSCT regardless of the donor type.

As UCB transplant has only recently become available, UCB patients of the L.E.A. cohort had a shorter follow-up duration than SD or MUD patients. More precisely, the date of the first UCB transplant reported to L.E.A. was May 1997. Thus, in the present study, only patients transplanted after that date were included, to both obtain a similar follow-up duration among the three groups and compare patients who had been treated in the same country during the same period of time. As a consequence, the follow-up duration (7.7 years after diagnosis and 6.2 years after HSCT) is shorter than that in other L.E.A. studies. This is a limitation of our study as some late effects may occur after a longer period of time. Some complications such as hypogonadism manifest during adulthood, thus requiring an extended follow-up period for detection. Other studies with a prolonged follow-up period are warranted to confirm our results. It is, however, important to note that more than one third of the patients in our cohort were adults at last assessment. The strengths of this study include cohort size and the large proportion of patients who received UCB transplantation (28%). To our knowledge, this represents the first comprehensive study to describe the long-term late effects and QoL after UCB transplant for childhood leukemia.

In conclusion, long-term acute leukemia survivors treated with HSCT during childhood are at risk for treatment-related sequelae, although donor type appears to have a very low impact on long-term outcomes and QoL. This analysis provides additional information for patients and physicians to assist in treatment decisions when a SD is not available and the transplant donor type must be selected between MUD and UCB. To prevent

324 and treat late events, while continually addressing issues that impact quality of survival, life-
325 long follow-up of transplant patients is recommended regardless of the donor type.

Accepted Manuscript

Acknowledgements

The study was funded in part by the French National Clinical Research Program, the French National Cancer Institute (InCA), the French National Research Agency (ANR), the Cancéropôle PACA, the Regional Council PACA, the Hérault and the Bouches-du-Rhône departmental comities of the Ligue Contre le Cancer and the French Institute for Public Health Research (IRESP).

The authors would like to thank the patients and their family as well as all members of the L.E.A. study group (Supplemental Data S1).

REFERENCES

1. Faraci M, Békássy AN, De Fazio V, et al. Non-endocrine late complications in children after allogeneic haematopoietic SCT. *Bone Marrow Transplant*. 2008; 41:S49–57.
2. Nieder ML, McDonald GB, Kida A, et al. NCI, NHLBI First International Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation: Long Term Organ Damage and Dysfunction Following Pediatric Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2011; 17:1573–1584.
3. Cohen A, Békássy AN, Gaiero A, et al. Endocrinological late complications after hematopoietic SCT in children. *Bone Marrow Transplant*. 2008; 41:S43–48.
4. Chow EJ, Anderson L, Baker KS, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. *Biol Blood Marrow Transplant*. 2016; 22: 782-795.
5. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. *Blood*. 2013; 122: 491–498.
6. Eapen M, Rubinstein P, Zhang M-J, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *The Lancet*. 2007; 369 : 1947–1954.
7. Benito AI, Diaz MA, González-Vicent M, et al. Hematopoietic stem cell transplantation using umbilical cord blood progenitors: review of current clinical results. *Bone Marrow Transplant*. 2004; 33:675–690.
8. Grewal SS, Barker JN, Davies SM, et al. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? *Blood*. 2003; 101:4233–4244.
9. Zheng C, Zhu X, Tang B, et al. Comparative analysis of unrelated cord blood transplantation and HLA-matched sibling hematopoietic stem cell transplantation in children with high-risk or advanced acute leukemia. *Ann Hematol*. 2015; 94:473–480.

10. Tang X, Chen J, Fang J, et al. Similar outcomes of allogeneic hematopoietic cell transplantation from unrelated donor and umbilical cord blood vs. sibling donor for pediatric acute myeloid leukemia: Multicenter experience in China. *Pediatr Transplant*. 2015; 19:413–421.
11. Peters C, Schrappe M, Stackelberg A von, et al. Stem-Cell Transplantation in Children With Acute Lymphoblastic Leukemia: A Prospective International Multicenter Trial Comparing Sibling Donors With Matched Unrelated Donors—The ALL-SCT-BFM-2003 Trial. *J Clin Oncol*. 2015; 33:1265–1274.
12. Gluckman E, Rocha V, Chevret S. Results of Unrelated Umbilical Cord Blood Hematopoietic Stem Cell Transplantation. *Rev Clin Exp Hematol*. 2001;5:87–99.
13. Zecca M, Prete A, Rondelli R, et al. Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. *Blood*. 2002; 100:1192–1200.
14. Bresters D, van Gils ICM, Kollen WJW, et al. High burden of late effects after haematopoietic stem cell transplantation in childhood: a single-centre study. *Bone Marrow Transplant*. 2009; 45:79–85.
15. Armenian SH, Sun C-L, Kawashima T, et al. Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). *Blood*. 2011; 118: 1413–1420.
16. Hows JM, Passweg JR, Tichelli A, et al. Comparison of long-term outcomes after allogeneic hematopoietic stem cell transplantation from matched sibling and unrelated donors. *Bone Marrow Transplant*. 2006; 38:799–805.
17. Baker KS, Gurney JG, Ness KK, et al. Late effects in survivors of chronic myeloid leukemia treated with hematopoietic cell transplantation: results from the Bone Marrow Transplant Survivor Study. *Blood*. 2004; 104:1898–1906.

18. Khera N, Storer B, Flowers MED, et al. Nonmalignant Late Effects and Compromised Functional Status in Survivors of Hematopoietic Cell Transplantation. *J Clin Oncol*. 2012; 30:71–77.
19. Sempé MA, Pédrón GA, Roy-Pernot M-PA. *Auxologie : méthodes et séquences*. Théraplix.1979.
20. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and Management of the Metabolic Syndrome An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005; 112:2735–2752.
21. Simeoni MC, Auquier P, Antoniotti S, et al. Validation of a French health-related quality of life instrument for adolescents: the VSP-A. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil*. 2000; 9: 393–403.
22. Sapin C, Simeoni M-C, El Khammar M, et al. Reliability and validity of the VSP-A, a health-related quality of life instrument for ill and healthy adolescents. *J Adolesc Health*. 2005; 36:327–336.
23. Simeoni MC, Sapin C, Antoniotti S, Auquier P. Health-related quality of life reported by French adolescents: a predictive approach of health status? *J Adolesc Health Off Publ Soc Adolesc Med*. 2001; 28:288–294.
24. Leplège A, Ecosse E, Verdier A, Perneger TV. The French SF-36 Health Survey. *J Clin Epidemiol*. 1998; 51: 1013–1023.
25. Reulen RC, Zeegers MP, Jenkinson C, et al. The use of the SF-36 questionnaire in adult survivors of childhood cancer: evaluation of data quality, score reliability, and scaling assumptions. *Health Qual Life Outcomes*. 2006; 4:77.
26. Katz MH. *Multivariable analysis: a practical guide for clinicians*. Cambridge; New York: Cambridge University Press; 2006.

27. Berbis J, Michel G, Chastagner P, et al. A French cohort of childhood leukemia survivors: impact of hematopoietic stem cell transplantation on health status and quality of life. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. 2013; 19:1065–1072.
28. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood*. 2001; 97:2962–2971.
29. Ferry C, Gemayel G, Rocha V, et al. Long-term outcomes after allogeneic stem cell transplantation for children with hematological malignancies. *Bone Marrow Transplant*. 2007; 40:219–224.
30. Girard P, Auquier P, Barlogis V, et al. Symptomatic osteonecrosis in childhood leukemia survivors: prevalence, risk factors and impact on quality of life in adulthood. *Haematologica*. 2013; 98:1089–1097.
31. Li X, Brazauskas R, Wang Z, et al. Avascular necrosis of bone following allogeneic hematopoietic cell transplantation in children and adolescents. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. 2014; 20:587–592.
32. McAvoy S, Baker KS, Mulrooney D, et al. Corticosteroid Dose as a Risk Factor for Avascular Necrosis of the Bone after Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2010; 16:1231–1236.
33. McClune B, Majhail NS, Flowers MED. Bone Loss and Avascular Necrosis of Bone After Hematopoietic Cell Transplantation. *Semin Hematol*. 2012; 49:59–65.
34. Sanders JE. Growth and development after hematopoietic cell transplant in children. *Bone Marrow Transplant*. 2007; 41:223–227.

35. Bernard F, Bordigoni P, Simeoni M-C, et al. Height growth during adolescence and final height after haematopoietic SCT for childhood acute leukaemia: the impact of a conditioning regimen with BU or TBI. *Bone Marrow Transplant*. 2009; 43:637–642.
36. Isfan F, Kanold J, Merlin E, et al. Growth hormone treatment impact on growth rate and final height of patients who received HSCT with TBI or/and cranial irradiation in childhood: a report from the French Leukaemia Long-Term Follow-Up Study (LEA). *Bone Marrow Transplant*. 2012; 47:684–693.
37. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended Screening and Preventive Practices for Long-term Survivors after Hematopoietic Cell Transplantation. *Bone Marrow Transplant*. 2012; 47: 337–341.
38. Michel G, Bordigoni P, Simeoni M-C, et al. Health status and quality of life in long-term survivors of childhood leukaemia: the impact of haematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2007; 40:897–904.
39. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2006; 108:2867–2873.
40. Sun C-L, Kersey JH, Francisco L, et al. Burden of morbidity in 10+ year survivors of hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant*. 2013; 19:1073–1080.
41. Löf CM, Winiarski J, Giesecke A, et al. Health-related quality of life in adult survivors after paediatric allo-SCT. *Bone Marrow Transplant*. 2008; 43:461–468.

FIGURE LEGENDS

Figure 1: Number of late effects per patient with respect to donor type.

SD: sibling donor, MUD: matched unrelated donor, UCB: umbilical cord blood.

Figure 2: SF-36 results in adults compared with sex- and age-matched French norms.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

PF: physical functioning, SF: social functioning, RP: role limitations due to physical health problems, RE: role limitations due to emotional problems, MH: mental health, VT: vitality, BP: bodily pain, GH: general health, PCS: physical composite score, MCS: mental composite score.

Table 1: Patient Characteristics (n=314)

<i>n</i> (%)	SD (n=127)	MUD (n=99)	UCB (n=88)	<i>p</i>
Gender				
Female	59 (46.5)	35 (35.4)	36 (40.9)	0.24
Male	68 (53.5)	64 (64.6)	52 (59.1)	
Age at diagnosis (years, mean \pm s.e)	8.4 \pm 0.4	7.2 \pm 0.5	6.6 \pm 0.5	0.02
Age at HSCT (years, mean \pm s.e)	9.8 \pm 0.4	8.9 \pm 0.5	8.4 \pm 0.6	0.14
Leukemia type				
ALL	76 (59.8)	67 (67.7)	59 (67.0)	0.07
AML	50 (39.4)	32 (32.3)	25 (28.4)	
Others	1 (0.8)	0 (0)	4 (4.5)	
Previous irradiation				
CNS	5 (3.9)	5 (5.1)	5 (5.7)	0.84
Testicular	1 (1.5)	2 (3.1)	3 (5.8)	0.45
History of relapse	44 (34.6)	48 (48.5)	54 (61.4)	0.001
Conditioning regimen				
TBI	74 (58.3)	68 (68.7)	58 (65.9)	0.24
Bu	53 (41.7)	31 (31.3)	30 (34.1)	
Hematologic status at time of transplant				
CR1	84 (66.1)	51 (51.5)	36 (40.9)	0.009
CR2	40 (31.5)	44 (44.4)	51 (58.0)	
CR3	1 (0.8)	2 (2.0)	1 (1.1)	
refractory	2 (1.6)	2 (2.0)	0 (0.0)	
GvHD				
Significant GvHD ^a	55 (43.3)	62 (62.6)	24 (27.3)	<10⁻³
Steroid therapy after HSCT	80 (63.0)	72 (72.7)	71 (80.7)	0.02
Age at last visit (years, mean \pm s.e)	16 \pm 0.5	15.1 \pm 0.6	14.4 \pm 0.6	0.11
< 8 year old	8 (6.3)	14 (14.1)	13 (14.8)	0.33
8 to 10 year old	19 (15)	13 (13.1)	14 (15.9)	
11 to 17 year old	53 (41.7)	44 (44.4)	37 (42)	
> 18 year old	47 (37)	28 (28.3)	24 (27.3)	
Time from diagnosis to last visit (years, mean \pm s.e)	7.6 \pm 0.3	7.9 \pm 0.4	7.8 \pm 0.5	0.82
Time from HSCT to last visit (years, mean \pm s.e)	6.3 \pm 0.3	6.2 \pm 0.4	5.9 \pm 0.4	0.77

HSCT, hematopoietic stem cell transplantation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; TBI, total body irradiation; Bu, Busulphan; CR, complete remission; GvHD, Graft versus host disease

^aSignificant GvHD: comprises acute GvHD grade II-IV and extensive chronic GvHD

Table 2: Occurrence of late effects according to donor type

	SD (n=127) n(%)	MUD (n=99) n(%)	UCB (n=88) n(%)	Multivariate analysis			
				MUD versus SD		UCB versus SD	
				OR (95% CI)	p	OR (95% CI)	p
Height growth failure							
Minor or major	40 (31.5)	44 (44.4)	27 (30.7)	1.68 (0.93 - 3.01)	0.08	0.94 (0.50 - 1.77)	0.84
Major	12 (9.4)	20 (20.2)	13 (14.8)	2.42 (1.06 - 5.56)	0.04	1.60 (0.65 - 3.97)	0.30
GH treatment	8 (6.3)	10 (10.1)	6 (6.8)	1.50 (0.54 - 4.18)	0.44	0.91 (0.29 - 2.86)	0.88
Overweight							
Minor or major	24 (18.9)	20 (20.2)	18 (20.5)	1.22 (0.61 - 2.44)	0.58	1.15 (0.55 - 2.41)	0.70
Major	7 (5.5)	8 (8.1)	7 (8.0)	1.57 (0.52 - 4.71)	0.42	1.32 (0.41 - 4.28)	0.64
Low weight	32 (25.2)	24 (24.2)	20 (22.7)	0.75 (0.39 - 1.42)	0.38	0.68 (0.35 - 1.35)	0.27
Gonadal dysfunction^a	37 (39.4)	26 (37.7)	24 (41.4)	1.17 (0.52 - 2.66)	0.71	1.41 (0.58 - 3.44)	0.45
Hypothyroidism	17 (13.4)	15 (15.2)	16 (18.2)	0.96 (0.42 - 2.17)	0.92	1.20 (0.53 - 2.73)	0.67
Second tumors							
All	4 (3.1)	2 (2.0)	7 (8.0)	0.61 (0.10 - 3.60)	0.59	2.71 (0.69 - 10.61)	0.15
All except basal-cell carcinomas and meningiomas	4 (3.1)	2 (2.0)	6 (6.9)	0.59 (0.10 - 3.47)	0.56	2.36 (0.59 - 9.38)	0.22
Cataract	27 (21.3)	21 (21.2)	25 (28.4)	0.80 (0.37 - 1.71)	0.56	1.65 (0.77 - 3.52)	0.20
Alopecia	10 (7.9)	6 (6.1)	4 (4.5)	1.00 (0.30 - 3.33)	1	0.64 (0.15 - 2.72)	0.55
Impaired cardiac function	2 (1.6)	4 (4.0)	7 (8.0)	2.03 (0.34-12.29)	0.44	4.14 (0.77 - 22.29)	0.10
Osteonecrosis	6 (4.7)	6 (6.1)	9 (10.2)	1.75 (0.51 - 5.99)	0.38	4.15 (1.23 - 14.04)	0.02
Low bone mineral density^b	3 (11.1)	5 (23.8)	6 (31.6)	2.49 (0.49-12.62)	0.27	3.62 (0.68 - 19.20)	0.13
Diabetes	1 (0.8)	1 (1.0)	3 (3.4)	1.14 (0.07-19.18)	0.93	4.77 (0.44 - 52.08)	0.20
Metabolic syndrome^c	4 (11.1)	4 (19.0)	2 (9.5)	2.26 (0.45-11.38)	0.32	0.83 (0.10 - 7.27)	0.87
Iron overload^d	63 (52.1)	54 (60.0)	37 (45.1)	1.78 (0.93 - 3.40)	0.08	0.84 (0.43 - 1.65)	0.61
CNS complications	2 (1.6)	6 (6.1)	5 (5.7)	3.59 (0.69-18.64)	0.13	2.86 (0.53 - 15.57)	0.22

All Odd Ratios are calculated using SD as reference group.

Co-variables: gender, leukemia type, age at diagnosis, age at last visit, relapse and conditioning (TBI/Bu).

^a:gonadal function was assessable in 221 patients (92 girls and 129 boys/94 SD, 69 MUD and 58 UCB)

^b: data available in 67 adults (27 SD, 21 MUD and 19 UCB)

^c: data of metabolic syndrome was assessable in 78 adults (36 SD, 21 MUD and 21 UCB)

^d: iron overload was assessable in 293 patients (121 SD, 90 MUD and 82 UCB)

Table 3 : QoL of adults (n=84) using SF-36 questionnaire.

Subscales of SF-36	Multivariate linear regression analysis						
	SD (n=41) mean ± SEM	MUD (n=22) mean ± SEM	UCB (n=21) mean ± SEM	MUD vs SD		UCB vs SD	
				β coeff	p	β coeff	p
Physical functioning	88.6±2.8	85.8±3.6	82.9±4.8	-0.09	0.44	-0.13	0.30
Social functioning	72.6±4.0	77.8±5.1	75.0±5.7	0.07	0.53	0.10	0.43
Role: physical	77.8±6.0	70.2±7.0	75.0±8.1	-0.10	0.42	-0.03	0.80
Role: emotional	64.2±5.0	72.7±5.6	60.3±7.5	0.11	0.34	-0.02	0.89
Mental health	65.8±2.6	66.3±3.2	63.4±4.5	0.03	0.81	-0.004	0.97
Vitality	58.1±2.7	59.3±3.5	57.4±4.6	0.01	0.94	0.04	0.72
Bodily pain	78.2±3.8	77.5±4.9	72.1±6.4	-0.02	0.86	-0.14	0.27
General health	63.5±3.8	69.3±3.9	63.2±3.9	0.09	0.44	0.02	0.85
Physical Composite Score	52.1±1.6	50.4±1.8	50.3±2.2	-0.11	0.36	-0.11	0.37
Mental Composite Score	43.4±1.4	47.3±1.7	43.3±2.6	0.18	0.13	0.06	0.60

Co-variates: gender, leukemia type, age at diagnosis, age at last visit, relapse and conditioning (TBI/Bu).

Table 4: QoL of children and adolescents reported by their parents (n=204) using VSP-Ap.

Subscales of VSPAP	Multivariate linear regression analysis						
	SD	MUD	UCB	MUD vs SD		UCB vs SD	
	(n=79) mean ± SEM	(n=67) mean ± SEM	(n=58) mean ± SEM	β coeff	p	β coeff	p
Relationship with parents	75.8±1.9	78.1±1.9	77.7±2.6	0.03	0.70	0.003	0.97
Body image	63.0±3.9	65.9±3.8	68.0±4.2	0.06	0.48	0.10	0.21
Vitality	69.4±2.1	72.7±1.8	71.9±2.3	0.08	0.29	0.06	0.47
Relationship with friends	67.0±2.5	62.0±3.2	66.2±3.2	-0.13	0.14	-0.008	0.93
Leisures activities	64.7±2.8	61.7±3.3	60.8±3.1	-0.09	0.25	-0.08	0.36
Psychological well-being	73.2±2.5	73.4±2.5	75.2±2.8	-0.02	0.82	0.02	0.82
Physical well-being	68.0±2.4	69.7±2.3	71.6±2.5	0.02	0.84	0.06	0.48
School work	73.2±2.4	68.1±2.5	69.3±3.4	-0.10	0.25	-0.06	0.46
Relationship with teachers	66.5±2.5	71.0±2.7	70.4±2.5	0.08	0.35	0.05	0.56
Summary score	68.4±1.7	68.8±2.0	69.8±1.9	-0.03	0.72	0.03	0.78

Co-variables: gender, leukemia type, age at diagnosis, age at last visit, relapse and conditioning (TBI/Bu).

Table 5 : QoL of children (n=35) using VSPAe questionnaire

Subscales of VSPAe	Multivariate linear regression analysis						
	SD (n=15) mean ± SEM	MUD (n=10) mean ± SEM	UCB (n=10) mean ± SEM	MUD vs SD		UCB vs SD	
				β coeff	p	β coeff	p
Relationship with parents	75.5±4.0	73.9±4.7	76.9±5.6	0.08	0.73	0.13	0.57
Body image	73.3±4.8	86.7±4.6	68.8±7.7	0.22	0.31	-0.02	0.93
Vitality	79.0±4.7	82.6±5.0	81.5±4.1	-0.01	0.98	0.08	0.77
Relationship with friends	54.6±7.1	48.1±9.7	52.1±9.3	0.13	0.60	0.34	0.16
Leisure activities	67.0±4.6	78.8±4.4	72.0±4.4	0.31	0.22	0.09	0.71
Psychological and physical well-being	77.7±4.2	80.8±4.6	74.7±3.2	-0.04	0.88	-0.27	0.26
School work	80.0±5.4	70.0±5.0	68.8±7.5	-0.16	0.49	-0.13	0.56
Summary score	72.4±3.4	74.4±3.7	70.3±4.2	0.12	0.65	0.09	0.73

Co-variates: gender, leukemia type, age at diagnosis, age at last visit, relapse and conditioning (TBI/Bu).

Table 6 : QoL of adolescents (n=130) using VSPA questionnaire.

Subscales of VSPA	Multivariate linear regression analysis					
	SD		MUD		UCB	
	(n=52) mean \pm SEM		(n=42) mean \pm SEM		(n=36) mean \pm SEM	
				β coeff	p	β coeff
						p
Vitality	68.8 \pm 2.2	74.6 \pm 2.6	76.4 \pm 2.4	0.15	0.12	0.19
Psychological well-being	72.4 \pm 3.0	77.3 \pm 2.6	71.3 \pm 3.8	0.04	0.70	-0.12
Relationship with friends	64.9 \pm 3.1	63.3 \pm 3.8	74.5 \pm 2.2	-0.08	0.43	0.19
Leisure activities	54.1 \pm 3.3	60.3 \pm 4.1	60.9 \pm 4.1	0.11	0.31	0.10
Relationship with parents	59.0 \pm 3.5	65.8 \pm 3.5	68.9 \pm 3.8	0.17	0.09	0.23
Physical well-being	67.8 \pm 2.6	76.2 \pm 2.9	72.1 \pm 3.8	0.12	0.21	0.05
Relationship with teachers	63.3 \pm 2.7	63.8 \pm 3.6	65.9 \pm 4.8	0.04	0.71	0.06
School work	70.1 \pm 2.6	59.1 \pm 4.2	67.1 \pm 4.2	-0.21	0.05	-0.07
Body image	64.2 \pm 3.9	64.9 \pm 4.4	71.9 \pm 5.7	0.03	0.75	0.10
Summary score	64.1 \pm 1.7	67.6 \pm 2.0	69.2 \pm 2.0	0.16	0.11	0.14

Co-variables: gender, leukemia type, age at diagnosis, age at last visit, relapse and conditioning (TBI/Bu).