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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.

Sandrine Visentin¹, Pascal Auquier, MD, PhD², Yves Bertrand, MD, PhD³, André Baruchel, MD, PhD⁴, Marie-Dominique Tabone, MD⁵, Cécile Pochon, MD⁶, Charlotte Jubert, MD⁷, Maryline Poirée, MD⁸, Virginie Gandemer, MD, PhD⁹, Anne Sirvent, MD¹⁰, Jacinthe Bonneau, MD⁹, Catherine Paillard, MD, PhD¹¹, Claire Freycon, MD¹², Justyna Kanold, MD, PhD¹³, Virginie Villes², Julie Berbis, MD, PhD², Claire Oudin, MD^{1,2}, Claire Galambrun, MD¹, Isabelle Pellier, MD, PhD¹⁴, Geneviève Plat, MD¹⁵, Hervé Chambost, MD, PhD¹, Guy Leverger, MD, PhD⁵, Jean-Hugues Dalle, MD, PhD⁴ and Gérard Michel, MD, PhD^{1,2}

¹Department of Pediatric Hematology and Oncology, Timone Enfants Hospital and Aix-Marseille University, Marseille, France

²Research Unit EA 3279 and Department of Public Health, Aix-Marseille University and Timone Hospital Marseille, France

³Department of Pediatric Hematology and Oncology, University Hospital of Lyon, France

⁴Pediatric Hematology Department, Robert Debré Hospital, Paris, France

⁵Pediatric Hematology Department, Trousseau Hospital, Paris, France

⁶Department of Pediatric Onco-Haematology, Hôpital d'Enfants de Brabois, Vandoeuvre Les Nancy, France

⁷Department of Pediatric Hematology and Oncology, University Hospital of Bordeaux, France

⁸Pediatric Hematology and oncology department, University Hospital L'Archet, Nice, France

⁹Department of Pediatric Hematology and Oncology, University Hospital of Rennes, France

¹⁰Pediatric Hematology and oncology department, University Hospital, Montpellier, France

¹¹Department of Pediatric Hematology-oncology, University Hospital, Strasbourg, France

¹²Department of Pediatric Hematology-Oncology, University Hospital of Grenoble, France

¹³Department of Pediatric Hematology and Oncology, CIC Inserm 501, University Hospital of Clermont-Ferrand, France

¹⁴Pediatric Hematology and Oncology department, University Hospital of Angers, Angers, France

¹⁵Department of Pediatric Onco-Hematology, CHU-Hospital Purpan, Toulouse, France

Corresponding author:

Sandrine VISENTIN,

Department of Pediatric Hematology-Oncology

Hôpital pour Enfants La Timone, 264 Rue St Pierre

13385 Marseille cedex 05, France

Phone number: +33491388776

Fax number: +33491384989

E-mail: sandrine.visentin@ap-hm.fr

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1 HIGHLIGHTS

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

5 SUMMARY

6 We compared the long-term impact of donor type (sibling donor (SD) versus matched
7 unrelated donor (MUD) or umbilical cord blood (UCB)) on late side effects and quality of life
8 (QoL) in childhood acute leukemia survivors treated with hematopoietic stem cell
9 transplantation. We included 314 patients transplanted from 1997 to 2012 and enrolled in the
10 multicenter French L.E.A. cohort. More than one third of the patients were adults at last visit;
11 mean follow-up duration was 6.2 years. At least one late effect was observed in 284/314
12 patients (90.4%). The average number of adverse late effects was 2.1 ± 0.1 , 2.4 ± 0.2 and
13 2.4 ± 0.2 , after SD, MUD and UCB transplantation, respectively. In a multivariate analysis,
14 considering the SD group as the reference, we did not detect an impact of donor type for most
15 sequelae, with the exception of increased risk of major growth failure after MUD
16 transplantation (OR=2.42) and elevated risk of osteonecrosis following UCB transplantation
17 (OR=4.15). The adults and children's parents reported comparable QoL among the three
18 groups. Adult patient QoL scores were lower than age- and sex-matched French reference
19 scores for almost all dimensions. We conclude that although these patients are heavily
20 burdened by long-term complications, donor type had a very limited impact on their long-
21 term health status and QoL.

22

23 **Keywords:** hematopoietic stem cell transplantation, late effects, quality of life, childhood
24 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,

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

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

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

63 **METHODS**

64 **Patients**

65 All patients described here were included in the L.E.A. program. This French
66 multicenter program was established in 2003 to prospectively evaluate the long-term health
67 status, QoL and socioeconomic status of childhood leukemia survivors. Patients were
68 included in L.E.A. program if they met the following criteria: treated for acute leukemia after
69 1980 in one of the participating centers, were younger than 18 years of age at the time of
70 diagnosis, and agreed (or their parents/legal guardians) to participate in the study. The present
71 L.E.A. study focused on patients who received allogeneic HSCT with HLA-identical SD,
72 MUD or UCB stem cells after a total body irradiation (TBI)- or busulfan-based myeloablative
73 conditioning regimen before June 2012. To avoid potential bias due to different treatment
74 periods and follow-up durations, we only included HSCTs performed after May 1997, the

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

81 **Evaluation of physical health status**

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

87 Height, weight and body mass index (BMI) were measured at transplantation, study
88 inclusion, and each subsequent medical examination. The measurements were then converted
89 to standard deviation scores (SDS) based on the normal values for the French population (19).
90 Growth failure (stunted height) was defined by a cumulative SDS change equal to or lower
91 than -1 (minor failure for a value between -1.0 and -1.9, and major failure for a value equal to
92 or lower than 2). Overweight was defined as a BMI of 25 kg/m² or more for adults (minor:
93 BMI of 25.0-29.9, major: BMI of 30 or more) and a cumulative SDS change of +1 or more
94 for children under 18 (minor: between 1.0 and 1.9, major: equal to or higher than 2). Low
95 weight was defined as a BMI lower than 18.5 kg/m² in adults and a cumulative loss in SDS of
96 -1.0 or more in children under 18. Children were not assessed for gonadal function if they
97 were under 15 years of age and had not experienced menarche (girls) or did not have any
98 pubertal signs (boys). Patients were diagnosed with gonadal dysfunction if they showed signs
99 of precocious puberty or hypergonadotropic hypogonadism (low estradiol levels with high

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

121 **Evaluation of quality of life (QoL)**

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

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

131 The SF-36 (the Medical Outcome Study Short Form 36 Health Survey) is a widely used QoL
132 measure that provides a non-disease-specific assessment of adult functioning and well-being,
133 which enables comparison with a broad range of age-matched norm groups (24, 25). The SF-
134 36 is a generic QoL scale for adults consisting of 36 items describing eight dimensions:
135 physical functioning, social functioning, role limitations due to physical health problems, role
136 limitations due to emotional health, mental health, vitality, bodily pain and general health.
137 Two summary scores are also calculated from the subscales: a physical component score and
138 a mental component score. This is a reliable instrument to assess self-perceived health status
139 in adult survivors of childhood cancer. The French version is well validated.

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

141

142 **Statistical analysis**

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

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

151 To determine the link between each assessed adverse effect and donor type (i.e., SD,
152 MUD or UCB), adjusted logistic regression models were performed. The six following
153 covariates were included in the models: gender, age at diagnosis, age at last visit, history of
154 relapse, conditioning regimen (TBI- versus busulfan-based), and leukemia type (acute
155 myeloid leukemia (AML) versus acute lymphoblastic leukemia (ALL)). GvHD was
156 considered as a potential intervening variable, i.e., a variable that is on the causal pathway
157 between the transplant source and health status. Consequently, GvHD was not included in the
158 model (26). Adjusted odds ratio (OR) and risk of having one type of late effect (including
159 95% confidence intervals) were estimated. Adjusted multiple linear regression models were
160 generated to explore the link between the long-term QoL scores and donor type with the same
161 covariates. Each model is presented with its standardized β coefficient, which measures the
162 strength of the effect of graft type on the QoL dimension score.

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

165 Statistical significance was defined as $p < 0.05$.

166 **RESULTS**

167 **Patient characteristics**

168 A total of 314 patients fulfilled all selection criteria and were included in the analysis.
169 The patient characteristics are summarized in Table 1. One hundred twenty-seven patients had
170 received stem cells from a SD (40.5%), 99 from a MUD (31.5%) and 88 from unrelated UCB
171 (28.0%). The mean follow-up duration from diagnosis and HSCT to last L.E.A. visit were
172 7.7 ± 0.2 and 6.2 ± 0.2 years, respectively. The mean age at acute leukemia diagnosis was
173 7.5 ± 0.3 years; UCB recipients were significantly younger at diagnosis ($p = 0.02$). As expected,

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

189 **Long-term late effects**

190 Overall, 284 of 314 patients (90.4%) were found to have at least one late effect,
191 without any apparent difference between the three groups. Among the SD survivors, 92.1%
192 suffered from at least one late effect compared with the MUD (92.9%) and UCB (85.2%)
193 survivors ($p=0.14$). The average number of adverse late effects was 2.1 ± 0.1 , 2.4 ± 0.2 and
194 2.4 ± 0.2 , respectively (non-significant). Twenty-two percent of the transplanted patients had
195 one late effect, 31% had two late effects and 37% had three or more late effects. As shown in
196 Figure 1, no significant difference was found between the donor cell sources ($p=0.52$).

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

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

204 **Quality of life**

205 *Adults*

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

212 *Parents' point of view*

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

217 *Children and Adolescents*

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

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

224 those of the MUD group ($p=0.05$) and a lower 'relationship with parents' mean score
225 compared with the UCB group ($p=0.03$). The summary scores were 64.1 ± 1.7 , 67.6 ± 2.0 and
226 69.2 ± 2.0 for the SD, MUD and UCB groups, respectively ($p=0.15$).

227 *Comparison to French norms*

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

232 **DISCUSSION**

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

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

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

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

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

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

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

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

319 In conclusion, long-term acute leukemia survivors treated with HSCT during
320 childhood are at risk for treatment-related sequelae, although donor type appears to have a
321 very low impact on long-term outcomes and QoL. This analysis provides additional
322 information for patients and physicians to assist in treatment decisions when a SD is not
323 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.

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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 ± s.e)	8.4±0.4	7.2±0.5	6.6±0.5	0.02
Age at HSCT (years, mean ± s.e)	9.8±0.4	8.9±0.5	8.4±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 ± s.e)				
< 8 year old	16±0.5	15.1±0.6	14.4±0.6	0.11
8 to 10 year old	8 (6.3)	14 (14.1)	13 (14.8)	0.33
11 to 17 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 ± s.e)	7.6±0.3	7.9±0.4	7.8±0.5	0.82
Time from HSCT to last visit (years, mean ± s.e)	6.3±0.3	6.2±0.4	5.9±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
<i>GH treatment</i>	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-variates: 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)		MUD (n=22)		UCB (n=21)		
	mean \pm SEM	mean \pm SEM	mean \pm SEM	mean \pm SEM	β coeff	p	
Physical functioning	88.6 \pm 2.8	85.8 \pm 3.6	82.9 \pm 4.8	-0.09	0.44	-0.13	0.30
Social functioning	72.6 \pm 4.0	77.8 \pm 5.1	75.0 \pm 5.7	0.07	0.53	0.10	0.43
Role: physical	77.8 \pm 6.0	70.2 \pm 7.0	75.0 \pm 8.1	-0.10	0.42	-0.03	0.80
Role: emotional	64.2 \pm 5.0	72.7 \pm 5.6	60.3 \pm 7.5	0.11	0.34	-0.02	0.89
Mental health	65.8 \pm 2.6	66.3 \pm 3.2	63.4 \pm 4.5	0.03	0.81	-0.004	0.97
Vitality	58.1 \pm 2.7	59.3 \pm 3.5	57.4 \pm 4.6	0.01	0.94	0.04	0.72
Bodily pain	78.2 \pm 3.8	77.5 \pm 4.9	72.1 \pm 6.4	-0.02	0.86	-0.14	0.27
General health	63.5 \pm 3.8	69.3 \pm 3.9	63.2 \pm 3.9	0.09	0.44	0.02	0.85
Physical Composite Score	52.1 \pm 1.6	50.4 \pm 1.8	50.3 \pm 2.2	-0.11	0.36	-0.11	0.37
Mental Composite Score	43.4 \pm 1.4	47.3 \pm 1.7	43.3 \pm 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 \pm SEM	(n=67) mean \pm SEM	(n=58) mean \pm SEM	β coeff	<i>p</i>	β coeff	<i>p</i>
Relationship with parents	75.8 \pm 1.9	78.1 \pm 1.9	77.7 \pm 2.6	0.03	0.70	0.003	0.97
Body image	63.0 \pm 3.9	65.9 \pm 3.8	68.0 \pm 4.2	0.06	0.48	0.10	0.21
Vitality	69.4 \pm 2.1	72.7 \pm 1.8	71.9 \pm 2.3	0.08	0.29	0.06	0.47
Relationship with friends	67.0 \pm 2.5	62.0 \pm 3.2	66.2 \pm 3.2	-0.13	0.14	-0.008	0.93
Leisures activities	64.7 \pm 2.8	61.7 \pm 3.3	60.8 \pm 3.1	-0.09	0.25	-0.08	0.36
Psychological well-being	73.2 \pm 2.5	73.4 \pm 2.5	75.2 \pm 2.8	-0.02	0.82	0.02	0.82
Physical well-being	68.0 \pm 2.4	69.7 \pm 2.3	71.6 \pm 2.5	0.02	0.84	0.06	0.48
School work	73.2 \pm 2.4	68.1 \pm 2.5	69.3 \pm 3.4	-0.10	0.25	-0.06	0.46
Relationship with teachers	66.5 \pm 2.5	71.0 \pm 2.7	70.4 \pm 2.5	0.08	0.35	0.05	0.56
Summary score	68.4 \pm 1.7	68.8 \pm 2.0	69.8 \pm 1.9	-0.03	0.72	0.03	0.78

Co-variates: 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 \pm SEM	MUD (n=10) mean \pm SEM	UCB (n=10) mean \pm SEM	MUD vs SD		UCB vs SD		<i>p</i>
				β coeff	<i>p</i>	β coeff	<i>p</i>	
Relationship with parents	75.5 \pm 4.0	73.9 \pm 4.7	76.9 \pm 5.6	0.08	0.73	0.13	0.57	0.57
Body image	73.3 \pm 4.8	86.7 \pm 4.6	68.8 \pm 7.7	0.22	0.31	-0.02	0.93	0.93
Vitality	79.0 \pm 4.7	82.6 \pm 5.0	81.5 \pm 4.1	-0.01	0.98	0.08	0.77	0.77
Relationship with friends	54.6 \pm 7.1	48.1 \pm 9.7	52.1 \pm 9.3	0.13	0.60	0.34	0.16	0.16
Leisure activities	67.0 \pm 4.6	78.8 \pm 4.4	72.0 \pm 4.4	0.31	0.22	0.09	0.71	0.71
Psychological and physical well-being	77.7 \pm 4.2	80.8 \pm 4.6	74.7 \pm 3.2	-0.04	0.88	-0.27	0.26	0.26
School work	80.0 \pm 5.4	70.0 \pm 5.0	68.8 \pm 7.5	-0.16	0.49	-0.13	0.56	0.56
Summary score	72.4 \pm 3.4	74.4 \pm 3.7	70.3 \pm 4.2	0.12	0.65	0.09	0.73	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 (n=52) mean \pm SEM	MUD (n=42) mean \pm SEM	UCB (n=36) mean \pm SEM	MUD vs SD β coeff	UCB vs SD β coeff	<i>p</i>
Vitality	68.8 \pm 2.2	74.6 \pm 2.6	76.4 \pm 2.4	0.15	0.12	0.06
Psychological well-being	72.4 \pm 3.0	77.3 \pm 2.6	71.3 \pm 3.8	0.04	0.70	0.19
Relationship with friends	64.9 \pm 3.1	63.3 \pm 3.8	74.5 \pm 2.2	-0.08	0.43	0.06
Leisure activities	54.1 \pm 3.3	60.3 \pm 4.1	60.9 \pm 4.1	0.11	0.31	0.35
Relationship with parents	59.0 \pm 3.5	65.8 \pm 3.5	68.9 \pm 3.8	0.17	0.09	0.03
Physical well-being	67.8 \pm 2.6	76.2 \pm 2.9	72.1 \pm 3.8	0.12	0.21	0.63
Relationship with teachers	63.3 \pm 2.7	63.8 \pm 3.6	65.9 \pm 4.8	0.04	0.71	0.59
School work	70.1 \pm 2.6	59.1 \pm 4.2	67.1 \pm 4.2	-0.21	0.05	0.50
Body image	64.2 \pm 3.9	64.9 \pm 4.4	71.9 \pm 5.7	0.03	0.75	0.28
Summary score	64.1 \pm 1.7	67.6 \pm 2.0	69.2 \pm 2.0	0.16	0.11	0.16

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