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A French Cohort of Childhood Leukemia Survivors: Impact of Hematopoietic Stem Cell Transplantation on Health Status and Quality of Life

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A B S T R A C T

The late effects and quality of life (QoL) in childhood acute leukemia survivors were compared between hematopoietic stem cell transplantation (HSCT) recipients and patients who underwent conventional therapy. The study included 943 patients, 256 of whom underwent HSCT (27.1%). Medical visits were conducted to detect the occurrence of physical late effects. Based on patient age, different questionnaires were used to assess QoL. To evaluate the association between HSCT and each type of late effect or QoL dimension, the appropriate multivariate regressions were performed. QoL mean scores were compared with those obtained for age- and sex-matched French control subjects. Of all the survivors, 674 (71.5%) had at least 1 late effect, with the risk being 5.0 CI95 (3.0-8.6) times higher for transplantation survivors. For child survivors, scoring of QoL showed no significant differences between the treatment groups. The adult HSCT survivors reported lower physical dimension QoL scores than chemotherapy survivors. Compared with French norms, the survivor group reported a significantly lower mental composite score; however, the physical composite score showed no significant difference. Thus, transplanted survivors have a high risk of developing late effects, resulting in a decreased physical well-being in adulthood. However, long after treatment completion, childhood leukemia survivors report that effects on psychological well-being are more important than they are in physical QoL dimensions.

INTRODUCTION

Regular advances in cancer treatment have dramatically changed the prognosis of children with acute leukemia. Survival rates have increased in the past few decades [1,2], benefiting more than 85% of children with acute lymphoblastic leukemia (ALL) and more than 65% of children with acute myelogenous leukemia (AML) [2]. These substantial improvements have raised concerns about the difficulties survivors and their families face, including the late physical effects, problems with social integration, and decreased quality of life (QoL).

Hematopoietic stem cell transplantation (HSCT) remains a high-risk treatment for childhood leukemia patients with potential severe adverse effects [3-6]. Currently, a substantial proportion of survivors have undergone HSCT, and most children experience at least 1 late-onset physical effect [7]. Both physical and psychological effects have long-term consequences for children and their families, leading to an interest in assessing QoL as well as clinical follow-up for surviving children [8,9].

In France, the LEA cohort (Leucémie de l'Enfant et de l'Adolescent [childhood and adolescent leukemia]) was initiated in 2003 with the aim of studying the long-term health status and QoL of children treated for leukemia after January 1980. Initial results, on a relatively small sample, have found that in spite of a higher risk of physical sequelae after HSCT than after conventional therapy, very few clinically significant differences in QoL were detectable [10]. Otherwise, few studies that have explored the impact of HSCT are currently available [11-14].

Using the 5-year data collected from the described cohort, the aim of this study was to produce an update of the first results published on the French LEA cohort [10], comparing HSCT with conventional treatment on late effects and QoL among childhood leukemia survivors.

METHODS

Subjects

The LEA cohort is a multicenter historical and prospective cohort of prevalent cases (diagnosed between the January 1, 1980 and the participation start date of the center) and incident cases (diagnosed after the participation start date of the center). From 2004 to 2009, the LEA program consisted of an exhaustive recruitment in 5 French pediatric cancer centers (Marseilles, Nancy, Nice, Clermont-Ferrand, and Grenoble).

The following four inclusion criteria were used: (1) diagnosis of de novo AML or de novo ALL since January 1980, not excluding secondary leukemias; (2) younger than age 18 years at the time of the diagnosis; (3) complete remission 24 months after the diagnosis for AML patients and ALL patients grafted in first complete remission, or complete remission at 48 months after the diagnosis for ALL patients not grafted in first complete remission; and (4) agreement to to participate in the study, with parents or legal

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guardians authorizing participation for any subject younger than age 18 years.

This study was approved by a review board (CNIL). All patients included during 2004 to 2009 were analyzed in the present study.

Evaluation of Medical Health Status

Clinical data relating to acute leukemia were obtained by reviewing each medical record. The four types of data reported were as follows: (1) subtype of leukemia, (2) age at time of diagnosis, (3) disease evolution and relapse occurrence, and (4) detailed history of treatments received, with special emphasis on chemotherapy drugs, use of radiotherapy, and HSCT. Medical visits were conducted to detect the occurrence of late effects based on clinical examinations and adequate laboratory exams.

Patient height, weight, and body mass index were measured at the time of diagnosis and on evaluation; values were compared with normality and converted to standard deviation scores (SDs) using tables of normal values for the French population [15,16]. The cumulative change in SDs was calculated as the SDs at the time of the evaluation visit minus the SDs at diagnosis. The overweight variable was defined as a body mass index of 25 or more for adults (minor if 25.0-29.9 and major if 30 or more) and by a cumulative SD change of +1 or more for children under 18 (minor for a value between 1.0 and 1.9 and major for a value equal to or higher than 2). Height growth failure was defined using a cumulative SD change equal to or lower than 1 (minor for a value between −1.0 and −1.9 and major for a value equal to or lower than −2).

A growth hormone deficiency was diagnosed using the measurement of growth hormone and insulin-like growth factor 1 after a minimum of 2 stimulation tests. Children were considered not assessable for gonadal function if they were younger than age 15 years and had never had menarche (girls) or did not exhibit any pubertal signs (boys). A gonadal side effect was defined by a hypergonadotropic hypogonadism or by the occurrence of precocious puberty. Hypothyroidism was defined as a nontransient elevation of thyroid-stimulating hormone.

A cardiac side effect was defined as an abnormal decrease in the echocardiographic shortening fraction or the requirement of a specific treatment. An ophthalmological evaluation for detecting cataracts was performed. Iron overload was defined as a serum ferritin dosage $\geq$ 350 ng/mL in the absence of concomitant abnormal erythrocyte sedimentation rate.

From 2007 to 2009, the assessment of metabolic syndrome was systematically proposed to all adults with a new LEA health status evaluation. Metabolic syndrome was defined according to the National Cholesterol Evaluation Program Adult Treatment Panel III, revised in 2005 [17]. During the same 2007-2008 period, femoral neck and lumbar bone mineral density was measured using dual-energy x-ray absorptiometry for all adults. A deficit was defined as a Z (SD) score no more than −2 in at least 1 of the 2 sites examined. For the "second tumor" item, all second malignancies (including basal cell carcinoma) and meningioma were taken into consideration.

A viral side effect was defined if positive for hepatitis B surface antigen, HIV, or hepatitis C virus with a detectable viral load. Other late effects reported were osteonecrosis, diabetes, severe neurological dysfunctions, and alopecia.

Evaluation of the Quality of Life

The QoL of adult patients was assessed using the SF-36 questionnaire [18], a reliable instrument in assessing self-perceived health status in adult survivors of childhood cancer [19]. The SF-36 is composed of 36 items describing 8 dimensions: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, general mental health, vitality, bodily pain, and general health perceptions (Table S1). Additionally, 2 summary composite scores are generated, namely the physical composite score and the mental composite score.

The QoL of children and adolescents 8 to 17 years of age was reported by their parents using the VSP-A questionnaire (Vécu et Santé Perçue de l'Adolescent et de l'enfant) [20-22]. The 37-item parent version (VSP-Ap), designed to be answered by parents of children or by adolescents of all ages, was used. The questionnaire responses described 9 dimensions and a summary score: psychological well-being, body image, vitality, physical well-being, leisure activities, relationships with friends, relationships with parents, relationships with teachers, and school work; it also described 1 complementary dimension, relationships with medical staff (Table S1).

For both the SF-36 and the VSP-Ap, all scores range between 0 and 100, with higher scores indicating better QoL. The French general population reference values for both adults [23] and children and adolescents age 8 to 17 years [20] are available for gender- and age-matched comparison purposes.

Statistical Methods

Binary variables were summarized using counts and percentages and continuous variables with means and SDs. To assess the representativeness of our sample, demographic and clinical variables between the respondent and nonrespondent groups were compared using chi-square tests (for percentages) and Student *t*-tests (for means).

To determine the link between the occurrence for each explored sequelae and treatment type, HSCT or chemotherapy, adjusted logistic regression models were performed. The following covariates were included in the models: gender, type of leukemia, relapse (yes or no), age at diagnosis, follow-up duration (between diagnosis and evaluation), central nervous system irradiation (yes or no), and decade of the start of treatment. Adjusted odds ratios and risk of having 1 type of late effect (including 95% confidence intervals) were estimated.

Similarly, adjusted multiple linear regression models were constructed to explore the link between the patient's long-term QoL scores and treatment type with the same covariates. Each model is presented with its standardized β coefficient, measuring the strength of the effect of transplantation on the QoL dimension's score. The goodness of fit of the models was measured using adjusted R-squared values. We divided the HSCT group into 2 subgroups with or without posttransplantation chronic graft-versus-host disease (cGVHD) and compared health status and QoL of each of them with the conventional chemotherapy group.

To help interpret the clinical significance of differences in the QoL dimension mean scores, effect sizes were calculated by dividing the difference between the mean score of the HSCT group and the mean score of the chemotherapy group by the SD of the chemotherapy group. We considered an effect size of .2 to .49 as "small," .5 to .79 as "medium," and .8 or higher as "large" [24].

The SF-36 or VSP-Ap mean scores reported by patients were compared with those obtained for age- and sex-matched French control subjects, using paired Student *t*-tests. All tests were 2-sided. Statistical analyses were performed using PASW Statistics software version 17.0.2. (IBM SPSS Inc., Chicago, IL).

RESULTS

Study Cohort

Among the 1115 childhood leukemia survivors fulfilling the inclusion criteria in the 5 participant centers, 943 patients agreed to participate in the study (response rate, 84.6%). The respondent group and the nonrespondent group did not differ significantly with respect to the descriptive variables collected in the medical records (gender, type of leukemia, age at diagnosis, history of relapse, and treatment by transplantation or not).

All 943 patients were evaluated during a medical examination where the current health status and late effects were documented. The QoL questionnaires were obtained for 761 subjects (80.7%), completed by adults or the survivors' parents based on survivor age. No significant differences were found between the QoL respondents and nonrespondents for the main sociodemographic and clinical variables.

Patient characteristics are summarized in Table 1. Survivors of the HSCT and chemotherapy groups were not significantly different in follow-up duration from diagnosis to evaluation, with an average of 11.9 $\pm$ 6.4 years. The 256 patients in the HSCT group were significantly older by an average of 1 year at diagnosis and an average of 2 years at the time of evaluation. The chemotherapy group had a significantly lower percentage of males, patients with AML, and patients with a history of relapse.

Late Effects

Of the survivors, 674 (71.5%) were found to have at least 1 late effect (Table 2). Among the HSCT survivors, 231 (90.2%) had a late effect, with an average of 3.3 $\pm$ 1.8 adverse effects, whereas in the chemotherapy group, 443 survivors (64.5%) had a late effect, with an average of 1.6 $\pm$ .8 adverse effects ($P < .001$).

After the adjustment, the risk of late effects for the transplanted group was higher than for the chemotherapy group. This increased risk was significant for each late effect, with the exception of overweight, bone mineral deficiencies,

Table 1
Patient Characteristics

	All Patients (N = 943)	Chemotherapy Group (N = 687)	HSCT Group (N = 256)	*P*
Gender				.003*
Female	423 (44.9)	329 (47.9)	94 (36.7)	
Male	520 (55.1)	358 (52.1)	162 (63.3)	
Leukemia subtype				<.001*
ALL	807 (85.6)	630 (91.7)	177 (69.1)	
AML	136 (14.4)	57 (8.3)	79 (30.9)	
Decade of the start of treatment				.027*
1980-1989	192 (20.4)	129 (18.8)	63 (24.6)	
1990-1999	417 (44.2)	299 (43.5)	118 (46.1)	
2000-2009	334 (35.4)	259 (37.7)	75 (29.3)	
Age at diagnosis, yr (mean ± SD)	6.4 ± 4.2	6.1 ± 4.0	7.1 ± 4.7	.004*
History of relapse	152 (16.1)	26 (3.8)	126 (49.2)	<.001*
Age at evaluation, yr (mean ± SD)	18.3 ± 7.1	17.8 ± 7.0	19.6 ± 7.1	<.001*
<8	55 (5.8)	43 (6.3)	12 (4.7)	
8-10	102 (10.8)	91 (13.2)	11 (4.3)	
11-17	294 (31.2)	211 (30.7)	83 (32.4)	
>18	492 (52.2)	342 (49.8)	150 (58.6)	
Follow-up duration from diagnosis to evaluation, yr (mean ± SD)	11.9 ± 6.4	11.7 ± 6.4	12.5 ± 6.4	.065
CNS irradiation		121 (17.6)	27 (10.5)	
Testicular irradiation		10	11	
Total body irradiation		-	186 (72.7)	
Testicular radiation boost		-	24	
Children who received more than 1HSCT		-	14 (5.5)	
Hematological status at the time of the first transplantation				
CR1		-	137 (53.5)	
CR2		-	110 (43.0)	
More advanced		-	9 (.4)	
Allogeneic transplantation		-	191 (74.6)	
Acute GVHD		-	112	
Chronic GVHD		-	51	
including chronic GVHD after prior acute GVHD		-	39	

CNS indicates central nervous system; CR, complete remission.
Values are n (%) unless otherwise noted.
* Significant at $P < .05$.

cardiac side effects, severe neurological dysfunctions, and viral transmission, in which the differences were not significant. Among the HSCT survivors, the risk of late effect was particularly increased for gonadal dysfunction, diabetes, cataracts, and hypothyroidism, with odds ratios ranging from 24.4 to 29.8 (Table 2).

Quality of Life

Parents' point of view

Regarding patient QoL, parent-reported scoring showed no significant differences between the treatment groups, except for relationships with teachers and relationships with medical staff, with a better perception significantly associated with having undergone transplantation. The calculated effect sizes were less than .2, with the exception of body image, although this effect was not significant (Table 3).

Parents of childhood leukemia survivors reported a significantly higher perception of their child's QoL than parents of the control population, except for psychological well-being, physical well-being, and relationships with friends. Conversely, the survivors' group reported a significantly lower body image mean score (Figure 1).

Adults

Overall, the HSCT survivors reported lower QoL scores than the chemotherapy group survivors, and the findings were statistically significant for physical functioning, bodily pain, and general health perceptions domains as well as the physical composite score with effect sizes ranging from .31 to .48 (Table 4). Compared with French population norms, survivors scored significantly lower for all domains of QoL except for general mental health, vitality, bodily pain, and the physical composite score (Figure 2).

DISCUSSION

More than 70% of the survivors and 90.2% of the transplantation survivors in this study developed at least 1 adverse effect. These findings are consistent with previous results. The Childhood Cancer Survivor Study (CCSS) found that 62.3% of adult survivors of pediatric cancer [25] had a long-term adverse effect, and Haddy et al. [26] reported sequelae for 74.1% of survivors after treatment for childhood acute leukemia. Ishida et al. [27] reported 78.0% of adults transplanted during childhood reported at least 1 late adverse effect, whereas Bresters et al. [28] found sequelae for 93.2% of children and adolescents after HSCT.

Our study reports a substantial effect of HSCT on the occurrence of late effects, as reported in our previous study, albeit with a lower level of accuracy [10]. Survivors who underwent HSCT reported a 5 times greater risk of having at least 1 adverse effect. Most late effects explored in this study appeared to be significantly more frequent among transplantation patients. In the literature, studies that compared long-term consequences of HSCT and chemotherapy in childhood leukemia are quite rare. Using a relatively small sample, Leahey et al. [29] reported a significant difference for estrogen supplementation in patients undergoing bone marrow transplantation versus those undergoing chemotherapy. Other authors [27,30] reported lower adjusted odds ratios than those in our study in less-homogeneous populations of patients

Table 2
Multivariate Logistic Regression Analyses for the Risk of Having One Type of Late Event

Type of Late Event	CT Group	HSCT Group	ORa*	CI95%	HSCT Group		CT versus (1)		CT versus (2)	
	n/N (%)	n/N (%)			without cGVHD (1)	with cGVHD (2)	ORa*	CI95%	ORa*	CI95%
Height growth failure										
Minor or Major	225/687 (32.8)	150/256 (58.6)	**4.1**	[2.7-6.2]	123/205 (60.0)	27/51 (52.9)	**3.7**	[2.3-5.7]	**4.1**	[2.0-8.4]
Major	49/687 (7.1)	82/256 (32.0)	**7.9**	[4.5-13.9]	66/205 (32.2)	16/51 (31.4)	**6.7**	[3.7-12.4]	**11.8**	[4.5-30.9]
GH treatment	3/687 (0.4)	23/256 (9.0)	**17.8**	[4.0-79.5]	17/205 (8.3)	6/51 (11.8)	**11.8**	[2.3-60.2]	**57.6**	[4.8-696.0]
Overweight										
Minor or Major	273/687 (39.7)	73/256 (28.5)	0.9	[0.6-1.3]	63/205 (30.7)	10/51 (19.6)	1.0	[0.6-1.5]	0.6	[0.3-1.4]
Major	115/687 (16.7)	29/256 (11.3)	0.8	[0.4-1.4]	26/205 (12.7)	3/51 (5.9)	0.9	[0.5-1.6]	0.5	[0.1-1.8]
Gonadal dysfunction (1)	24/501 (4.8)	105/205 (51.2)	**24.4**	[12.3-48.1]	85/164 (51.8)	20/41 (48.8)	**18.9**	[9.4-37.8]	**36.5**	[11.4-116.3]
Thyroid										
Hypothyroidism	10/687 (1.5)	65/256 (25.4)	**29.8**	[12.7-69.7]	51/205 (24.9)	14/51 (27.5)	**26.7**	[11.0-64.7]	**284.5**	[38.9-2083.3]
Malignant thyroid tumor	3/687 (0.4)	8/256 (3.1)	**19.7**	[3.6-108.0]	7/205 (3.4)	1/51 (2.0)	**19.9**	[3.4-117.8]		
Second tumor										
All	20/687 (2.9)	26/256 (10.2)	**8.1**	[3.3-19.9]	23/205 (11.2)	3/51 (5.9)	**7.1**	[2.8-18.0]	**6.7**	[1.3-34.8]
Except BCC and meningioma	14/687 (2.0)	22/256 (8.6)	**6.4**	[2.5-16.4]	20/205 (9.8)	2/51 (3.9)	**6.3**	[2.4-16.9]	3.0	[0.4-20.0]
Bone mineral deficiency (2)	7 /106 (6.6)	4/57 (7.0)	2.9	[0.4-21.5]	2/42 (4.8)	2/15 (13.3)	1.4	[0.1-12.9]	6.9	[0.5-93.6]
Alopecia	5/687 (0.7)	27/256 (10.5)	**13.6**	[4.2-44.3]	14/205 (6.8)	13/51 (25.5)	**8.9**	[2.3-33.9]	**60.6**	[9.7-380.3]
Cardiac side effect	11/687 (1.6)	13/256 (5.1)	1.0	[0.4-3.0]	9/205 (4.4)	4/51 (7.8)	1.2	[0.4-3.8]	1.4	[0.3-7.0]
Cataract	18/687 (2.6)	97/256 (37.9)	**28.9**	[14.9-55.7]	78/205 (38.0)	19/51 (37.3)	**25.9**	[13.0-51.8]	**54.8**	[18.0-166.9]
Severe neurological dysfunctions	12/687 (1.7)	10/256 (3.9)	2.0	[0.7-6.1]	8/205 (3.9)	2/51 (3.9)	1.8	[0.6-5.9]	2.0	[0.3-12.4]
Diabetes	1/687 (0.1)	5/256 (2.0)	**26.0**	[1.9-346.8]	4/205 (2.0)	1/51 (2.0)	**18.8**	[1.1-315.9]		
Metabolic syndrome (2)	12/202 (5.9)	14/96 (14.6)	**5.5**	[1.8-16.8]	9/74 (12.2)	5/22 (22.7)	3.6	[1.0-13.1]	**23.4**	[4.0-136.8]
Iron overload (3)	30/497 (6.0)	61/196 (31.1)	**5.3**	[2.6-10.6]	45/159 (28.3)	16/37 (43.2)	**5.7**	[2.7-12.3]	2.7	[0.8-9.0]
Osteonecrosis	9/687 (1.3)	15/256 (5.9)	**5.0**	[1.7-14.8]	5/205 (2.4)	10/51 (19.6)	2.0	[0.4-9.1]	**21.9**	[5.3-90.6]
Viral transmission	9/687 (1.3)	9/256 (3.5)	2.9	[0.7-11.1]	9/205 (4.4)	0/51 (0.0)	3.2	[0.8-12.5]		
At least one late event	443/687 (64.5)	231/256 (90.2)	**5.0**	[3.0-8.6]	183/205 (89.3)	48/51 (94.1)	**4.3**	[2.5-7.6]	**10.0**	[2.9-34.6]

CT indicates chemotherapy; HSCT, hematopoietic stem cell transplantation; Ora, adjusted Odds Ratio; CI, confidence interval; GH, growth hormone; BCC, basal cell carcinoma; CNS, central nervous system; cGVHD, chronic graft-versus-host disease.
n : number of patients w ho experienced the type of long-tem side effect N : number of patients with a valid information.
(1) N = assessable patients (2) N = assessable adults (3) N = serum ferritin dosage performed.
Bold values : ORa significant (value 1 w as out of CI95%).
* Reference group : chemotherapy. Co-variables: gender, leukaemia subtype, relapse, age at diagnosis, follow -up duration, CNS irradiation, decade of the start of treatment.

surviving all types of childhood cancer. Finally, our results are consistent with more recently published data on a smaller sample of patients receiving HSCT [12].

Our study provides insight on the effects of childhood acute leukemia and its treatment on QoL. First, when compared with patients treated without HSCT, the transplanted adult population reported a lower level of QoL for the dimensions describing physical well-being (physical functioning, bodily pain, general health perceptions), with significant effect sizes up to .48 for the physical composite score. However, no difference was found in the psychological composite score, as reported by Ishida et al. [11] on a smaller sample and Armenian et al. [12] using a nonstandardized QoL assessment. As suggested in our previous study [10], our current results reflect more precisely the long-term impact of sequelae on QoL in adults. They are consistent with previous findings that

Table 3
Effect of Treatment Modalities on QoL in Children and Adolescents (8-17 Years of Age) Reported by Their Parents: Multivariate Linear Regression Analyses

Subscales of VSP-Ap	Chemotherapy Group	HSCT Group	Comparison CT-HSCT*				HSCT Group		Comparison	
							without cGVHD (1)	with cGVHD (2)	CT-(1)*	CT-(2)*
	n = 251 mean ± s.d.	n = 77 mean ± s.d.	β	*P*	Adjusted-R^2	Effect size	n = 64 mean ± s.d.	n = 13 mean ± s.d.	*P*	*P*
Psychological well-being	74.8 ± 19.5	77.5 ± 18.6	0.10	.20	0.04	0.14	77.1 ± 18.6	79.4 ± 18.8	.35	.46
Body image	76.5 ± 29.5	66.2 ± 30.2	−0.06	.39	0.12	0.35	67.7 ± 29.1	58.8 ± 35.3	.50	.22
Vitality	72.5 ± 16.2	74.3 ± 16.3	0.07	.38	0.04	0.11	74.5 ± 15.6	73.1 ± 21.9	.74	.54
Physical well-being	73.1 ± 19.6	73.0 ± 20.3	0.04	.57	0.05	0.01	73.3 ± 20.7	71.6 ± 21.1	.58	.90
Leisure activities	63.2 ± 21.7	64.9 ± 23.2	−0.02	.78	−0.01	0.08	65.8 ± 23.0	60.1 ± 24.1	.49	.50
Relationships with friends	66.4 ± 20.3	67.9 ± 18.9	0.02	.82	0.00	0.07	67.7 ± 19.2	69.2 ± 18.2	.87	.39
Relationships with parents	75.3 ± 15.6	75.9 ± 14.4	0.06	.43	0.02	0.04	76.1 ± 14.7	74.8 ± 13.0	.50	.75
Relationships with teachers	68.9 ± 22.2	71.7 ± 18.5	0.16	**.04**	0.08	0.13	70.7 ± 19.3	77.1 ± 12.4	.13	.07
School work	72.0 ± 22.2	73.7 ± 21.4	0.12	.10	0.05	0.08	72.6 ± 22.4	78.8 ± 14.8	.22	.12
Summary score	71.4 ± 12.5	71.7 ± 12.9	0.07	.36	0.09	0.02	71.7 ± 12.7	71.5 ± 14.8	.54	.48
Relationships with medical staff	56.6 ± 34.6	62.1 ± 32.9	0.18	**.02**	0.04	0.16	61.7 ± 33.7	64.4 ± 29.6	**.04**	.50

QoL indicates quality of life; HSCT, haematopoietic stem cell transplantation; s.d., standard deviation; β, standardised β-coefficients; CNS, central nervous system; cGVHD, chronic graft-versus-host disease.
Bold values: $P < 0.05$ was significant.
* Reference group: chemotherapy. Co-variables: gender, leukaemia subtype, relapse, age at diagnosis, follow-up duration, CNS irradiation, decade of the start of treatment.

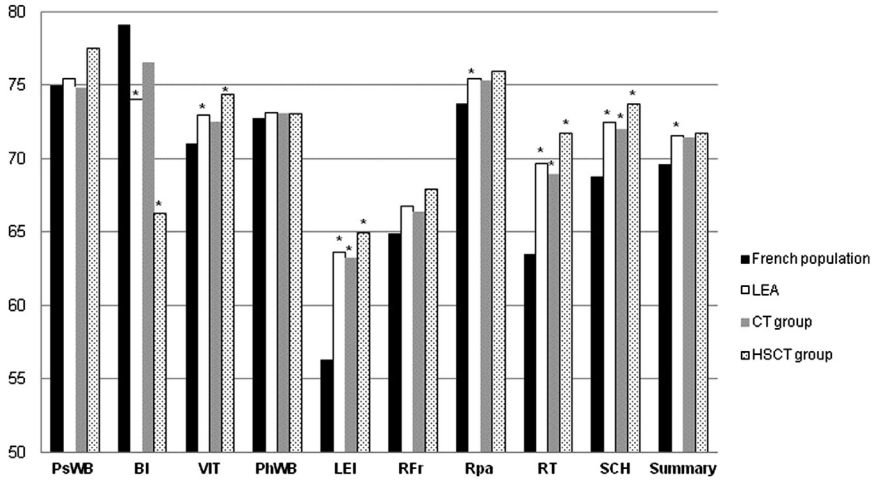

Figure 1. Comparison of the QoL assessments by the parents of the LEA survivor cohort of children and adolescents (8-17 years old) and of a French population sample (VSP-Ap). *French population reference group $P < .05$ paired for age and sex. LEA indicates parents of the cohort's children and adolescent (8-17 years old) survivors; CT, chemotherapy; PsWB, psychological well-being; BI, body image; VIT, vitality; PhWB, physical well-being; LEI, leisure activities; RFr, relationships with friends; Rpa, relationships with parents; RT, relationships with teachers; SCH, school work.

a sufficient time frame from diagnosis is required to entirely observe the negative effects of the treatment on survivors' health [25,31-33]. The HSCT population reports low levels of physical QoL , as reported by Ishida et al. [27] or in more heterogeneous samples, including nontransplantation cancer patients [34-36]. Interestingly, all survivors of our study, regardless of the therapeutic management, reported levels of psychological well-being (mental composite score) significantly below the general population norms. Similar results were not reported by a Finnish study [37] or by studies issued from the Canadian Childhood Cancer Surveillance and Control Program [38], the British Childhood Cancer Survivor Study [31], and the CCSS [39]. However, these results are consistent with those reported by Hudson et al. [13] comparing adults who experienced childhood leukemia with the general population. This notable impact on psychological well-being should be taken into account during the follow-up of survivors in the future.

In the adolescent population, transplantation survivors QoL assessed by their parents was better than in the chemotherapy group, although the effect size is small. To our knowledge, no other results comparing these two populations on QoL are currently available. Surprisingly, parents of leukemia survivors, whatever the treatment modality, report a higher level of QoL for their child than parents of the general pediatric population, except for the perception of body image that seems to be altered early by the experience of leukemia.

The impact of HSCT on QoL in childhood leukemia survivors, based on in-depth assessments with well-developed questionnaires [19], is poorly explored in the literature [40]. Perkins et al. [41] did not show a significant difference in the level of QoL between 17 children who underwent grafting and the standardized norms, whereas Forinder et al. [42] did report a lower QoL among children who underwent HSCT for specific dimensions, such as bodily pain, general health, and self-esteem, although the general behavior was higher. Our

Table 4
Effect of Treatment Modalities on QoL of Adults: Multivariate Linear Regression Analyses

Subscales of SF-36	Chemotherapy Group	HSCT Group	Comparison CT-HSCT*				HSCT Group		Comparison	
							without cGVHD (1)	with cGVHD (2)	CT-(1)*	CT-(2)*
	n = 296 mean ± s.d.	n = 137 mean ± s.d.	β	*P*	Adjusted-R^2	Effect size	n = 108 mean ± s.d.	n = 29 mean ± s.d.	*P*	*P*
Physical functioning	93.0 ± 15.7	88.1 ± 18.6	−0.15	**.01**	0.04	0.31	89.5 ± 18.5	82.8 ± 18.5	.14	**.004**
Social functioning	80.4 ± 22.1	75.8 ± 23.6	−0.05	.41	0.02	0.21	75.9 ± 23.8	75.4 ± 23.3	.58	.59
Role: physical	88.8 ± 24.2	80.6 ± 31.8	−0.11	.08	0.07	0.34	82.3 ± 29.6	74.1 ± 38.7	.25	.09
Role: emotional	72.2 ± 26.5	70.1 ± 30.9	0.00	.98	−0.01	0.08	69.8 ± 30.1	71.3 ± 34.2	.68	.66
Mental health	67.9 ± 18.8	67.8 ± 17.9	0.06	.30	0.03	0.01	68.0 ± 17.8	67.3 ± 18.8	.18	.67
Vitality	62.3 ± 19.5	61.4 ± 19.6	−0.04	.57	0.03	0.05	61.7 ± 19.7	60.4 ± 19.4	.63	.57
Bodily pain	83.7 ± 22.3	76.9 ± 24.1	−0.14	**.02**	0.05	0.3	78.6 ± 23.9	70.6 ± 24.2	.14	**.01**
General health	75.3 ± 21.1	66.6 ± 22.3	−0.21	**.001**	0.06	0.41	69.1 ± 21.8	57.5 ± 22.0	**.04**	**<.001**
Physical composite score	55.4 ± 7.1	52.0 ± 8.4	−0.25	**<.001**	0.10	0.48	53.0 ± 7.8	48.2 ± 9.6	**.003**	**<.001**
Mental composite score	45.1 ± 9.9	45.4 ± 10.0	0.08	.23	0.01	0.03	45.2 ± 9.6	46.4 ± 11.4	.21	.27

QoL indicates quality of life; HSCT, haematopoietic stem cell transplantation; s.d., standard deviation; β, standardised β-coefficients; CNS, central nervous system; cGVHD, chronic graft-versus-host disease.
Bold values: $P < 0.05$ was significant.
* Reference group: chemotherapy. Co-variables: gender, leukaemia subtype, relapse, age at diagnosis, follow-up duration, CNS irradiation, decade of the start of treatment.

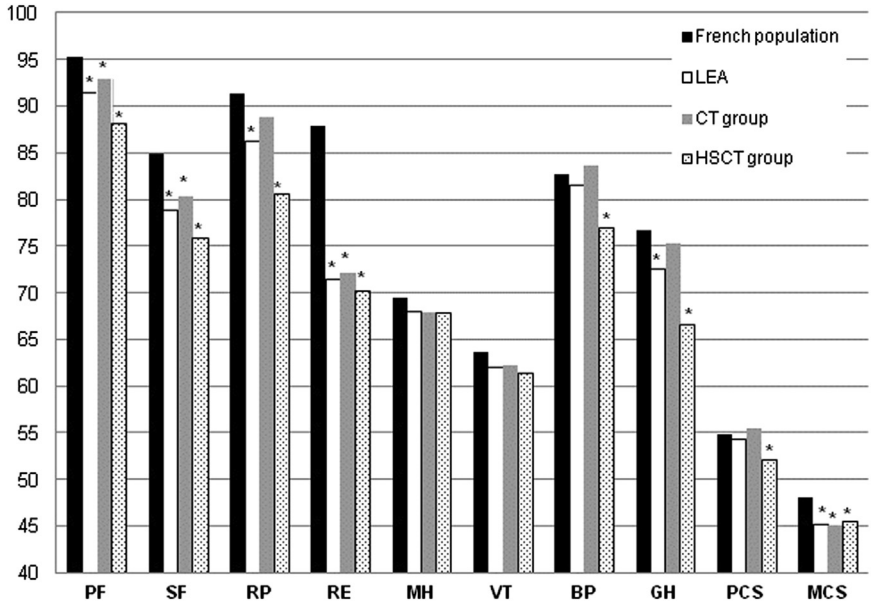

Figure 2. Comparison of the assessment of QoL of the LEA cohort adult survivors and a French population sample (SF-36). *French population reference group $P < .05$ paired for age and sex. LEA indicates adult survivors; CT, chemotherapy; PF, physical functioning; SF, social functioning; RP, role limitations due to physical health problems; RE, role limitations due to emotional problems; MH, general mental health; VT, vitality; BP bodily pain; GH, general health perception; PCS, physical composite score; MCS, mental composite score.

results are consistent with those found in the CCSS, comparing the levels of QoL of children having experienced leukemia with standardized data [43] as well as with results reported by Pogorzola et al. [44]. However, Shankar et al. [45] did not observe a significant effect.

Parental reports of QoL in young survivors demonstrates little difference between treatment groups and higher scores when compared with French norms. The adult evaluation of QoL, however, shows significant differences between treatment groups and overall decreased scores when compared with French norms. There are several possible explanations for the difference between adult survivor perceptions and those of parents of children. First, the point of view expressed is not the same, because the QoL assessment of adult survivors is self-reported, whereas the QoL assessment of child survivors is proxy-reported. Second, cognitive adaptation and coping may also explain this difference in results depending of the age of survivors. Fertility concerns, such as hypogonadism, could be experienced differently in adulthood than in younger survivors, for instance. Finally, since 1980, changes in treatment of acute leukemia occurred, and younger survivors are more likely to have received improved treatment modalities. However, we included the decade of the start of treatment in our multivariate models, as an adjusted variable, to take into account the impact of this evolution in treatment over time.

Occurrence of posttransplantation cGVHD is a potentially devastating complication, which could influence both physical sequelae and QoL. This might explain in part the differences observed between the transplanted and nontransplanted groups. We explored this hypothesis in secondary analyses by dividing the transplanted group according to whether or not posttransplantation cGvHD occurred (Tables 2, 3, and 4). Transplanted survivors with cGVHD had a higher risk of having late effects and reported a more altered QoL. Overall, however, the long-term health status of both subgroups of transplanted survivors (with or without experiencing cGVHD) was adversely affected when compared with survivors receiving chemotherapy only.

Quality of data collected in this study can be analyzed. First, a high response rate was observed in the study, and no significant differences were found between respondent and nonrespondent patients regarding demographic and clinical characteristics. Furthermore, although the sample size is smaller than those examined in the most complete national cohorts performed thus far [25,31], it remains significantly larger than those reported in most studies involving the same age group [38,43,44,46] or specifically comparing the long-term impact of HSCT versus conventional treatment among childhood leukemia survivors [11,12].

The main aim of this study was to report the results of a longitudinal French cohort on childhood leukemia survivors. Several cohorts of childhood cancer survivors have been established. The CCSS remains the most important cohort [47-49] to report health status based mainly on patient self-reported outcomes, whereas the LEA study is based on clinical assessments. Although several previous studies have explored the late effects and QoL in long-term survivors of childhood cancer, there are several potential limitations to these studies [50-54]: the population studied was not limited to leukemia survivors and thus was less homogeneous, the assessment was focused on a specific age class, QoL measures were compared with a controversial control group such as siblings or patients suffering from other diseases, and there were limited samples of transplanted patients [11,12]. In contrast, the LEA cohort, which includes patients diagnosed since 1980, allows the study of a large sample of patients who have undergone HSCT. Nevertheless, given the type of transplantation and the time frame of therapy, the population is relatively heterogeneous. We have taken this point into account in our multivariate models, and further analyses are in progress to explore the long-term health and QoL of specific subgroups within the LEA cohort, especially differences between allogeneic and autologous transplantation.

The study found that the population of transplantation survivors had a higher risk of late effects compared with survivors treated without HSCT. As a result, adulthood physical well-being decreased. Whether the patients were treated with HSCT or not, adults surviving childhood leukemia reported lower scores on psychological domains of QoL than the normal population. These findings should be better taken into account by healthcare providers.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbmt.2013.04.015.

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