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The PETALE study: Late adverse effects and biomarkers in childhood acute lymphoblastic leukemia survivors

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Abstract

Background: Childhood cancer survivorship issues represent an established public health challenge. Most late adverse effects (LAEs) have been demonstrated to be time and treatment dependent. The PETALE study is a multidisciplinary research project aiming to comprehensively characterize LAEs and identify associated predictive biomarkers in childhood acute lymphoblastic leukemia (cALL) survivors.

Methods: cALL survivors treated at Sainte-Justine University Health Center with Dana-Farber Cancer Institution-ALL protocols 87-01 through 2005-01 were eligible. During Phase I of the study, the participants underwent comprehensive clinical, biologic, and psychosocial investigation targeting metabolic syndrome, cardiotoxicity, bone morbidity, neurocognitive problems, and quality of life issues. Whole-exome sequencing was performed for all participants. Subjects identified with an extreme phenotype during Phase I were recalled for additional testing (Phase II).

Results: Phase I included 246 survivors (recall rate 71.9%). Of those, 85 participants completed Phase II (recall rate 88.5%). Survivors agreeing to participate in Phase I (n = 251) were similar to those who refused (n = 31) in terms of relapse risk profile, radiotherapy exposure, and age at the time of study. Participants, however, tended to be slightly older at diagnosis (6.1 vs. 4.7 years old, $P = 0.08$), with a higher proportion of female agreeing to participate compared with males (93.2 vs. 86.5%, $P = 0.07$).

Conclusion: The PETALE study will contribute to comprehensively characterize clinical, psychosocial, biologic, and genomic features of cALL survivors using an integrated approach. Expected outcomes include LAE early detection biomarkers, long-term follow-up guidelines, and recommendations for physicians and health professionals.

KEYWORDS

acute lymphoblastic leukemia, biomarkers, childhood cancer, late adverse effects, next-generation sequencing, survivorship

Abreviations: ALL, acute lymphoblastic leukemia; BMC, bone mineral composition; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; cALL, childhood ALL; CNS, central nervous system; DEXA, dual energy X-ray absorptiometry; EP, extreme phenotype; GC, glucocorticoid; HDL-C, high-density lipoprotein cholesterol; HSCT, hematopoietic stem cells transplant; LAE, late adverse effect; LDL-C, low-density lipoprotein cholesterol; LTFU, long-term follow-up; MRI, magnetic resonance imaging; MTX, methotrexate; NGS,

1 | INTRODUCTION

The cure rates of childhood acute lymphoblastic leukemia (cALL) are now reaching 90%[1] and, consequently, survivors represent a growing population. According to the latest estimates from the American Cancer Society, "approximately 1 in 530 young adults between the age of 20 and 39 years is a childhood cancer survivor."[2] It is well established that survivors are at higher risk of mortality[3] and morbidity,[4] with an increasing probability of suffering from disabling treatment-related late adverse effects (LAEs) with time.[5]

Numerous LAEs have been linked to specific anticancer drugs and radiation therapy exposure.[6] Indeed, cALL survivors are at higher risk of developing one or several metabolic syndrome determinants including obesity,[7] insulin resistance,[8] hypertension,[9] and dyslipidemia.[10] Anthracyclines have been linked to cardiotoxicity in a dose-dependent manner.[11] Musculoskeletal morbidities can be caused by the osteotoxic drugs methotrexate (MTX) and glucocorticoids (GCs),[12,13] while altered bone growth and development can affect bone strength and compromise bone health years later.[14] Muscle disuse, inadequate nutrition, and radiotherapy exposure can also be among the contributive risk factors.[15,16] A significant subset of cALL survivors is likely to suffer from neuropsychological deficits,[17] whether or not they have been exposed to radiation therapy.[18] Finally, cALL survivors have been shown to be a particularly vulnerable subgroup with respect to quality of life (QoL) issues (distress, anxiety, etc.) and social milestones achievements (education, employment, marriage, etc.).[19]

Our team has designed and implemented the PETALE study, which is a multiphase cALL survivor cohort study based at Sainte-Justine University Health Center (SJUHC, Montréal, Canada). Our design combines extensive clinical, biologic, and psychosocial profiling in addition to whole-exome sequencing (WES). Our aims are to (1) characterize early-onset LAEs in a young population of cALL survivors; (2) identify predictive biochemical, clinical, and genetic biomarkers associated with unfavorable LAE risk profiles; and (3) propose guidelines and interventions mitigating LAE apparition and severity.

2 | METHODS

Our integrated multidisciplinary team is composed of experts in cardiology, exercise science, biochemistry, nutrition, neuropsychology, psychiatry, psychology, neuroimaging, hematology-oncology, endocrinology, pharmacology, pharmacogenetics, genomics, bioinformatics, statistics, and epidemiology. Our institution has been a member of the Dana-Farber Cancer Institution (DFCI)-ALL consortium since 1987. Several members of our team previously collaborated to our ongoing oncogenomics research program in childhood leukemia (QcALL study).

2.1 | Eligibility and recruitment

Eligible participants (detailed eligibility criteria is available in Box 1) were diagnosed with cALL and treated according to DFCI-ALL protocols 87-01 to 2005-01 at SJUHC. Briefly, event-free patients at who have not suffered from refractory ALL, relapsed, or received a hematopoietic stem cells transplant 5 years or more after diagnosis were eligible. A total of 434 potential participants were initially identified based on these criteria. The sample target was set at 250 participants, assuming a conservative recruitment rate of nearly 60%. The project was evaluated and approved by our Institutional Review Board. To optimize free consent, eligible patients were first contacted by phone by a clinical research coordinator previously unknown to them. For patients less than 18 years old, the parents were contacted first. Details of the study objectives and inclusion/exclusion criteria were explained over the phone. An informed consent form was mailed to those interested in the project, and a follow-up phone appointment was made. To facilitate recruitment, appointments were made to coincide with participants' annual visit to the long-term follow-up (LTFU) clinic, if applicable. Compensation for participation included an information package with personalized recommendations based on tests results, along with an allocation covering meals and parking fees.

PHASE I

Main goals

- Assess the prevalence of most common LAE of cancer treatments with respect to cardiac toxicity, bone morbidity, neurocognitive effects, cardiometabolic problems and quality of life issues.
- Characterize LAE-associated genetic components.
- Identify predictive clinical, genetic and biochemical biomarkers for LAE.

Eligible participants

- Patients of European origin having received an ALL diagnosis between 1987 and 2010, while at the age of < 19 years old.
- Having received treatments at our institution following DFCI-ALL protocol 87-01, 91-01, 95-01, 2000-01 or 2005-01.
- Being ≥ 5 years post-diagnosis.
- Having provided informed consent if ≥ 18 years old, or having provided assent and parental informed consent if < 18 years old.
- Patients unable to cooperate, who underwent hematopoietic stem cells transplant, who relapsed, who suffered from refractory ALL, with congenital bone disease or who received osteotoxic drugs for non-ALL disease were excluded from the study.

PHASE II

Main goals

- Further investigate the extent of LAE and genetic risk profiles.
- Identify predictive clinical, genetic and biochemical biomarkers for LAE.

Eligible participants

Participants identified during Phase I as those presenting the best and the worst outcomes with respect to LAE in each of the above mentioned categories (referred to as 'Extreme phenotypes').

BOX 1 PETALE Research Program. Details of Phase I and Phase II specific goals and eligibility criteria

2.2 | Data collection and biobanking

The PETALE study was structured in two phases (Box 1). In Phase I, the aim was to assess LAE prevalence and associated variables while identifying participants presenting an "Extreme phenotype" (EP). Briefly stated, EP participants were those showing either the best outcomes (i.e., healthiest) or the worst outcomes in terms of LAEs at the follow-up. A detailed list of Phase I tests and questionnaires, which required participants' availability for an entire day (7:00 a.m. to 5:00 p.m.), is found in Supplementary Table S1. Importantly, tests assessing neurocognitive skills were performed early in the day to minimize potential fatigue effects. Participants with the most important morbidities

next-generation sequencing; QoL, quality of life; SJUHC, Sainte-Justine University Health Center; TC, total cholesterol; TG, triglycerides; WES, whole-exome sequencing

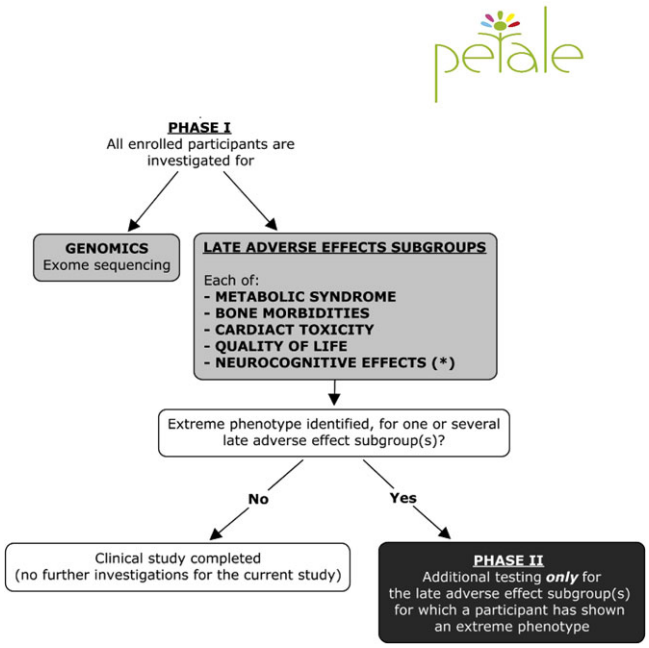

FIGURE 1 PETALE study flowchart. All eligible participants complete Phase I tests and analyses specific to the five working groups. (*) Of note, patients from protocols 91-01 and 95-01 undergo on the same occasion an additional time-point evaluation to pursue an ongoing longitudinal study on neurocognitive effects. Blood samples are collected during Phase I for WES and genetic association studies. Participants with extreme phenotypes identified in Phase I are eligible for Phase II tests and analyses

were identified as "EP-positive," while the healthiest were referred to as "EP-negative." Combined with the WES data, this extreme phenotype sampling approach is particularly suitable to uncover genetic variants associated to, or predictive of, LAEs.[20,21] Furthermore, it will provide an extensive, high-quality sequence variation database for upcoming studies. Only participants identified as presenting an EP for at least one of the working groups were eligible for the second phase of the study (Phase II; Fig. 1) in which identified morbidities were further characterized (Supplementary Table S1). In addition to the information package containing personalized recommendations based on tests results, appropriate referral resources had been planned by each working group for clinically actionable LAEs and incidental findings.

Biobanking protocols and procedures were as per our QcALL biobanking project.[22] Briefly, a blood sample was drawn using 21-G gauge BD Vacutainer Safety-Lok Blood Collection Set (BD, Mississauga, Canada) and aliquots were immediately stored at -80 °C. DNA collected from salting-out extractions was collected in TE-low buffer. WES was achieved on an Illumina HiSeq2500 sequencer (Illumina, San Diego, USA) using Agilent SureSelect Clinical Exome (Agilent Technologies, Santa Clara, USA) or Nextera Rapid Capture Exome Enrichment (Illumina, San Diego, USA). For participants already sequenced as part of the QcALL cohort (n = 83), a SOLiD 4.0 sequencer (ThermoFisher Scientific, Waltham, USA) and an Agilent SureSelect XT All Exon V4 exome capture kit (Agilent Technologies, Santa Clara, USA) were used.

2.3 | Statistical analyses

Descriptive (Table 1) and univariate statistical analyses performed to compare participating and nonparticipating subpopulations were completed using SPSS (Version 17.0). Detailed statistical power calculations for multiple linear regression are available in Supplementary Table S2.

2.4 | Metabolic syndrome

The prevalence of metabolic syndrome components (obesity, insulin resistance, hypertension, dyslipidemia) in Phase I participants was determined as previously reported.[23] Insulin was measured using an ultrasensitive Access Immunoassay System (Beckman Coulter, CA, USA), glucose was measured by the glucose oxidase method, and lipids—triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) concentrations—were determined enzymatically on a Synchron LX® 20 (Beckman Coulter, Brea, USA) with Beckman Instruments reagents. Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated according to the Friedewald equation. Non-HDL-C concentrations were obtained by subtracting the HDL-C from the TC concentrations. Apolipoproteins A-I and B were appreciated using commercial kit. Nondenaturing 2–16% polyacrylamide gradient gel electrophoresis was used to characterize LDL particle size distribution, as previously described.[24] The presence of oxidative stress and lipid peroxidation markers (malondialdehyde, protein carbonyls, oxidized LDL, 8-hydroxy-2′-deoxyguanosine), as well as the endogenous antioxidant defense (superoxide dismutase, catalase, glutathione peroxidase) along with antioxidant vitamins (α-tocopherol, γ-tocopherol, β-carotene, retinol) were assessed in fasting plasma and erythrocytes by high performance liquid chromatography (HPLC), gas chromatography/mass spectrometry (GC-MS), and enzymatic assays. ELISA commercial kits were employed to estimate low-grade and visceral inflammation (C-reactive protein (CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-6, adiponectine, leptin, resistin, PAI-1, visfatin), whereas participants' vascular endothelium integrity was evaluated through echographic measurement of carotid artery intima-media thickness and analysis of cell adhesion molecules (ICAM, VCAM, E-selectin) by commercial ELISA kits. Dietary intakes were assessed using a validated interviewer-administered food frequency questionnaire specific for our population combined with a 3-day food record. In Phase II, EP-positive and EP-negative participants were subsequently compared regarding their glucose tolerance and HDL functionality, lipidomic, and proteomic profile. Participants' microbiome taxonomic composition and diversity was determined following stool DNA isolation and 16S v4 region amplification and sequencing using the open-source Quantitative Insights Into Microbial Ecology v.1.6.0 toolkit (QIIME; http://qiime.org/).

2.5 | Cardiotoxicity

Phase I participants were questioned and examined for symptomatic heart failure according to New York Heart Association functional criteria.[25] Current use of medication modulating cardiovascular state was noted. Physical activity questionnaires were administered by

TABLE 1 Participants' sociodemographic characteristics

DFCI protocol	87-01	91-01	95-01	2000-01	2005-01	Combined
Participants, n (%)[a]	24 (9.8)	47 (19.1)	73 (29.7)	76 (30.9)	26 (10.6)	246 (100)
Gender						
Female, n (%)	14 (58.3)	22 (46.8)	33 (45.2)	42 (55.3)	13 (50.0)	124 (50.4)
Male, n (%)	10 (41.7)	25 (53.2)	40 (54.8)	34 (44.7)	13 (50.0)	122 (49.6)
Ethnicity						
European, n (%)	23 (95.8)	46 (97.9)	68 (93.2)	72 (94.7)	26 (100)	235 (95.5)
Other, n (%)	1 (4.2)	1 (2.1)	5 (6.8)	4 (5.3)	0 (0)	11 (4.5)
Highest education level achieved[b]						
High school not completed, n (%)	5 (20.8)	6 (12.8)	22 (30.1)	51 (67.1)	14 (53.8)	98 (39.8)
High school, n (%)	6 (25.0)	17 (36.2)	30 (41.1)	11 (14.5)	6 (23.1)	70 (28.5)
College, n (%)	9 (37.5)	16 (34.0)	14 (19.2)	7 (9.2)	5 (19.2)	51 (20.7)
University, n (%)	4 (16.7)	8 (17.0)	7 (9.6)	7 (9.2)	1 (3.8)	27 (11.0)
Average age at diagnosis (SD of distribution)	5.9 (4.6)	5.5 (4.7)	5.6 (4.4)	5.7 (4.1)	10.3 (4.4)	6.1 (4.6)
Average number of years after diagnosis (SD of distribution)	23.9 (1.6)	21.0 (1.3)	15.9 (2.0)	11.7 (1.8)	7.4 (1.4)	15.5 (5.2)
Average age at Phase I (SD of distribution)	29.7 (4.5)	26.5 (4.5)	21.5 (5.3)	17.5 (4.4)	17.8 (4.1)	21.6 (6.3)

[a]Participants meeting all inclusion criteria and having completed Phase I.
[b]Including all participants having completed Phase I and meeting all inclusion criteria. The young age of some participants at study enrollment must be taken into account, as those from latest treatment protocols may not have completed their highest education level yet.

an exercise physiologist to estimate daily physical activities and energy expenditure using the Minnesota Leisure Time Physical Activity Questionnaire, the Tecumseh Self-Administered Occupational Physical Activity Questionnaire, and the general questions on sedentary activities, as previously used by Conway et al.[26] Echographic measurement of cardiac function and structures were collected. Wall stress and circumferential fiber-shortening measurements were used to evaluate a load-independent index of ventricular function. Furthermore, participants underwent an incremental exercise test where gas exchange data, 12-lead ECG, cardiac hemodynamic, and muscle oxygenation were measured in accordance with the McMaster Protocol for children and adults.[27] Noninvasive cardiac hemodynamic parameters were obtained by impedance cardiography during the exercise session. Near-infrared spectroscopy was used to obtain tissue oxygen saturation, muscular hemoglobin, blood flow, and muscle oxygen levels. Finally, NT-pro BNP level was measured and a 24-hr Holter recording was obtained. For Phase II participants (Supplementary Table S1), ventricular volumes, myocardial properties, and extent of left ventricle fibrosis were quantified by magnetic resonance imaging (MRI) using a Skyra Siemens 3 Tesla imaging system, based on a previously established protocol.[28]

2.6 | Bone morbidity

In addition to general exclusion criteria described above, participants with hereditary bone diseases, sickle-cell anemia, Legg–Calvé–Perthes disease, or ongoing treatment with GCs, heparin, or osteotoxic agents were excluded from the bone morbidities assessments. Lateral thoracolumbar spine radiographs were obtained for all patients with vertebral fracture assessment based on the Genant semi-quantitative method from T4 to L4.[29] Lumbar and total body bone mineral density (BMD) and bone mineral content (BMC) were measured by dual energy X-ray absorptiometry (DXA) using a GE Lunar prodigy device. Radius and tibia bone structure and strength were measured by peripheral quantitative computed tomography (pQCT) using a XCT 2000 scanner (Stratec Inc., Pforzheim, Germany). Of note, DXA-based BMD and BMC data from previous follow-up were available for a subset of our QcALL cohort (n = 130), which will allow the study of bone mass accrual over time. Phase I data were intended to quantify the prevalence of low bone density, vertebral fractures, and muscle function deficit. A 6-min walk test, a muscle force and power assessment using a Leonardo Mechanograph Ground Reaction Force Platform (Novotec Medical GmbH, Pforzheim, Germany), and a Medup Linear electronic handheld dynamometer (Atlas Medic, Québec, Canada), as well as a daily activity energy expenditure estimation using a questionnaire were led by a kinesiologist and a physiotherapist. An endocrinologist reviewed the medical history and screened for metabolic, endocrine, and musculoskeletal complications, as well as calcium and vitamin D intake and status. On Phase II, EP-positive and EP-negative participants were compared for vertebral fracture associated to low bone density prevalence and asymptomatic osteonecrosis prevalence based on Phase II hip MRI evaluation. Finally, circulating serological levels of A2M protein, a validated biomarker of osteonecrosis in a rat model developed by collaborators,[30] were measured.

2.7 | Neurocognitive effects

Excluding those with a previously diagnosed neurological condition, Phase I participants were evaluated using questionnaires assessing behavioral problems, ADHD and executive functions, and underwent neuropsychological tests contributing to the DIVERGT battery.[31] Phase II participants were tested using a more extensive neuropsychological battery and participated in magneto/electroencephalographic studies, as well as in anatomical and functional

MRI studies (all tests/studies performed are listed in Supplementary Table S1). These tests and studies mainly focused on the functional and anatomical substrates of attention and short-term and working memory. Of note, this neuropsychological evaluation represents an additional time point in an ongoing longitudinal study involving DFCI-ALL 91-01 and 95-01 survivors,[32] while it is the first done for DFCI-ALL 87-01, 2000-01, and 2005-01 survivors.

2.8 | QoL impact

Self-reported questionnaires were used to assess QoL-related outcomes and associated psychosocial factors of interest (Supplementary Table S1). During Phase I, measures of health status (15D-16D-17D) and perceived QoL (PedsQL generic) yielded a description of physical, emotional, social, and school/work dimensions. A specific focus on mood evaluation by assessment of anxiety, depression, and mixed distress, while emotionality and trauma-related symptoms and concerns toward cancer and cancer recurrence were also addressed. The BYI-Anxiety and Depression modules were administered to participants under 19 years old, while the BSI-18, BAI, and BDI-II were administered to adult participants. If the measures of anxiety and depression on these instruments exceeded the cut-off points for clinical or moderate depression, anxiety, or distress, the participant was invited to complete Phase II investigations. As a cross-validation mean of Phase I diagnoses, standardized screening tools were then used to confirm susceptibility for mood disorders (GAD-7, PHQ-9). In addition, the DRS/DT and PANAS/PANAS-C were used to ascertain diagnostic consistency over time. Phase II questionnaires additionally assessed potential factors and mediators of the previously identified mental health issues, namely unmet needs, well-being deficits, emotional approach coping, suppression and reappraisal strategies, affect intensity, and social support.

3 | RESULTS/DISCUSSION

To reach the recruitment target of 250 participants, a total of 342 survivors were contacted. Two hundred and forty-six participants had completed Phase I tests and evaluations (Fig. 1), while 31 declined to participate, corresponding to a 71.9% recall rate. Lack of time or interest was the main reason for refusal. Sixty survivors were either lost to follow-up or living abroad, representing 13.8% of the 434 survivors initially identified as eligible. Nineteen survivors were excluded because of either severe psychiatric disorder or relapse after their transfer to adult care. Five additional participants were excluded from analyses because of missing data (one patient), or administration of other treatment protocols prior to receiving a DFCI protocol (four patients). For those defined as EP for at least one of the working groups, 85 out of 96 participants accepted to take part in Phase II, representing an 88.5% recall rate.

Participants' sociodemographic characteristics are detailed in Table 1. Eligible survivors agreeing (n = 251) and refusing (n = 31) to participate in Phase I were slightly different in terms of age at diagnosis (6.1 vs. 4.7 years old; $P = 0.08$) but similar with respect to relapse risk profile ($P = 0.13$), proportion of participants exposed to radiotherapy ($P = 0.32$), age at participation (21.7 vs. 21.6 years old; $P = 0.95$), and the number of years from diagnosis to study participation (15.5 vs. 17.0 years; $P = 0.14$). A nearly significant higher proportion of males refused to take part in the study ($\%_{refusal}$ females = 6.8 vs. $\%_{agree}$ females = 93.2; $\%_{refusal}$ males = 13.5 vs. $\%_{agree}$ males = 86.5; χ^2, $P = 0.07$).

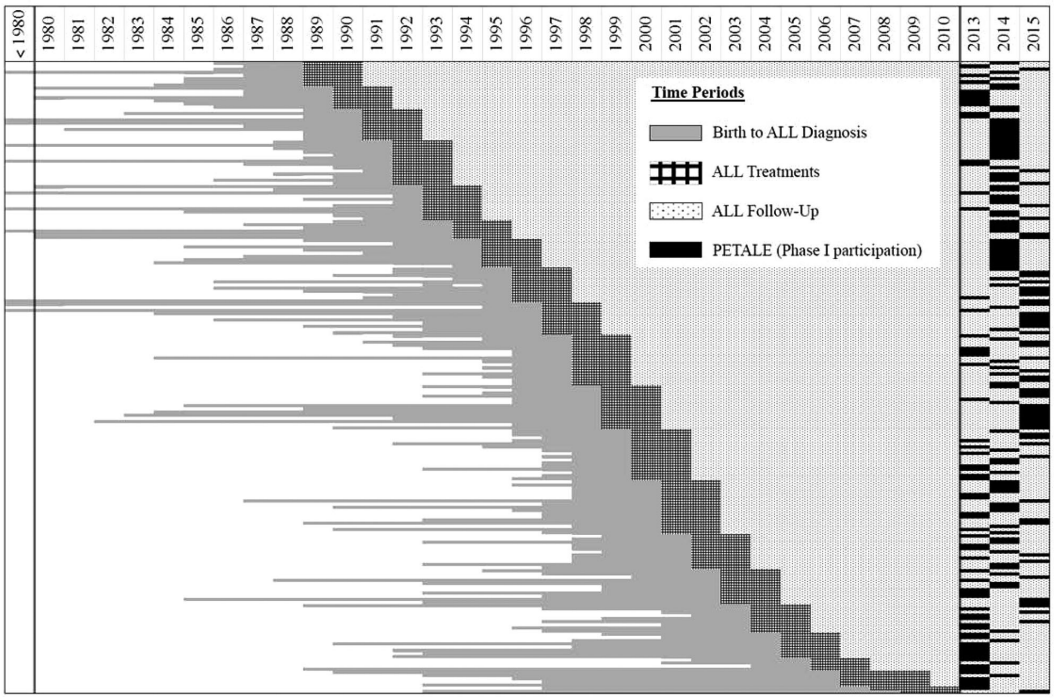

FIGURE 2 PETALE study participant timeline. Each line represents a single participant (n = first 200 patients, to illustrate time global time frame coverage)

The PETALE study aims to comprehensively characterize clinical, psychosocial, biologic, and genomic features of cALL survivors using an extensive evaluation. The multidisciplinary nature of our team fosters close interaction and synergy in hypotheses generation and data analysis. This study was carefully planned and designed to optimize high-quality data collection in a restricted time frame to facilitate participation. Our comprehensive and integrative approach will certainly lead to specific hypotheses and models that could not be otherwise tested.

As an example, the role of oxidative stress exposition and modulation in explaining LAE prevalence heterogeneity in survivors will be assessed. Indeed, panels of oxidative stress, inflammation, and antioxidant biomarker will be central to the analyses of several outcomes. The genetic contribution of protective antioxidant capacity and pro-oxidative pathways[33] has been well demonstrated in the development of metabolic syndrome, emphasizing these interesting and relevant starting points to define and predict ALL survivors' individual susceptibility. Exacerbated oxidative stress could also be central to anthracyclin-associated cardiotoxicity by mediating disturbances in diastolic and systolic function, pathologic cardiac remodeling, and increased wall stress.[34,35] Furthermore, oxidative stress could also mediate the irradiation-associated musculoskeletal morbidities by inhibiting osteoblast differentiation and mineralization, as well as skeletal muscle dysfunctions.[36,37] Finally, oxidative damage could underlie neuropsychological LAE,[38] and some genetic determinants of oxidative damage susceptibility have already been identified.[32,39,40]

A pivotal role for genetics in explaining LAE prevalence heterogeneity in survivors has been proposed.[41] However, relevant association studies so far remain scarce and are derived from the candidate genes approach.[42] Evidences suggest that multiple common and rare variants, rather than a few specific genes, could form the underlying genetic architecture of a wide range of diseases.[43] In addition to association studies confirming a role for lifestyle changes in mitigating some LAEs,[44] a genetic risk profile-based approach could allow treatment personalization to minimize molecular and cellular damages upstream of LAE apparition.[41,42] In this context, next-generation sequencing (NGS) is expected to be more informative than other genetic data analysis approaches. The PETALE study will be among the first childhood cancer survivor cohort for which such NGS information will be available.

The homogeneity of PETALE participants regarding treatments received and ethnic background is a significant advantage for association studies by reducing the number of confounding variables. Indeed, the PETALE cohort is comprised almost exclusively (>95%) of European-descent cALL survivors from the province of Québec, a population with an established genetic founder effect.[22,45] This feature lessens the confounding genetic background while preserving the single nucleotide polymorphisms variance expected in a less restricted population.[46]

Another methodological asset of our study is that biomedical data are collected by health professionals and not self-reported, thus avoiding underestimation by the participants, especially in youngsters.[47] Moreover, we make use of standard patient-reported outcomes such as QoL and fatigue. In addition, since acute toxicity may lead to significant doses discrepancies for some cALL patients[48] (Marcoux, Chapdelaine, Robaey, Sinnett, Krajinovic, Laverdière; submitted), both predicted and received drugs doses are retrieved from medical charts and will be considered in analyses.

The PETALE study's limitations include its monocentric design and relatively limited sample size as compared with other European and American cohorts.[49,50] These issues are counterbalanced by the excellent participation rate (71.9 and 88.5% for Phase I and Phase II, respectively), which significantly limits the potential issues associated with selection bias. Our high participation rate would also be a major asset in performing a follow-up study 5 years after Phase I, as we are currently considering to do so, making our study a longitudinal one. We also established collaborations with other groups analyzing survivorship cohorts to validate our upcoming findings. Extending the data collection to survivors of other types of childhood cancer would also be of interest in the future.

The design and execution of the PETALE study constituted a scientific journey from which many lessons have been learned. The implementation of an efficient and rapid communication and decision-making process was crucial to the success of this study. Monthly working meetings including project leaders, project coordinators, collaborators, technicians, and graduate students were key to idea exchanges, expertise sharing, critical thinking, and logistic problems resolution.

Recall rate was significantly affected by lost-to-follow-up patients, an issue that might be minimized in the future by follow-up clinics. Finally, many participants considered that the conception and distribution of personalized information packages detailing their comprehensive health status and providing related life habits recommendations was a significant incentive to participate.

The PETALE study offers a novel and comprehensive perspective on LAE predisposition factors and physiopathology in cALL survivors. It leverages high-quality data gathered by health professional coupled to WES, with the aim of generating integrated clinical, psychosocial, and genomic models of survivorship paths. In addition, the clinical data available from uninterrupted historical cohorts (Fig. 1) offer a unique opportunity to study LAE incidence evolution. Ultimately, we expect that our findings will contribute to LAE prevention and improved QoL for cALL survivors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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