BMJ Open

Traumatic stress symptoms in family caregivers of patients with acute leukemia: protocol for a multisite mixed methods, longitudinal, observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065422
Article Type:	Protocol
Date Submitted by the Author:	02-Jun-2022
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Keywords:	Leukaemia < HAEMATOLOGY, Leukaemia < ONCOLOGY, Adult palliative care < PALLIATIVE CARE, Paediatric palliative care < PALLIATIVE CARE, Anxiety disorders < PSYCHIATRY, QUALITATIVE RESEARCH

TITLE PAGE

Title of the article

Traumatic stress symptoms in family caregivers of patients with acute leukemia: protocol for a multisite mixed methods, longitudinal, observational study

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Word count: 3,397

ABSTRACT

Introduction The diagnosis, progression, or recurrence of cancer is often highly traumatic for family caregivers (FCs), but systematic assessments of distress and approaches for its prevention and treatment are lacking. Acute leukemia (AL) is a life-threatening cancer of the blood, which most often presents acutely, requires intensive treatment, and is associated with severe physical symptoms. Consequently, traumatic stress may be common in the FCs of patients with AL. We aim to determine the prevalence, severity, longitudinal course, and predictors of traumatic stress symptoms in FCs of patients with AL in the first year after diagnosis, and to understand their lived experience of traumatic stress and perceived support needs.

Methods and analysis This two-site longitudinal, observational, mixed methods study will recruit 223 adult FCs of pediatric or adult patients newly diagnosed with AL from 2 tertiary care centres. Quantitative data will be collected from self-report questionnaires at enrolment, and 1, 3, 6, 9 and 12-months after admission to hospital for initial treatment. Quantitative data will be analyzed using descriptive and machine learning approaches and a multi-level modelling approach will be used to confirm machine learning findings. Semi-structured qualitative interviews will be conducted at 3, 6, and 12-months and analyzed using a grounded theory approach.

Ethics and dissemination This study is funded by the Canadian Institutes of Health Research (CIHR #PJT 173255) and has received ethical approval from the Ontario Research Ethics Board (CTO Project ID: 2104). The data generated have the potential to inform the development of targeted psychosocial interventions for traumatic stress, which is a public health priority for high-risk populations such as FCs of patients with hematological malignancies. An integrated and end-of-study knowledge translation strategy that involves FCs and other stakeholders will be used to interpret and disseminate study results.

Keywords cancer; hematological malignancies; acute leukemia; supportive care; psychosocial intervention; traumatic stress; caregivers

ARTICLE SUMMARY

Strengths and limitations of this study

- This will be the first longitudinal study to examine traumatic stress symptoms and the related lived experience of family caregivers of patients diagnosed with acute leukemia.
- This study will include the family caregivers of patients of all ages and will provide an opportunity to understand the impact of patient age and relationship of the caregiver to the patient on caregivers' traumatic stress symptoms.
- The findings from this study will inform the development of a tailored psychosocial intervention to prevent and alleviate traumatic stress in this high-risk population.
- Limitations of this study include potential impact of the COVID-19 pandemic on recruitment and the potential for loss to follow-up in longitudinal research.

INTRODUCTION

Acute leukemia (AL) is a life-threatening hematological malignancy characterized by rapid onset, the requirement for immediate hospitalization to initiate care, and intensive and prolonged medical treatment. The primary types of AL are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Both occur in patients of all ages, but the epidemiology, disease features, and outcomes vary with age and disease type. Treatment of AL is associated with the risk of serious and potentially fatal side effects including bleeding, infection, mucositis, nausea and vomiting, pain, and multiple other drug-specific side effects.[1-3] There is now robust evidence showing that the diagnosis of AL in patients from infants to older adults is a singularly stressful event, followed by a period of intense and difficult life choices and experiences.[4-9] Those who are cured of AL may still endure long-term treatment sequelae including neurocognitive deficits, infertility, endocrine, musculoskeletal and cardiac impairments, and risk of secondary cancers.[6,10-14]

The impact of AL on family caregivers

The diagnosis of AL and its treatment impose a substantial burden on family caregivers (FCs), who may be partners, adult children, or parents.[7-9] FCs of patients with cancer are increasingly expected to assume lead roles in complex clinical tasks, such as coordination of care, symptom management, medication administration, and direct patient care, while maintaining other ongoing responsibilities, such as employment and care for other dependents.[15-23] These multiple roles, coupled with financial strain due to the cost of non-reimbursed medical care, travel, other family caregiving and home responsibilities, and the loss of employment income, are major sources of distress for FCs.[16,24,25] This burden of caring,[24] which falls disproportionately on women, [26] and the constant threat that a partner, parent, or child will suffer or die, constitute substantial threats to the mental and physical health of FCs.[27-29]

Traumatic stress symptoms

The immediate psychological response to the diagnosis of a life-threatening cancer of both patients and FCs is often traumatic stress (TS) symptoms.[4,5,28,30] These symptoms include hyperarousal (e.g., hypervigilance, decreased concentration, heightened startle response, insomnia, irritability), intrusive thoughts (e.g., nightmares, flashbacks, altered sense of reality), emotional detachment or numbing, and depression.[31,32] Symptoms of TS occurring within one month of the traumatic event may meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for acute stress disorder (ASD) and those that persist for longer than a month may meet diagnostic criteria for post-traumatic stress disorder (PTSD).[31] Risk factors for ASD and PTSD following a traumatic event include younger age, female sex, feminine gender role, and direct or vicarious exposure to traumatic events, including in first responders to trauma victims.[33-35] Gender is not only a risk factor for PTSD in its own right but is also a proxy for multiple interacting social, economic, and political influences on distress.[36] As a whole, traumatic stress disorders are highly disturbing to those affected and are associated with a subsequent ten-fold increase in the risk of completed suicide[37] and an increased risk of cardiovascular, metabolic, and musculoskeletal disorders[38] and all-cause mortality.[39]

The social context of traumatic stress symptoms

The social environment in which individuals exposed to trauma are situated has been shown to directly affect the severity and nature of TS symptoms.[36] In that regard, the inverse relationship between symptoms of PTSD and social support, including that received from healthcare

professionals (HCPs), is one of the most consistent relationships observed in trauma research.[40-42] Internalized representations of support and the capacity to make use of it, reflected in the construct of attachment security,[43] have also been shown to protect from the development of PTSD following exposure to trauma.[44] Measured on dimensions of attachment anxiety and attachment avoidance,[45,46] attachment security has been shown to play a critical role in the management of terror, specifically that related to death anxiety.[47]

Traumatic stress symptoms in family caregivers

Clinically significant TS symptoms are common in FCs of patients with metastatic cancer, with similar rates in partners and parents of patients.[28,48] Risk factors that have been identified for the development of TS in FCs of patients include: (i) FC variables such as female sex,[49] identification with traditionally feminine gender roles,[28,50] younger age,[27] less social support and less attachment security,[51] lower family income,[29] and higher perceived burden of caregiving tasks;[52,53] (ii) patient variables such as younger age[54] and greater disease severity;[55] and (iii) the nature of the caregiver-patient relationship,[56] with close familial relationships being associated with greater TS.[57,58]

Research has demonstrated the psychological impact of metastatic cancer on patients[59,60] and their FCs.[58] Several studies have highlighted the psychological impact of hematological malignancies on patients.[4,5,61] However, there has been little research attention to the psychological consequences of hematological malignancies on FCs, and systematic approaches to prevent and alleviate distress in this high-risk population have not been developed. The acute onset of AL, the intensive and prolonged treatment, the substantial burden of caregiving, and the uncertainty regarding clinical outcomes suggest that TS symptoms may be common in FCs. However, the prevalence, severity, and predictors of TS over time, and the experience of FCs of patients with AL across the life course have not been determined.

Study objectives

The objectives of the present study are to determine in FCs of patients with AL:

1. The prevalence, severity, longitudinal course, and predictors of TS symptoms over the first year following a new diagnosis of AL;
2. The FC experience of TS, including the impact of AL on their lives and that of their families, the nature of their distress, their relationship with HCPs, and their perceived resources and met and unmet support needs.

The findings from this study will provide essential information to inform research, clinical practice, and health policy regarding the comprehensive and family-centred treatment of AL.

METHODS AND ANALYSIS

Patient and public involvement

This study will be conducted with the early and ongoing engagement of FCs and other stakeholders. Specifically, our FC- and HCP-collaborators have informed the construction of this study, including the mixed methods approach and relevant sampling timepoints, will be closely involved in the interpretation and dissemination of the data, and will lead in advocacy efforts to support

policy change related to the care of FCs. The patient and family advisory councils at our study sites will also be engaged to support study conduct from implementation to dissemination.

Study design and setting

This is a prospective, observational study using mixed quantitative and qualitative methodology. FCs will be recruited from the Princess Margaret Cancer Centre, part of the University Health Network, and the Hospital for Sick Children, in Toronto, Canada.

Eligibility criteria

FCs will be: (i) the self-identified primary or co-primary caregiver (i.e., person assuming at least 40% of patient care activities) of a pediatric or adult patient newly diagnosed with primary AL (AML or ALL) within three months of admission to either of our study sites; (ii) ≥18 years old; and (iii) fluent in English.

Ineligibility criteria

FCs of patients with acute promyelocytic leukemia (APML) or who do not receive induction chemotherapy with curative intent will be ineligible.

Data collection

FC recruitment will occur over 36 months and is expected to be completed in 2024. Following informed consent, participating FCs will complete a demographics questionnaire and the disease-related characteristics of the associated patient will be abstracted from the patient's medical chart (Table 1). FCs will then complete a baseline outcome questionnaire package on REDCap (i.e., a secure online browser-based application for building and managing online surveys and research databases), and follow-up online outcome questionnaire packages at 1, 3, 6, 9 and 12-months after the patient's admission to the hospital for a new diagnosis of AL (Table 1). Questionnaire package completion time is expected to be 20-30 minutes at each assessment point. A subgroup of FCs will be invited to participate in audio- and/or video-recorded, semi-structured, qualitative interviews at 3, 6, and 12-months. Interviewees may participate in interviews at more than one sampling timepoint. Sampling for interviews will be purposeful in an attempt to achieve maximum variation in FC characteristics including age, sex, gender, gender role, FC-patient relationship, scores on quantitative measures, race, ethnicity, and patient's AL type. The interviews will be conducted by a trained interviewer and will focus on the FC experience of caring for someone with AL, the impact of caring on the lives of FCs and that of their families, FC met and unmet support needs, and the FC experience with the patient's treatment and HCPs (Table 2). Interviews are expected to last between 30-60 minutes.

Table 1. Timeline of study activities

	Enrollment Baseline	**1-Month** Follow-up Baseline*	**3-Months** Follow-up Baseline*	**6-Months** Follow-up	**9-Months** Follow-up	**12-Months** Follow-up
Recruitment						
Confirm Eligibility	✓	*	*			
Initial Approach	✓	*	*			
Caregiver Quantitative Informed Consent	✓	*	*			
Caregiver Qualitative Informed Consent			✓			
Patient Informed Consent/Assent**	✓	*	*			
Quantitative Data Collection						
Demographics	✓	*	*			
PCL-5	✓	✓	✓	✓	✓	✓
SASRQ	✓	✓	✓	✓	✓	✓
ECR-M16	✓	✓	✓	✓	✓	✓
PHQ-9	✓	✓	✓	✓	✓	✓
CRA	✓	✓	✓	✓	✓	✓
ESSI	✓	✓	✓	✓	✓	✓
FAMCARE	✓	✓	✓	✓	✓	✓
TMF	✓	*	*			
Qualitative Data Collection						
Interview			✓	✓		✓
Patient Chart Data Collection						
Medical Abstraction	✓	✓	✓	✓	✓	✓

Table 1 Footnotes:

**FCs recruited two weeks to three months after admission to the hospital will complete a baseline questionnaire package at either the 1-month or 3-month timepoint. Follow-up questionnaire packages will be completed at subsequent timepoints.*

***Adult patients with AL (≥18 years of age) and pediatric patients with AL will be asked to provide their informed consent and/or assent, respectively, to allow medical chart information regarding their disease and its treatment to*

be extracted and documented over the course of this study. The determination of whether consent or assent is necessary for the pediatric patients will be based on a capacity assessment by a regulated healthcare professional from the research or clinical team.

Abbreviations: PCL-5 = PTSD Checklist for DSM-5; PTSD = Post-Traumatic Stress Disorder; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SASRQ = Stanford Acute Stress Reaction Questionnaire; ECR-M16 = modified and brief Experiences in Close Relationships scale; PHQ-9 = Patient Health Questionnaire-9; CRA = Caregiver Reaction Assessment scale; ESSI = ENRICHD Social Support Instrument; FAMCARE = Family Satisfaction with End-of-Life Care scale; TMF = Traditional Masculinity-Femininity scale.

Table 2. Example questions from the semi-structured qualitative interview guide

Impact of the Disease	
	Can you describe what it was like for you when you first heard about [patient's] diagnosis of leukemia?
	How, if at all, have things changed for you since [patient's] diagnosis of leukemia?
Experience of Support	
	How supported have you felt?
	What types of support have you received?
Experience of Care	
	What is your experience with the care [patient] has received from the hospital?
	Can you describe your relationship with the medical team?

Outcome measures

Primary outcome

(i) Traumatic stress symptoms, will be measured with the 30-item Stanford Acute Stress Reaction Questionnaire (SASRQ)[62,63] updated to be DSM-5-concordant[31] for ASD symptoms. This scale is one of the most widely used scales for measuring TS symptoms and has demonstrated test-retest reliability,[62.63] and predictive, construct, discriminant, and convergent validity across diverse samples.[62-66] The DSM-5-concordant version of the SASRQ has not yet been validated. Therefore, the 20-item PTSD Checklist for DSM-5 (PCL-5) will also be administered.[67] The PCL-5 is widely used to assess TS symptoms and the revised DSM-5 version has demonstrated good psychometric properties.[68-70]

Predictors

(i) ***Attachment security,*** will be measured with the modified and brief Experiences in Close Relationships (ECR-M16) scale.[46] The ECR-M16 is a widely used, reliable, and valid 16-item measure of attachment security with subscales assessing anxious and avoidant attachment.

(ii) ***Depressive symptoms***, will be measured with the Patient Health Questionaire-9 (PHQ-9).[71] The PHQ-9 is a reliable and valid 9-item measure routinely administered to screen for depressive symptoms in cancer. Two additional items assessing suicidal intent and interference with life have been added.[72,73]

(iii) ***Caregiver burden,*** will be measured with the Caregiver Reaction Assessment (CRA) scale.[74] The CRA is a reliable and valid 24-item scale assessing positive and negative reactions to five domains of caregiver burden: disrupted schedule, financial problems, lack of family support, health problems, and the impact on self-esteem.

(iv) ***Perceived social support***, will be measured with the ENRICHD Social Support Instrument (ESSI).[75] The ESSI is a 7-item scale assessing the perceived availability of social support. This measure has been used in AL and has shown good reliability and validity.[76,77]
(v) ***FC satisfaction with care***, will be measured with the Family Satisfaction with End-of-Life Care (FAMCARE) scale.[78] The FAMCARE is a reliable and valid 20-item scale measuring satisfaction with the behaviour of HCPs towards FCs and the patients they care for diagnosed with advanced cancer.
(v) ***Gender role***, will be measured *(at baseline only)* with the Traditional Masculinity-Femininity (TMF) scale.[79] The TMF is a 6-item scale that assesses the degree to which people view their interests, selves, behaviour, and other aspects as masculine or feminine. It has been validated in multiple cultural and age-group contexts.[80]

Sample size
Quantitative
Our sample size calculation for determining TS prevalence in FCs is based on the following established formula[81] to estimate sample sizes for descriptive studies:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n = sample size, $Z = Z$ statistic for confidence level, P = expected prevalence, and d = level of precision. Based on previous prevalence estimates of TS in our adult sample of patients with AL (i.e., 14% meeting criteria for ASD as measured with the SASRQ)[4] and the 11.8% PTSD prevalence in FCs of solid tumor patients,[48] we have conservatively set our expected prevalence to .14, Z to 1.96, and d to .05 (an appropriate precision for the expected prevalence[81]). The necessary sample size is 185. Our anticipated attrition rate is 15% based on previous longitudinal research at our study sites.[5,82] To compensate for attrition, the enrollment of at least 213 FCs is required to achieve our objective of determining TS prevalence in FCs. Based on expected new AL cases at both sites we can feasibly recruit 223 within our 36-month recruitment period and will therefore aim for this target.

We will also use multi-level modelling (MLM) as a non-machine learning (ML) benchmark model to determine potential TS predictors and have therefore calculated a power estimate for N=185 using GLIMMPSE version 3 online software,[83,84] which performs power and sample size calculations for multilevel designs. We derived power estimates for the following parameters, with the SASRQ total score as the outcome: a design with eight groups (i.e., to reflect crossing of caregiver gender [categorical predictor; female/male], patient age [continuous predictor; younger/older], and attachment security [continuous predictor; lower/higher] as the possible main three MLM predictors of interest) and six timepoints; decreasing intercorrelation across repeated measures, from .60 to .52; and mean and SD scaling factors of 1 and 1.5, to account for uncertainty about observed means and SDs. Power estimates were calculated for each two-way predictor x time interaction as the main hypothesis tested. Entered mean and SD estimates for the SASRQ were based on estimates from a recent phase II longitudinal clinical trial of a psychological-palliative care intervention for patients with acute leukemia.[1] The ranges of computed power estimates for a calculated sample size of 184 are: for caregiver gender x time, .34–.89 (power

estimate for means and SDs without scaling=.51); for attachment security x time, .81–1.00 (power estimate without scaling=.95); and for patient age x time, .85–1.00 (power without scaling=.97).

Qualitative
Our interview sample size will be determined by data saturation. Based on our previous qualitative work and our heterogenous sample, we estimate that a purposeful subgroup of 30 FCs will participate in interviews at the 3, 6, and 12-month timepoints.[85-88]

Analysis
Quantitative
All quantitative analyses will be conducted with R software and alpha will be set to .05.[89] Descriptive statistics will be used for FC sociodemographic and patient medical characteristics. We will descriptively characterize the prevalence and severity (with variability) of TS symptoms.

A broad range of candidate predictors of TS symptoms have been identified.[90] However, the heterogeneity of risk factors, the clinical appearance, and etiology of TS hampers the analysis of risk factors using traditional regression models.[91] The high dimensionality and likely multicollinearity among predictors and interaction of predictors pose challenges for statistical models and require the application of advanced computational approaches.[92] Studies using advanced ML have been developed to examine predictors of psychiatric risk such as PTSD risk and to facilitate the implementation of precision psychiatry into clinical practice.[93-98] We will use a supervised ML approach that is based on well-established methodologies in clinical prediction modelling including data pre-processing, such as handling of missing values, guarding against "overfitting", and rigorous model evaluation in terms of established metrics for discrimination and calibration.[99-104] Confidence intervals for all point estimates will be calculated to communicate uncertainty of the model. Moreover, to assess the generalization ability of the model on data not used to develop the model, we will partition the data to perform a held-out validation test.[104,105]

We will use latent growth mixture modelling (LGMM) to identify heterogeneous longitudinal trajectories of TS response.[106] Individuals will be assigned to trajectories based on their most likely class membership. The best-fitting model will be selected based on the Information Criteria [Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and Sample Size Adjusted Bayesian Information Criteria (SSBIC)], along with fit statistics (such as the Bootstrap Log Likelihood Test), as well as parsimony and interpretability consistent with recommendations from the literature.[107,108] We will test diverse predictive models for robustness in predicting LGMM trajectories, including random forest (RF) and support vector machines (SVM). As the final model, we will select the simplest model within one standard error of the best model to allow for a more parsimonious model. We will benchmark our predictive model with computational simpler models (including MLM). Predictors included in our models will be FC age, sex, gender, gender role, family income, baseline attachment security, perceived social support, caregiver burden, and satisfaction with provided care, relationship to patient, and patient age and treatment response. We will use Explainable Machine Learning using SHAP (SHapley Additive exPlanation)[109] to identify those features that are mainly responsible for driving the individual outcome prediction. It is an additive feature attribution method that uses kernel functions and a

well-established method to interpret ML models.[109] We will also use SHAP dependence plots to examine potential interactions among the three most important predictors in the ML model.

We will confirm our predictor-related findings using MLM, which permits cases with missing data to be included in longitudinal modeling. In this case, we will use the three most important predictors to prevent "overfitting", identified in the ML approach to test for direct linear relationships. The main effects of each of these predictors, their individual interactions with Time, and their random effects will be examined. Sociodemographic and medical covariates, including disease type (ALL vs. AML) and depressive symptoms, will be entered to control for their effects.

Qualitative

All interview audio-recordings will be transcribed verbatim by a trained transcriptionist, verified for accuracy, de-identified to protect privacy, and imported, along with field notes, into NVivo software[110] for data management and analysis. Consistent with a constant comparative method, data analyses will begin once the first interview has been transcribed, allowing data from early interviews to inform later interviews.[111] Data will be independently coded in duplicate using a line-by-line approach by trained qualitative analysts using a coding tree developed using the team's expertise and the TS scientific literature. Using content analysis, codes will be grouped into categories based on between-code relationships and categories will then be grouped into themes according to the predictors and longitudinal course of TS symptoms.[112,113] Categories and themes will then be compared across FC traits to understand similarities and differences in experiences depending on these characteristics. Quantitative data will be integrated into the analysis process to illustrate or clarify qualitative results related to the FC experience using a mixed methods matrix approach.[114] Any discrepancies in opinion regarding coding will be resolved using arbitration with our study team and such meetings will occur regularly at data analysis review meetings. An audit trail consisting of a detailed chronology of data collection and analytical decisions will be kept to enhance validity.[115]

ETHICS AND DISSEMINATION

Ethics

The study received provincial approval from the Ontario Research Ethics Board (CTO Project ID: 2104) on July 22, 2021, and centre approval for both sites in October, 2021. Institutional Authorization was provided by both sites in November, 2021.

Dissemination

We have designed an evidence-based dissemination strategy aimed at increasing awareness and knowledge of the psychological risks to FCs of patients with AL,[116] as well as FC- and patient-level factors associated with these risks, to inform scientific investigation in the field and change point-of-care practice. Our dissemination strategy will include the presentation of results at major psychosocial and medical oncology conferences, publications in leading medical or oncology journals, and postings on key websites such as the Global Institute of Psychosocial, Palliative and End-of-Life Care (GIPPEC; www.gippec.org) based at the Princess Margaret Cancer Centre and the University of Toronto, affiliated hospitals and universities, and via our collaborative partnerships with local, national, and international oncology groups. The following materials will also be developed and disseminated: (i) a 1-page brochure for oncology HCPs at adult and pediatric centres; (ii) a 3-minute YouTube video; (iii) media releases; and (iv) fact sheets to support patients

and FCs across Canada to advocate for policy change, if warranted. Furthermore, specific implications pertaining to FC subgroups (e.g., those differing across sex, gender, ethnicity, caregiver role, etc.) will be highlighted in manuscripts and other knowledge translation efforts to bolster impacts across the diversity of FCs.

Conclusion

The present mixed methods, longitudinal study of the psychological impact on FCs of individuals diagnosed with AL across the life cycle is the first of its kind and will provide a comprehensive understanding of the FC lived experience and subjective distress, as well as associated supportive care needs. The quantitative and qualitative results will inform the development of a tailored psychosocial intervention to prevent or alleviate TS in this high-risk population and have the potential to be applied to other life-threatening medical conditions.

Acknowledgements

The authors thank research coordinators Elham Hashemi at the Hospital for Sick Children, and Kyle Fitzgibbon at the Princess Margaret Cancer Centre, for their continued support of this project.

Authors' contributions

GR and LJ are co-principal investigators. GR, LJ, SA, AR, and CM conceptualised, wrote, and approved the final protocol, and revised and approved the final manuscript for submission. SG, AS, CZ, SH, RN, and CM contributed to the writing of the original protocol, as did KS and KM, who also conducted the sample size calculations and wrote the statistical analysis sections. SN revised the protocol and wrote manuscript for submission. All authors read and approved the final version.

Funding statement This work was supported by a project grant from the Canadian Institutes of Health Research (CIHR) grant number PJT 173255.

Competing interests ADS has received research funding from Takeda Pharmaceuticals, BMS and Medivir AB, and consulting fees/honorarium from Takeda, Novartis, Jazz, and Otsuka Pharmaceuticals. ADS is named on a patent application for the use of DNT cells to treat AML.

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BMJ Open

Traumatic stress symptoms in family caregivers of patients with acute leukemia: protocol for a multisite mixed methods, longitudinal, observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065422.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Sep-2022
Complete List of Authors:	Jibb, Lindsay; The Hospital for Sick Children, Child Health Evaluative Sciences; University of Toronto, Nursing Nanos, Stephanie; Princess Margaret Hospital Cancer Centre, Supportive Care; The Hospital for Sick Children, Child Health Evaluative Sciences Alexander, Sarah; The Hospital for Sick Children, Haematology/Oncology; University of Toronto, Pediatrics Malfitano, Carmine; Princess Margaret Hospital Cancer Centre, Supportive Care Rydall, Anne; Princess Margaret Hospital Cancer Centre, Supportive Care Gupta, Sumit; The Hospital for Sick Children, Haematology/Oncology; University of Toronto, Pediatrics Schimmer, Aaron; Princess Margaret Hospital Cancer Centre, Medical Oncology/Hematology; University of Toronto, Medical Biophysics Zimmermann, Camilla; Princess Margaret Hospital Cancer Centre, Supportive Care; University of Toronto, Psychiatry Hales, Sarah; Princess Margaret Hospital Cancer Centre, Supportive Care; University of Toronto, Psychiatry Nissim, Rinat; Princess Margaret Hospital Cancer Centre, Supportive Care; University of Toronto, Psychiatry Marmar, Charles; New York University, Psychiatry Schultebraucks, Katharina; Columbia University Irving Medical Center, Emergency Medicine; Columbia University, Psychiatry Mah, Kenneth; Princess Margaret Hospital Cancer Centre, Supportive Care Rodin, Gary; Princess Margaret Hospital Cancer Centre, Supportive Care; University of Toronto, Psychiatry
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Mental health, Palliative care
Keywords:	Leukaemia < ONCOLOGY, Adult palliative care < PALLIATIVE CARE, Paediatric palliative care < PALLIATIVE CARE, Anxiety disorders < PSYCHIATRY, QUALITATIVE RESEARCH, MENTAL HEALTH

TITLE PAGE

Title of the article

Traumatic stress symptoms in family caregivers of patients with acute leukemia: protocol for a multisite mixed methods, longitudinal, observational study

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Word count: 3,425

ABSTRACT

Introduction The diagnosis, progression, or recurrence of cancer is often highly traumatic for family caregivers (FCs), but systematic assessments of distress and approaches for its prevention and treatment are lacking. Acute leukemia (AL) is a life-threatening cancer of the blood, which most often presents acutely, requires intensive treatment, and is associated with severe physical symptoms. Consequently, traumatic stress may be common in the FCs of patients with AL. We aim to determine the prevalence, severity, longitudinal course, and predictors of traumatic stress symptoms in FCs of patients with AL in the first year after diagnosis, and to understand their lived experience of traumatic stress and perceived support needs.

Methods and analysis This two-site longitudinal, observational, mixed methods study will recruit 223 adult FCs of pediatric or adult patients newly diagnosed with AL from 2 tertiary care centres. Quantitative data will be collected from self-report questionnaires at enrolment, and 1, 3, 6, 9 and 12-months after admission to hospital for initial treatment. Quantitative data will be analyzed using descriptive and machine learning approaches and a multi-level modelling approach will be used to confirm machine learning findings. Semi-structured qualitative interviews will be conducted at 3, 6, and 12-months and analyzed using a grounded theory approach.

Ethics and dissemination This study is funded by the Canadian Institutes of Health Research (CIHR #PJT 173255) and has received ethical approval from the Ontario Research Ethics Board (CTO Project ID: 2104). The data generated have the potential to inform the development of targeted psychosocial interventions for traumatic stress, which is a public health priority for high-risk populations such as FCs of patients with hematological malignancies. An integrated and end-of-study knowledge translation strategy that involves FCs and other stakeholders will be used to interpret and disseminate study results.

Keywords cancer; hematological malignancies; acute leukemia; supportive care; psychosocial intervention; traumatic stress; caregivers

ARTICLE SUMMARY

Strengths and limitations of this study

- This study will examine the longitudinal course and predictors of traumatic stress symptoms of family caregivers of patients diagnosed with acute leukemia at key timepoints in their disease and treatment trajectory.
- Qualitative interviews analyzed using a grounded theory approach will preserve the complexity and context of the caregiver experience and will integrate with the quantitative data to deepen our understanding of their traumatic stress symptoms.
- The inclusion of a diverse group of family caregivers with variance in characteristics such as age, sex, gender, race, ethnicity, attachment style, relationship to patient, and type of leukemia provides an opportunity to understand the impact of caregiver factors on traumatic stress symptoms.
- The generalizability of our findings may be limited by caregiver enrolment from cancer care centres in a single metropolitan area and the potential for selection bias.

INTRODUCTION

Acute leukemia (AL) is a life-threatening hematological malignancy characterized by rapid onset, the requirement for immediate hospitalization to initiate care, and intensive and prolonged medical treatment. The primary types of AL are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Both occur in patients of all ages, but the epidemiology, disease features, and outcomes vary with age and disease type. Treatment of AL is associated with the risk of serious and potentially fatal side effects including bleeding, infection, mucositis, nausea and vomiting, pain, and multiple other drug-specific side effects.[1-3] There is now robust evidence showing that the diagnosis of AL in patients from infants to older adults is a singularly stressful event, followed by a period of intense and difficult life choices and experiences.[4-9] Those who are cured of AL may still endure long-term treatment sequelae including neurocognitive deficits, infertility, endocrine, musculoskeletal and cardiac impairments, and risk of secondary cancers.[6,10-14]

The impact of AL on family caregivers

The diagnosis of AL and its treatment impose a substantial burden on family caregivers (FCs), who may be partners, adult children, or parents.[7-9] FCs of patients with cancer are increasingly expected to assume lead roles in complex clinical tasks, such as coordination of care, symptom management, medication administration, and direct patient care, while maintaining other ongoing responsibilities, such as employment and care for other dependents.[15-23] These multiple roles, coupled with financial strain due to the cost of non-reimbursed medical care, travel, other family caregiving and home responsibilities, and the loss of employment income, are major sources of distress for FCs.[16,24,25] This burden of caring,[24] which falls disproportionately on women, [26] and the constant threat that a partner, parent, or child will suffer or die, constitute substantial threats to the mental and physical health of FCs.[27-29]

Traumatic stress symptoms

The immediate psychological response to the diagnosis of a life-threatening cancer of both patients and FCs is often traumatic stress (TS) symptoms.[4,5,28,30] These symptoms include hyperarousal (e.g., hypervigilance, decreased concentration, heightened startle response, insomnia, irritability), intrusive thoughts (e.g., nightmares, flashbacks, altered sense of reality), emotional detachment or numbing, and depression.[31,32] Symptoms of TS occurring within one month of the traumatic event may meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for acute stress disorder (ASD) and those that persist for longer than a month may meet diagnostic criteria for post-traumatic stress disorder (PTSD).[31] Risk factors for ASD and PTSD following a traumatic event include younger age, female sex, feminine gender role, and direct or vicarious exposure to traumatic events, including in first responders to trauma victims.[33-35] Gender is not only a risk factor for PTSD in its own right but is also a proxy for multiple interacting social, economic, and political influences on distress.[36] As a whole, traumatic stress disorders are highly disturbing to those affected and are associated with a subsequent ten-fold increase in the risk of completed suicide[37] and an increased risk of cardiovascular, metabolic, and musculoskeletal disorders[38] and all-cause mortality.[39]

The social context of traumatic stress symptoms

The social environment in which individuals exposed to trauma are situated has been shown to directly affect the severity and nature of TS symptoms.[36] In that regard, the inverse relationship between symptoms of PTSD and social support, including that received from healthcare

professionals (HCPs), is one of the most consistent relationships observed in trauma research.[40-42] Internalized representations of support and the capacity to make use of it, reflected in the construct of attachment security,[43] have also been shown to protect from the development of PTSD following exposure to trauma.[44] Measured on dimensions of attachment anxiety and attachment avoidance,[45,46] attachment security has been shown to play a critical role in the management of terror, specifically that related to death anxiety.[47]

Traumatic stress symptoms in family caregivers

Clinically significant TS symptoms are common in FCs of patients with metastatic cancer, with similar rates in partners and parents of patients.[28,48] Risk factors that have been identified for the development of TS in FCs of patients include: (i) FC variables such as female sex,[49] identification with traditionally feminine gender roles,[28,50] younger age,[27] less social support and less attachment security,[51] lower family income,[29] and higher perceived burden of caregiving tasks;[52,53] (ii) patient variables such as younger age[54] and greater disease severity;[55] and (iii) the nature of the caregiver-patient relationship,[56] with close familial relationships being associated with greater TS.[57,58]

Research has demonstrated the psychological impact of metastatic cancer on patients[59,60] and their FCs.[58] Several studies have highlighted the psychological impact of hematological malignancies on patients.[4,5,61] However, there has been little research attention to the psychological consequences of hematological malignancies on FCs, and systematic approaches to prevent and alleviate distress in this high-risk population have not been developed. The acute onset of AL, the intensive and prolonged treatment, the substantial burden of caregiving, and the uncertainty regarding clinical outcomes suggest that TS symptoms may be common in FCs. However, the prevalence, severity, and predictors of TS over time, and the experience of FCs of patients with AL across the life course have not been determined.

Study objectives

The objectives of the present study are to determine in FCs of patients with AL:

1. The prevalence, severity, longitudinal course, and predictors of TS symptoms over the first year following a new diagnosis of AL;
2. The FC experience of TS, including the impact of AL on their lives and that of their families, the nature of their distress, their relationship with HCPs, and their perceived resources and met and unmet support needs.

The findings from this study will provide essential information to inform research, clinical practice, and health policy regarding the comprehensive and family-centred treatment of AL.

METHODS AND ANALYSIS

Patient and public involvement

This study will be conducted with the early and ongoing engagement of FCs and other stakeholders. Specifically, our FC- and HCP-collaborators have informed the construction of this study, including the mixed methods approach and relevant sampling timepoints, will be closely involved in the interpretation and dissemination of the data, and will lead in advocacy efforts to support

policy change related to the care of FCs. The patient and family advisory councils at our study sites will also be engaged to support study conduct from implementation to dissemination.

Study design and setting

This is a prospective, observational study using mixed quantitative and qualitative methodology. FCs will be recruited from the Princess Margaret Cancer Centre, part of the University Health Network, and the Hospital for Sick Children, in Toronto, Canada.

Eligibility criteria

FCs will be: (i) the self-identified primary or co-primary caregiver (i.e., person assuming at least 40% of patient care activities) of a pediatric or adult patient newly diagnosed with primary AL (AML or ALL) within three months of admission to either of our study sites; (ii) ≥18 years old; and (iii) fluent in English.

Ineligibility criteria

FCs of patients with acute promyelocytic leukemia (APML) or who do not receive induction chemotherapy with curative intent will be ineligible.

Data collection

FC recruitment will occur over 36 months and is expected to be completed in 2024. Following informed consent, participating FCs will complete a demographics questionnaire and the disease-related characteristics of the associated patient will be abstracted from the patient's medical chart (Table 1). FCs will then complete a baseline outcome questionnaire package on REDCap (i.e., a secure online browser-based application for building and managing online surveys and research databases), and follow-up online outcome questionnaire packages at 1, 3, 6, 9 and 12-months after the patient's admission to the hospital for a new diagnosis of AL (Table 1). Questionnaire package completion time is expected to be 20-30 minutes at each assessment point. A subgroup of FCs will be invited to participate in audio- and/or video-recorded, semi-structured, qualitative interviews at 3, 6, and 12-months. Interviewees may participate in interviews at more than one sampling timepoint. Sampling for interviews will be purposeful in an attempt to achieve maximum variation in FC characteristics including age, sex, gender, gender role, FC-patient relationship, scores on quantitative measures, race, ethnicity, and patient's AL type. The interviews will be conducted by a trained interviewer and will focus on the FC experience of caring for someone with AL, the impact of caring on the lives of FCs and that of their families, FC met and unmet support needs, and the FC experience with the patient's treatment and HCPs (Table 2). Interviews are expected to last between 30-60 minutes.

Table 1. Timeline of study activities

	Enrollment Baseline	**1-Month** Follow-up Baseline*	**3-Months** Follow-up Baseline*	**6-Months** Follow-up	**9-Months** Follow-up	**12-Months** Follow-up
Recruitment						
Confirm Eligibility	✓	*	*			
Initial Approach	✓	*	*			
Caregiver Quantitative Informed Consent	✓	*	*			
Caregiver Qualitative Informed Consent			✓			
Patient Informed Consent/Assent**	✓	*	*			
Quantitative Data Collection						
Demographics	✓	*	*			
PCL-5	✓	✓	✓	✓	✓	✓
SASRQ	✓	✓	✓	✓	✓	✓
ECR-M16	✓	✓	✓	✓	✓	✓
PHQ-9	✓	✓	✓	✓	✓	✓
CRA	✓	✓	✓	✓	✓	✓
ESSI	✓	✓	✓	✓	✓	✓
FAMCARE	✓	✓	✓	✓	✓	✓
TMF	✓	*	*			
Qualitative Data Collection						
Interview			✓	✓		✓
Patient Chart Data Collection						
Medical Abstraction	✓	✓	✓	✓	✓	✓

Table 1 Footnotes:

**FCs recruited two weeks to three months after admission to the hospital will complete a baseline questionnaire package at either the 1-month or 3-month timepoint. Follow-up questionnaire packages will be completed at subsequent timepoints.*

***Adult patients with AL (≥18 years of age) and pediatric patients with AL will be asked to provide their informed consent and/or assent, respectively, to allow medical chart information regarding their disease and its treatment to*

be extracted and documented over the course of this study. The determination of whether consent or assent is necessary for the pediatric patients will be based on a capacity assessment by a regulated healthcare professional from the research or clinical team.

Abbreviations: PCL-5 = PTSD Checklist for DSM-5; PTSD = Post-Traumatic Stress Disorder; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SASRQ = Stanford Acute Stress Reaction Questionnaire; ECR-M16 = modified and brief Experiences in Close Relationships scale; PHQ-9 = Patient Health Questionnaire-9; CRA = Caregiver Reaction Assessment scale; ESSI = ENRICHD Social Support Instrument; FAMCARE = Family Satisfaction with End-of-Life Care scale; TMF = Traditional Masculinity-Femininity scale.

Table 2. Example questions from the semi-structured qualitative interview guide

Impact of the Disease	
	Can you describe what it was like for you when you first heard about [patient's] diagnosis of leukemia?
	How, if at all, have things changed for you since [patient's] diagnosis of leukemia?
Experience of Support	
	How supported have you felt?
	What types of support have you received?
Experience of Care	
	What is your experience with the care [patient] has received from the hospital?
	Can you describe your relationship with the medical team?

Outcome measures

Primary outcome

(i) Traumatic stress symptoms, will be measured with the 30-item Stanford Acute Stress Reaction Questionnaire (SASRQ)[62,63] updated to be DSM-5-concordant[31] for ASD symptoms. This scale is one of the most widely used scales for measuring TS symptoms and has demonstrated test-retest reliability,[62.63] and predictive, construct, discriminant, and convergent validity across diverse samples.[62-66] The DSM-5-concordant version of the SASRQ has not yet been validated. Therefore, the 20-item PTSD Checklist for DSM-5 (PCL-5) will also be administered.[67] The PCL-5 is widely used to assess TS symptoms and the revised DSM-5 version has demonstrated good psychometric properties.[68-70]

Predictors

(i) ***Attachment security,*** will be measured with the modified and brief Experiences in Close Relationships (ECR-M16) scale.[46] The ECR-M16 is a widely used, reliable, and valid 16-item measure of attachment security with subscales assessing anxious and avoidant attachment.

(ii) ***Depressive symptoms***, will be measured with the Patient Health Questionaire-9 (PHQ-9).[71] The PHQ-9 is a reliable and valid 9-item measure routinely administered to screen for depressive symptoms in cancer. Two additional items assessing suicidal intent and interference with life have been added.[72,73]

(iii) ***Caregiver burden,*** will be measured with the Caregiver Reaction Assessment (CRA) scale.[74] The CRA is a reliable and valid 24-item scale assessing positive and negative reactions to five domains of caregiver burden: disrupted schedule, financial problems, lack of family support, health problems, and the impact on self-esteem.

(iv) ***Perceived social support***, will be measured with the ENRICHD Social Support Instrument (ESSI).[75] The ESSI is a 7-item scale assessing the perceived availability of social support. This measure has been used in AL and has shown good reliability and validity.[76,77]
(v) ***FC satisfaction with care***, will be measured with the Family Satisfaction with End-of-Life Care (FAMCARE) scale.[78] The FAMCARE is a reliable and valid 20-item scale measuring satisfaction with the behaviour of HCPs towards FCs and the patients they care for diagnosed with advanced cancer.
(v) ***Gender role***, will be measured *(at baseline only)* with the Traditional Masculinity-Femininity (TMF) scale.[79] The TMF is a 6-item scale that assesses the degree to which people view their interests, selves, behaviour, and other aspects as masculine or feminine. It has been validated in multiple cultural and age-group contexts.[80]

Sample size
Quantitative
Our sample size calculation for determining TS prevalence in FCs is based on the following established formula[81] to estimate sample sizes for descriptive studies:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n = sample size, $Z = Z$ statistic for confidence level, P = expected prevalence, and d = level of precision. Based on previous prevalence estimates of TS in our adult sample of patients with AL (i.e., 14% meeting criteria for ASD as measured with the SASRQ)[4] and the 11.8% PTSD prevalence in FCs of solid tumor patients,[48] we have conservatively set our expected prevalence to .14, Z to 1.96, and d to .05 (an appropriate precision for the expected prevalence[81]). The necessary sample size is 185. Our anticipated attrition rate is 15% based on previous longitudinal research at our study sites.[5,82] To compensate for attrition, the enrollment of at least 213 FCs is required to achieve our objective of determining TS prevalence in FCs. Based on expected new AL cases at both sites we can feasibly recruit 223 within our 36-month recruitment period and will therefore aim for this target.

We will also use multi-level modelling (MLM) as a non-machine learning (ML) benchmark model to determine potential TS predictors and have therefore calculated a power estimate for N=185 using GLIMMPSE version 3 online software,[83,84] which performs power and sample size calculations for multilevel designs. We derived power estimates for the following parameters, with the SASRQ total score as the outcome: a design with eight groups (i.e., to reflect crossing of caregiver gender [categorical predictor; female/male], patient age [continuous predictor; younger/older], and attachment security [continuous predictor; lower/higher] as the possible main three MLM predictors of interest) and six timepoints; decreasing intercorrelation across repeated measures, from .60 to .52; and mean and SD scaling factors of 1 and 1.5, to account for uncertainty about observed means and SDs. Power estimates were calculated for each two-way predictor x time interaction as the main hypothesis tested. Entered mean and SD estimates for the SASRQ were based on estimates from a recent phase II longitudinal clinical trial of a psychological-palliative care intervention for patients with acute leukemia.[1] The ranges of computed power estimates for a calculated sample size of 184 are: for caregiver gender x time, .34–.89 (power

estimate for means and SDs without scaling=.51); for attachment security x time, .81–1.00 (power estimate without scaling=.95); and for patient age x time, .85–1.00 (power without scaling=.97).

Qualitative
Our interview sample size will be determined by data saturation. Based on our previous qualitative work and our heterogenous sample, we estimate that a purposeful subgroup of 30 FCs will participate in interviews at the 3, 6, and 12-month timepoints.[85-88]

Analysis
Quantitative
All quantitative analyses will be conducted with R software and alpha will be set to .05.[89] Descriptive statistics will be used for FC sociodemographic and patient medical characteristics. We will descriptively characterize the prevalence and severity (with variability) of TS symptoms.

A broad range of candidate predictors of TS symptoms have been identified.[90] However, the heterogeneity of risk factors, the clinical appearance, and etiology of TS hampers the analysis of risk factors using traditional regression models.[91] The high dimensionality and likely multicollinearity among predictors and interaction of predictors pose challenges for statistical models and require the application of advanced computational approaches.[92] Studies using advanced ML have been developed to examine predictors of psychiatric risk such as PTSD risk and to facilitate the implementation of precision psychiatry into clinical practice.[93-98] We will use a supervised ML approach that is based on well-established methodologies in clinical prediction modelling including data pre-processing, such as handling of missing values, guarding against "overfitting", and rigorous model evaluation in terms of established metrics for discrimination and calibration.[99-104] Confidence intervals for all point estimates will be calculated to communicate uncertainty of the model. Moreover, to assess the generalization ability of the model on data not used to develop the model, we will partition the data to perform a held-out validation test.[104,105]

We will use latent growth mixture modelling (LGMM) to identify heterogeneous longitudinal trajectories of TS response.[106] Individuals will be assigned to trajectories based on their most likely class membership. The best-fitting model will be selected based on the Information Criteria [Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and Sample Size Adjusted Bayesian Information Criteria (SSBIC)], along with fit statistics (such as the Bootstrap Log Likelihood Test), as well as parsimony and interpretability consistent with recommendations from the literature.[107,108] We will test diverse predictive models for robustness in predicting LGMM trajectories, including random forest (RF) and support vector machines (SVM). As the final model, we will select the simplest model within one standard error of the best model to allow for a more parsimonious model. We will benchmark our predictive model with computational simpler models (including MLM). Predictors included in our models will be FC age, sex, gender, gender role, family income, baseline attachment security, perceived social support, caregiver burden, and satisfaction with provided care, relationship to patient, and patient age and treatment response. We will use Explainable Machine Learning using SHAP (SHapley Additive exPlanation)[109] to identify those features that are mainly responsible for driving the individual outcome prediction. It is an additive feature attribution method that uses kernel functions and a

well-established method to interpret ML models.[109] We will also use SHAP dependence plots to examine potential interactions among the three most important predictors in the ML model.

We will confirm our predictor-related findings using MLM, which permits cases with missing data to be included in longitudinal modeling. In this case, we will use the three most important predictors to prevent "overfitting", identified in the ML approach to test for direct linear relationships. The main effects of each of these predictors, their individual interactions with Time, and their random effects will be examined. Sociodemographic and medical covariates, including disease type (ALL vs. AML) and depressive symptoms, will be entered to control for their effects.

Qualitative

All interview audio-recordings will be transcribed verbatim by a trained transcriptionist, verified for accuracy, de-identified to protect privacy, and imported, along with field notes, into NVivo software[110] for data management and analysis. Consistent with a constant comparative method, data analyses will begin once the first interview has been transcribed, allowing data from early interviews to inform later interviews.[111] Data will be independently coded in duplicate using a line-by-line approach by trained qualitative analysts using a coding tree developed using the team's expertise and the TS scientific literature. Using content analysis, codes will be grouped into categories based on between-code relationships and categories will then be grouped into themes according to the predictors and longitudinal course of TS symptoms.[112,113] Categories and themes will then be compared across FC traits to understand similarities and differences in experiences depending on these characteristics. Quantitative data will be integrated into the analysis process to illustrate or clarify qualitative results related to the FC experience using a mixed methods matrix approach.[114] Any discrepancies in opinion regarding coding will be resolved using arbitration with our study team and such meetings will occur regularly at data analysis review meetings. An audit trail consisting of a detailed chronology of data collection and analytical decisions will be kept to enhance validity.[115]

ETHICS AND DISSEMINATION

Ethics

The study received provincial approval from the Ontario Research Ethics Board (CTO Project ID: 2104) on July 22, 2021, and centre approval for both sites in October, 2021. Institutional Authorization was provided by both sites in November, 2021.

Dissemination

We have designed an evidence-based dissemination strategy aimed at increasing awareness and knowledge of the psychological risks to FCs of patients with AL,[116] as well as FC- and patient-level factors associated with these risks, to inform scientific investigation in the field and change point-of-care practice. Our dissemination strategy will include the presentation of results at major psychosocial and medical oncology conferences, publications in leading medical or oncology journals, and postings on key websites such as the Global Institute of Psychosocial, Palliative and End-of-Life Care (GIPPEC; www.gippec.org) based at the Princess Margaret Cancer Centre and the University of Toronto, affiliated hospitals and universities, and via our collaborative partnerships with local, national, and international oncology groups. The following materials will also be developed and disseminated: (i) a 1-page brochure for oncology HCPs at adult and pediatric centres; (ii) a 3-minute YouTube video; (iii) media releases; and (iv) fact sheets to support patients

and FCs across Canada to advocate for policy change, if warranted. Furthermore, specific implications pertaining to FC subgroups (e.g., those differing across sex, gender, ethnicity, caregiver role, etc.) will be highlighted in manuscripts and other knowledge translation efforts to bolster impacts across the diversity of FCs.

Conclusion

The present mixed methods, longitudinal study of the psychological impact on FCs of individuals diagnosed with AL across the life cycle is the first of its kind and will provide a comprehensive understanding of the FC lived experience and subjective distress, as well as associated supportive care needs. The quantitative and qualitative results will inform the development of a tailored psychosocial intervention to prevent or alleviate TS in this high-risk population and have the potential to be applied to other life-threatening medical conditions.

Acknowledgements

The authors thank research coordinators Elham Hashemi at the Hospital for Sick Children, and Kyle Fitzgibbon at the Princess Margaret Cancer Centre, for their continued support of this project.

Authors' contributions

All authors in this manuscript have contributed to the conception, design, acquisition, analysis or interpretation of data. GR, LJ, SA, AR, and CM conceptualised the project. SG, ADS, CZ, SH, RN, and CM contributed to design, as did KS and KM, who conceived the sample size calculations and statistical analysis. SN revised the protocol, and is responsible for data collection, analysis, interpretation. GR, LJ, AR, SH, RN, KS and KM will also analyse and interpret the data. All authors read and provided final approval for this manuscript to be published. The authors understand their role in taking responsibility and being accountable for what is published. They are committed to transparency and have disclosed all relationships, activities and interests related to the content of this manuscript.

Funding statement This work was supported by a project grant from the Canadian Institutes of Health Research (CIHR) grant number PJT 173255.

Competing interests ADS has received research funding from Takeda Pharmaceuticals, BMS and Medivir AB, and consulting fees/honorarium from Takeda, Novartis, Jazz, and Otsuka Pharmaceuticals. ADS is named on a patent application for the use of DNT cells to treat AML.

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