

Late adverse effects related to treatment in a cohort of survivors of childhood and adolescent cancer

Annemeri Livinalli, MD, Marcus Tolentino Silva, PhD, Luciane Cruz Lopes, PhD*

Abstract

Taking into consideration the progress in cancer treatment, an increase in the number of adult survivors of childhood cancer is expected. These survivors will have received treatment that predisposes them to late morbidity and increased risk of early mortality. The aim of this single-center retrospective cohort study was to describe the frequency and identify risk factors associated with late adverse events related to cancer treatment in survivors of childhood and adolescent cancer.

Patients were recruited from 2010 to 2014. All possible late adverse effects identified, were classified according to CTCAE grading system version 4.0. The variables were characterized and stratified according to the presence or not of late effects. Odds ratio was used as a measure of association in bivariate analysis to identify characteristics associated with the late effects of treatment. Among 111 potentially eligible participants, 62 survivors met the inclusion criteria; 17 (27.4%) had abnormal test results observed in the systems: 8 (47%) in the endocrine and metabolic, 7 (41.2%) in the cardiovascular, 5 (29.4%) in the musculoskeletal, and 1 (5.9%) in auditory and renal systems. Frequency and severity of late adverse events were not affected by treatments employed; except for radiotherapy which was associated with a higher risk of late adverse effect occurrences.

Abbreviations: CCSS = Childhood Cancer Survivor Study, COG = Children's Oncology Group, CT = chemotherapy, CTCAE = Common Terminology Criteria for Adverse Events, GRENDACC = Group for the Defense of the Child with Cancer, INCA = National Cancer Institute, ISCD = International Society for Clinical Densitometry, LAE = late adverse effects, OR = odds ratio, US NCI = US National Cancer Institute, VER = Living the Hope of Restarting.

Keywords: cancer chemotherapy, cancer survivorship, childhood cancer, common toxicity criteria, late adverse effects

1. Introduction

Childhood cancer, accounting for 1% to 3% of all malignancies, is considered rare when compared to cancer affecting adults. The National Cancer Institute (INCA) estimates that there will be 12,500 new cases in Brazil in 2018 and 2019.^[1]

In the United States, there are approximately 300,000 childhood cancer survivors.^[2] In Europe, it is estimated there are between 300,000 and 500,000 childhood cancer survivors.^[3] In Brazil, this data is not available. With progress in cancer treatment, the number of adults surviving childhood cancer is expected to continue to increase. About 75% of these survivors will have a chronic health problem and 40% will have a serious,

disabling, life-threatening health condition or will die from a chronic condition resulting from their cancer treatment.^[4]

The Childhood Cancer Survivor Study (CCSS) has assembled the largest cohort to date for the assessment of late mortality and they found the overall cumulative mortality as 18.1% (95% CI, 17.3–18.9) at 30 years from diagnosis.^[5] In a study involving nearly 10,400 childhood cancer survivors and about 3000 siblings, the risk of chronic diseases, such as myocardial infarction, congestive heart failure, and second neoplasm was 8 times greater in survivors than in their siblings.^[6] Regular follow-up of these survivors with early detection and treatment of late adverse events, combined with education about modifiable risks can positively affect survivors' quality of life and long-term health.^[7]

Some late adverse effects (LAE) can be identified early and treated without further consequences. Others LAE may persist, appear in adulthood as chronic diseases, or contribute to the progression of other diseases, or both.^[8] Several countries have already developed guidelines for late effects surveillance and have joined to standardize these recommendations internationally enhancing long-term follow-up care and quality of life for survivors.^[9]

The identification of the severity of health problems in the childhood cancer survivor population can alert primary care practitioners to the specific health concerns of survivors and contribute to the preparation of earlier interventions. Ideally, this would result in an introduction of differentiated care of childhood cancer survivors, as well as help develop specific training for both professionals specialized in pediatric care and those who serve the adult population.

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Pharmaceutical Sciences Master Course, University of Sorocaba, UNISO, São Paulo, Brazil.

* Correspondence: Luciane Cruz Lopes, Postgraduate Program of Pharmaceutical Sciences, University of Sorocaba, Rodovia Raposo Tavares, km 92.5 - Cidade Universitária Professor Aldo Vannucchi, Sorocaba, SP 18023-000, Brazil (e-mail: luslopesbr@gmail.com).

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of childhood and adolescent cancer. The study participants were from an outpatient clinic of the *Grupo em Defesa da Criança com Câncer* (Group for the Defense of the Child with Cancer [GRENDACC]) located in a municipality in the state of Sao Paulo, Brazil.

2. Methods

2.1. Design, setting, and context

This is a retrospective cohort study to investigate LAE defined as treatment-related complications or adverse events that persist or appear after cancer treatment.^[10] The study was performed in a single treatment center of pediatric oncology. All patients who adhered to the annual follow-up in the outpatient clinic *Vivendo a Esperança do Recomeço* (Living the Hope of Restarting [VER]) were included. The clinic addresses the needs of patients who are at least 2 years after the end of their cancer treatment. This study was approved by the appropriate institutional research ethics committee (Protocol number: 16240213.4.0000.5500) and was performed in accordance with the ethical standards as established in the Helsinki Declaration (1964). Informed consent was obtained from all participants included in the study.

2.2. Sample selection

The present study included individuals seen at the VER Outpatient Clinic from October 2010, when the program began, to December 2014. The individuals received cancer diagnosis and treatment between July 1995 and December 2011. Once admitted to the outpatient clinic, the patients receive annual follow up appointments with an oncologist indefinitely.

Eligibility criteria included age less than 18 years at diagnosis, 2 years of disease-free survival, continuation of regular follow up tests and examinations, and their return for evaluation in the outpatient clinic. Patients diagnosed with the following types of cancer were included: leukemia, tumors of the central nervous system, lymphoma, neuroblastoma, sarcomas, kidney cancer, germ cell tumor, or bone cancer. The excluded patients were those: with cancer who had undergone surgery only, whose treatment information from another institution other than GRENDACC was insufficient for follow-up, who did not return to the VER outpatient clinic, who returned without results of bone densitometry, echocardiogram, pulmonary function evaluation, or a combination of those results, and who did not agree or were unable to sign the informed consent form. The selection of participants is described in Figure 1.

2.3. Data collection

Patients were selected from a list of individuals who had annual follow up appointments at the survivor clinic. The list was generated in December 2014 from the records service system.

The annual follow up appointments with the oncologists in the clinic followed the guidelines “The Long-Term Follow-up Guidelines for Survivors of Childhood, adolescent and Young adult cancers (LTFU)” developed by the Children’s Oncology Group (COG).^[10] These guidelines provide recommendations to support screening of both symptomatic and asymptomatic individuals.

During the appointment, the oncologist explained to the survivor about the possible LAE that they could develop and carry out a clinical examination. The examination focused on the organs or systems that could have been affected by the treatment,

for example, cardiovascular, renal, and auditory systems, among others. Depending on the treatment received and the systems determined to be at risk, the physician requested radiological, laboratory and other exams, and referred the survivor to other specialists. At the end of the appointment, the survivor was advised to adopt healthy lifestyles that could minimize the severity or the delay onset of LAE. After performing the requested exams and appointments with specialists, the survivor was instructed to return to the outpatient clinic for reassessment and identification of abnormal results in the exams

The following information was obtained from the patient’s chart: sociodemographic data; type of cancer; age at diagnosis; staging; recurrence; second neoplasm; medication including drugs, route of administration, start and end date of treatment; radiotherapy including dose, site, start and end of treatment; bone marrow transplantation including type conditioning regime, and whether there was graft versus host disease; and surgery including type, location and completion date.

All LAE were classified according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0) developed by the US National Cancer Institute (US NCI).^[11] This tool differentiates the severity of the event and classifies them from grade 1 to 5 according to the clinical description for each event (grade 1—mild, grade 2—moderate, grade 3—severe, grade 4—risk for death, and grade 5—death).

To assess the severity of changes in the bone densitometry examination, Z-score was considered in the interpretation according to the recommendation of the International Society for Clinical Densitometry (ISCD), appropriate for children and adolescents.^[12] The terms “osteopenia” and “osteoporosis” were not used in this study; the term “low bone mineral density” was adopted as recommended by the ISCD for children and adolescents.

2.4. Statistical analysis

Continuous data are presented as the mean including standard deviation, or median, including minimum and maximum values as appropriate; and for binary variables proportions were used.

The variables were characterized and stratified according to the presence or not of LAE. Nominal variables were calculated as proportions, and continuous variables were calculated as mean with standard deviation. In order to identify characteristics associated with the late effects of treatment, odds ratio (OR) was used as a measure of association in bivariate analysis. The OR of each variable has been adjusted for sex, age, and treatment at the beginning of the follow-up using logistic regression. The significance level $P < .05$ and 95% confidence intervals (CIs) was used. For the statistically significant results, a sensitivity analysis has been performed for 50 replicates of the logistic regression with random samples of the database (bootstrap). All calculations were performed in the statistical package STATA, version 11.2.

3. Results

A total of 111 survivors were identified at the VER outpatient clinic for our retrospective analysis. Sixty-two were eligible and agreed to participate in the study, 17 (27,4%) potential cases of LAE were identified. Patients mean age at diagnosis was 7.14 ± 4.8 years. Post-treatment periods ranged from 3 to 16 years. Participants were treated in childhood or adolescence for the following cancers: acute lymphoid leukemia, non-Hodgkin

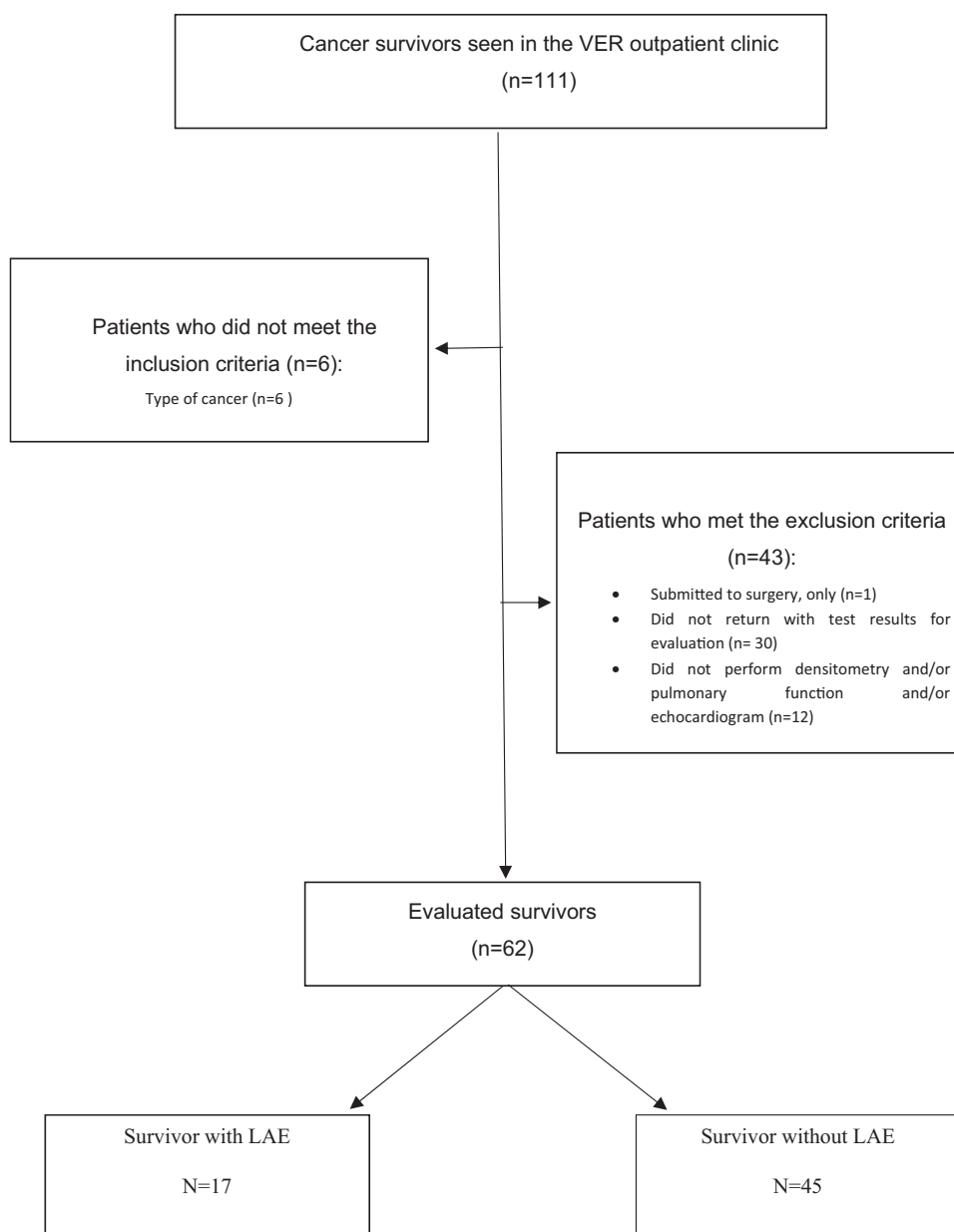


Figure 1. Sample composition flowchart. LAE=late adverse effects, VER=Living the Hope of Restarting.

lymphoma, Hodgkin lymphoma, Burkitt lymphoma, neuroblastoma, Wilms tumor, renal carcinoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and germ cell tumor. Chemotherapy (CT) alone was used in 32 (51.6%) patients, and 9 (14.5%) had undergone CT with surgery and radiotherapy (Table 1). Patients treated with radiation were 16 (25.8%), 100% of them also received CT and were mainly treated for Hodgkin lymphoma (43.7%). Among patients that received this treatment modality, LAE was present in 9 (56.2%) participants. The average dose was 35 Gy and median age at radiation was 9,5 years. The radiation fields were: cervical (n=4), abdominal (n=4), mediastinal (n=4), cranial (n=3), and bone (n=1).

In the group with LAE, when evaluated by body system, 8 (47.0%) participants presented a potential late adverse effect in the endocrine-metabolic system, 7 (41.2%) in the cardiovascular system, 5 (29.4%) in the musculoskeletal system, and 1 (5.9%) in

each of the auditory and renal systems (Table 2). Adverse effects in 2 systems concomitantly were observed in 4 (23.5%) survivors. No survivor presented more than 2 systems affected.

Grade 2 hypothyroidism, the most frequent endocrine disorder, was identified in 4 (6.5%) participants. Hypercholesterolemia, hyperglycemia, and obesity were also observed in other survivors and graded as 1.

In the cardiovascular system, alterations were observed in 7 (41.2%) survivors, in which alteration in the mitral valve was the most prevalent (n=5). Changes in the tricuspid valve, hypertension, and left ventricular hypertrophy were also observed. Of the total of 9 LAE observed in this system, 7 were classified as grade 1, 1 as grade 2, and 1 as grade 3.

Changes in the skeletal muscle system included low bone mineral density (n=3), scoliosis (n=1) and muscle hypoplasia (n=1). The 3 participants with low bone mineral density had risk

Table 1
Characteristics of the study population.

Characteristic	Survivor with LAE N = 17	Survivor without LAE N = 45	Total N = 62 (%)
Gender			
Female	8	21	29 (46.8)
Male	9	24	33 (53.2)
Race/ethnicity*			
Caucasian	9	31	40 (83.3)
Black	3	4	7 (14.6)
other	1	0	1 (2.1)
Age at diagnosis, yr			
Mean ± SD			7.14 ± 4.8
0 to 5	5	24	29 (46.8)
6 to 11	8	13	21 (33.9)
12 to 18	4	8	12 (19.3)
Age at baseline (first appointment in the outpatient clinic), yr			
Mean ± SD			14.2 ± 6.16
0 a 10	4	14	18 (29.0)
11 a 20	7	27	34 (54.8)
21 a 30	6	4	10 (16.2)
Years since diagnosis, range			3–16
Diagnosis			
Solid tumor	7	15	22 (35.5%)
Hematologic Cancer	10	30	40 (64.5%)
Overall treatment category			
Chemotherapy only	5	27	32 (51.6)
Chemotherapy + Radiation	4	3	7 (11.3)
Chemotherapy + surgery + radiation	5	4	9 (14.5)
Chemotherapy + surgery	3	11	14 (22.6)

LAE = late adverse effects.

* N = 14—no information about race/ethnicity in the patient's chart.

factors in their history of treatment, among them, the use of methotrexate in high doses and corticosteroids.

Only 1 survivor presented changes in the auditory system and 1 in the renal system. In the other systems (neurological, visual, and

pulmonary), no changes were detected in physical, radiological or laboratory tests.

Only 3 participants received cranial radiotherapy at doses of 18 Gy and 45 Gy. None of the survivors presented motor dysfunction, coordination difficulties, or sensorial loss. In the statistical analysis, radiotherapy was associated with the risk of LAE as described in Table 3.

Table 2
Late adverse effects graded by organ system using Common Toxicity Criteria for Adverse Events. Version 4.0.

Category	Grade 1	Grade 2	Grade 3
Patient*	11	6	1
Event	15	6	2
Cardiovascular			
Disease of mitral valve	5	–	–
Disease of tricuspid valve	1	1	–
Hypertension	–	–	1
Left ventricular hypertrophy	1	–	–
Endocrine-metabolic			
Hypothyroidism	–	4	–
Obesity	–	–	1
Hyperglycemia	1	–	–
Hypercholesterolemia	3	–	–
Hypertriglyceridemia	1	–	–
Skeletal muscle			
Scoliosis	1	–	–
Muscle hypoplasia	1	–	–
Auditory			
Deficit	–	1	–
Renal			
Decreased glomerular filtration	1	–	–

* 3 participants showed multiple late effects (≥2), grade 1 and grade 2 concomitantly.

4. Discussion

In Brazil, this is one of the few studies conducted in childhood cancer survivors and the first to use the toxicity grading system developed by the US NCI in a survivor population of childhood cancer. The LAE were observed in 27.4% of the survivors, with acute lymphoid leukemia and lymphoma being the most prevalent initial diagnoses in this group.

Of the organ systems evaluated, changes were observed in 5 (endocrine-metabolic, cardiovascular, musculoskeletal, auditory and renal systems), which may have been caused by cancer treatment in childhood or adolescence. Hypothyroidism was the main dysfunction observed in the survivors who presented changes in the endocrine-metabolic system.

Cardiac toxicity was identified in 11.3% (n = 7/62) survivors, with dysfunction in mitral valve the most predominant. Survivors were asymptomatic at the time of the diagnosis by echocardiography and the dysfunctions were considered grade 1.

Patients treated with radiation were 16 (25.8%) of which 9 were with LAE. In our results, radiotherapy was associated with the risk of LAE.

Table 3**Characteristics associated with the late adverse effects.**

Variable	Survivor with LAE N = 17	Survivor without LAE N = 45	Odds ratio (95% CI) adjusted [†]	P value bicaudal
Gender			0.98 (0.28–3.53)	.600
Female	8 (27.6)	21 (72.4)	–	–
Male	9 (27.3)	24 (72.7)	–	–
Race				
Other	4 (50)	4 (50)	–	–
Caucasian	9 (22.5)	31 (77.5)	4.76 (0.85–26.68)	.076
Treatment				
Radiation	9 (56.3)	7 (43.7)	4.77 (1.47–25.45)	.007
Drug (ATC code [*])				
Asparaginase (L01XX02)	5 (17.9)	23 (82.1)	0.39 (0.10–1.49)	.159
Bleomycin (L01DC01)	4 (50)	4 (50)	1.96 (0.50–19.17)	.199
Carboplatin (L01XA02)	2 (50)	2 (50)	3.35 (0.19–41.98)	.301
Cyclophosphamide (L01AA01)	10 (27)	27 (73)	1.32 (0.27–3.54)	1.000
Cisplatin (L01XA01)	3 (33.3)	6 (66.7)	1.41 (0.20–7.62)	.696
Cytarabine (L01BC01)	6 (19.4)	25 (80.6)	0.43 (0.11–1.58)	.255
Dacarbazine (L01AX04)	4 (50)	4 (50)	1.96 (0.50–19.17)	.199
Dactinomycin (L01DA01)	5 (41.7)	7 (58.3)	4.45 (0.47–10.04)	.283
Daunorubicin (L01DB02)	6 (20.7)	23 (79.3)	0.49 (0.14–1.88)	.393
Dexamethasone (H02AB02)	5 (17.2)	24 (82.8)	0.37 (0.09–1.36)	.153
Doxorubicin (L01DB01)	12 (26.7)	33 (73.3)	1.04 (0.22–3.85)	1.000
Etoposide (L01CB01)	4 (23.5)	13 (76.5)	0.70 (0.15–3.12)	.759
Ifosfamide (L01AA06)	3 (23.1)	10 (76.9)	0.76 (0.12–3.55)	1.000
Mercaptopurine (L01BB02)	6 (20.7)	23 (79.3)	0.49 (0.14–1.88)	.393
Methotrexate (L01BA01)	8 (21.6)	29 (78.4)	0.48 (0.14–1.77)	.254
Prednisone (H02AB07)	8 (26.7)	22 (73.3)	0.95 (0.26–3.28)	1.000
Tioguanine (L01BB03)	4 (22.2)	14 (77.8)	0.81 (0.14–2.78)	.756
Vinblastine (L01CA01)	4 (50)	4 (50)	1.96 (0.50–19.17)	.199
Vincristine (L01CA02)	13 (27.7)	34 (72.3)	1.52 (0.25–5.34)	1.000

CI = confidence interval, LAE = late adverse effects.

* Anatomical Therapeutic Chemical classification system.

[†] Odds ratio adjusted for sex, age, and treatment.

4.1. Comparison with previous studies

Hypothyroidism is the most commonly reported abnormality of the thyroid gland after radiation exposure, but hyperthyroidism and development of thyroid nodules occur as well. The association between hypothyroidism and higher radiation doses has been well established.^[13]

In an evaluation of 1791 Hodgkin lymphoma survivors in the CCSS cohort, 34% reported at least 1 thyroid abnormality. Hypothyroidism was most commonly reported (relative risk [RR] = 17.1; $P < .001$ compared to the sibling population).^[14]

Doses of radiation greater than 10 Gy in the thyroid region can cause hypothyroidism and, more rarely, hyperthyroidism. Doses above 25 Gy may also predispose the individual to the development of thyroid nodules. Doses higher than 30 Gy increase the risk of developing thyroid cancer.^[15] Hypothyroidism was diagnosed in 4 of the 8 survivors with damage in endocrine-metabolic system. The 4 survivors had received radiotherapy in the cervical region (doses of 20Gy–50Gy).

Cardiac toxicity may be considered a complication in cancer patients during and after treatment and contributes significantly to the increased morbidity and mortality of patients treated with this disease. Both CT and radiotherapy are recognized as cardiotoxic therapies.^[16]

A total of 52 (84%) patients had received doses of anthracyclines. Of these, 7 had some type of late adverse effect in the cardiovascular system, 5 of these survivors had an irregular condition of the mitral valve and 2 also had alterations in the

tricuspid valve observed in the echocardiogram. These disorders were not observed in the baseline exams.

In the retrospective analysis of the CCSS that evaluated the risk factors associated with cardiac changes in survivors of cancer in childhood and adolescence, the researchers identified an increased risk of valvulopathy in patients who received high doses of anthracycline when compared to their siblings.^[16]

Of the 3 participants who had received cranial radiation therapy at doses of 18 Gy and 45 Gy, none of them presented with motor dysfunction, coordination, or sensory loss. However, hearing loss may occur for other treatment-related reasons, for example, exposure to therapeutic agents such as platinum compounds as well as radiation therapy. A study by Grewal and colleagues^[17] found 50% of children treated with cisplatin developed some permanent degree of hearing loss. At cumulative doses of 400 mg/m², up to 90% of children may develop moderate to severe hearing loss, with up to 25% developing severe hearing loss.^[17,18] Of the 9 participants in this study who had received cisplatin, 7 had received doses above 400 mg/m²; but so far, only 1 survivor has been diagnosed with hearing loss, which was classified as grade 2.

Cancer treatments associated with renal injury and/or increased blood pressure include antineoplastic agents (cisplatin, carboplatin, ifosfamide, and methotrexate), renal radiation therapy, and nephrectomy.^[19] Among the participants of our study, only 1 participant presented grade 1 decreased glomerular filtration rate. This participant had suffered neuroblastoma and

had undergone unilateral nephrectomy. Another participant presented grade 3 arterial hypertension; he had been diagnosed with Wilms tumor and had also undergone unilateral nephrectomy.

Eight participants were treated with bleomycin for Hodgkin lymphoma and after the end of treatment, they did not present changes in their spirometry or pulmonary function tests. In addition, 4 survivors had received radiotherapy to the mediastinum concomitant with bleomycin; however, none developed pulmonary alteration. Pulmonary toxicity due to CT, radiotherapy in the mediastinum, or both is also observed and may consist of an initial phase, resulting from interstitial lung damage that may occur in the months after treatment.^[20] Drugs that have been shown to cause pulmonary toxicity include bleomycin, mitomycin, nitrosoureas (carmustine and lomustine), busulfan, and cyclophosphamide.^[21]

Late effects of radiation therapy may be evident soon after therapy or decades later as second malignant neoplasms. Multiple factors may affect the incidence and severity of radiation-related late effects: organs and tissues included in the treatment field, type of radiation administered, daily fractional and cumulative radiation dose, and age at treatment.^[22]

Radiation-related late effects include neurocognitive deficits, growth hormone deficiency, obesity, valvular disease, hypothyroidism, pulmonary disease, renal insufficiency, musculoskeletal changes, different types of second cancers, among others.^[22] Probably the short follow-up in our study was not sufficient to identify the occurrence of second malignancy but other LAE were observed and may be consequence of this treatment modality. In our statistical analysis, the radiation therapy showed to be associated with the occurrence of LAE.

4.2. Limitations and strengths

The present study is limited by a possible selection bias due to the retrospective nature of the study. Other limitations may be considered. First, physicians used a checklist format based on a guideline to investigate late adverse effects; they may tend to collect information only described in the checklist. During clinical examination, they may evaluate only the recommendations of what of the COG guidelines and may not perceive or observe other health problems due to the checklist used during the appointment. However, the guidelines cover most of the events that may appear; so, we can assume that our result, compared to the other studies, shows the most important effects that are possible to be detected. Second, the survivor's lifestyle (diet, physical activity, social behavior, etc) and family history can be a variable that may have interfered with the interpretations of some tests results. Third, there was a difficulty in clearly distinguishing the chronology between the exposure and the onset of the disease; since some survivors were included in the specialized and systematized outpatient clinic many years after the end of the treatment. At which time, some of tests had never been previously requested. The short follow-up time at the VER Outpatient Clinic (October 2010–December 2014) may have interfered with the identification of changes that will appear later on. Continuous follow-up might identify additional cases.

Another limitation was that this study involved a single center and a relatively small number of patients, which may lead to admission rate bias.

Our study did not include many patients who received cranial radiotherapy for the treatment of tumors in the central nervous system, which is the location of the highest incidence of solid

tumors in the pediatric age group. The fact that the institution did not have a pediatric neurosurgeon could explain the low prevalence of this type of treatment and the lack of LAE associated with treatment.

The strength of this study is the quality of the data obtained, collected through interviews of the cancer survivors by the trained team of the VER Outpatient Clinic during the follow-up appointments. The laboratory tests were carried out at the institution itself, on the study site, which facilitated access to the results with the additional possibility of consulting those survivors that had not yet performed the requested examination.

Considering that there are few published studies on this subject with Brazilian survivors, and none of the studies published used the CTCAE, this study represents an important contribution in terms of service implementation, effectiveness of early detection of adverse effects according to the Children Oncology Group model, and severity assessment according to CTCAE.

4.3. Practices implications

The experience of the VER Outpatient Clinic, where care has been implemented in a systematic manner, has shown that there are LAE that occur in pediatric oncology patients. According to scientific literature, we presume that early identification can lead to intervention that minimizes the complications arising from the treatment of cancer in childhood and adolescence.

Providing care in the VER Outpatient Clinic to patients who have received cancer treatment at GRENDAACC itself is a unique opportunity to offer prevention and detection of LAE related to antineoplastic treatment. In Brazil, there are no published reports from any other institution that offers systematized care in the COG model; thus, the experience at this institution can serve as a model for other institutions providing similar care.

5. Conclusion

We found no variations in frequency and severity in the analysis by race, sex, and antineoplastic treatment. Only radiotherapy was associated with the occurrence of treatment-related LAE.

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Author contributions

Conceptualization: Luciane Cruz Lopes, Annemeri Livinalli.

Data curation: Marcus Tolentino Silva.

Formal analysis: Annemeri Livinalli, Marcus Tolentino Silva.

Investigation: Annemeri Livinalli.

Methodology: Luciane Cruz Lopes, Annemeri Livinalli.

Project administration: Luciane Cruz Lopes.

Resources: Annemeri Livinalli.

Software: Marcus Tolentino Silva.

Supervision: Luciane Cruz Lopes.

Writing – original draft: Annemeri Livinalli.

Writing – review & editing: Luciane Cruz Lopes.

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