HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Int J Cancer. 2021 May 01; 148(9): 2079–2089. doi:10.1002/ijc.33361.

Role of Radiotherapy and Chemotherapy in the Risk of Leukemia after Childhood Cancer: An International Pooled Analysis

Rodrigue S. Allodji, PhD[1,2,3,4,‡], **Margaret A. Tucker, MD**[5], **Michael M. Hawkins, MD PhD**[6], **Marie-Cécile Le Deley, MD PhD**[7], **Cristina Veres, MS**[1,2,3], **Rita Weathers, MS**[8], **Rebecca Howell, PhD**[8,9], **Dave Winter, MS**[6], **Nadia Haddy, PhD**[1,2,3], **Carole Rubino, MD PhD**[1,2,3], **Ibrahima Diallo, PhD**[1,2,3], **Mark P. Little, DPhil**[5], **Lindsay M. Morton, PhD**[5], **Florent de Vathaire, PhD**[1,2,3]

[1]Radiation Epidemiology Group, Unit 1018 INSERM-CESP, Villejuif, F-94805, France

[2]Gustave Roussy, Villejuif, F-94805, France

[3]Université Paris–Saclay, Villejuif, F-94805, France

[4]Polytechnic School of Abomey-Calavi (EPAC), University of Abomey-Calavi, 01 P.O. Box 2009, Cotonou, Benin

[5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

[6]Centre for Childhood Cancer Survivor Studies, School of Health and Population Sciences, University of Birmingham, Public Health Bldg, Edgbaston, Birmingham B15 2TT, United Kingdom

[7]Methodology and Biostatistic Unit, Centre Oscar Lambret, Lille, France

[8]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[9]The University of Texas Graduate School of Biomedical Sciences (GSBS), TX, USA

Abstract

Childhood cancer survivors are at increased risk for second primary leukemia (SPL), but there is little consensus on the magnitude of some risk factors because of the small size of previous studies. We performed a pooled analysis of all published studies with detailed treatment data, including estimated active bone marrow (ABM) dose received during radiation therapy and doses of specific chemotherapeutic agents for childhood cancer diagnosed from 1930 through 2000, in order to more thoroughly investigate treatment-related risks of SPL. A total of 147 SPL cases (of which 69% were acute myeloid leukemia [AML]) were individually-matched to 522 controls, all from four case–control studies including patients from six countries (France, United Kingdom,

‡**Corresponding author**: Dr Rodrigue S. Allodji, Radiation Epidemiology Group / CESP - Unit 1018 INSERM, Gustave Roussy, B2M, 114, rue Édouard Vaillant, 94805 Villejuif Cedex, Tel 01 42 11 54 98 / Fax 01 42 11 53 15, rodrigue.allodji@gustaveroussy.fr.

Conflict of interest: The authors declare no conflict of interest.

Ethics statement: Each collaborating site obtained local institutional review board (IRB) issues approval for their study. Principal investigators of studies have signed data transfer agreement (DTA), thereafter, the complete original data set of the study was collected and harmonized according to a pre-specified format at the data coordinating center (GR/CESP-INSERM). All databases received were in fully anonymised form.

United States, Canada, Italy, Netherlands). Odds ratios (OR) and corresponding 95% confidence intervals (CIs) were calculated using conditional logistic regression, and the excess OR per gray (EOR/Gy) was also calculated. After accounting for the other therapies received, topoisomerase II inhibitor was associated with an increased SPL risk (highest tertile vs. none: OR=10.0, 95%CI:3.7-27.3). Radiation dose to the ABM was also associated with increased SPL risk among those not receiving chemotherapy (EOR/Gy=1.6, 95%CI:0.1-14.3), but not among those who received chemotherapy. SPL were most likely to occur in the first decade following cancer treatment. Results were similar when analyses were restricted to AML. The evidence of interaction between radiation and chemotherapy has implications for leukemogenic mechanism. The results for topoisomerase II inhibitors are particularly important given their increasing use to treat childhood cancer.

Keywords

Secondary leukemia; childhood cancers survivors; chemotherapy; Topoisomerase II inhibitors; alkylating agents; radiotherapy; radiation dose to active bone marrow

Introduction

The survival of children with cancer has improved substantially over recent decades, and consequently, adverse effects of more current treatment have become increasingly important.[1–5] One of the most serious late effects is the occurrence of second malignant neoplasms (SMN).[1–5] Ionizing radiation is a known carcinogen, and sensitivity to radiation is highest early in life.[5] Leukemia is the most radiation-sensitive malignancy, often appearing sooner after exposure than any other cancer.[5–10] However, second primary leukemia (SPL) is also associated with various chemotherapeutic agents.[11–20] Potential associations between SPL risk and various chemotherapy drugs have been evaluated in a number of cohorts of pediatric or young adult cancer survivors.[12–16,19,20] Those studies have demonstrated strongly increased risk of acute myeloid leukemia (AML) after certain types of chemotherapy, in particular, alkylating agents (e.g., cyclophosphamide, melphalan, ifosfamide, procarbazine, or nitrogen mustard) and topoisomerase II inhibitors (e.g., epipodophyllotoxins, anthracyclines). However, because drugs are often given in combination, individual studies have had limited ability to disentangle risks associated with specific agents. Another key unresolved question is the potential role for radiotherapy in leukemia risk, either with or without chemotherapy, with some previous studies suggesting increased risk but others not.[12–14,16,19]

To address these gaps in knowledge, we pooled data from prior studies of SPL after childhood cancer with high quality information on specific chemotherapy agents and radiation dose to the active bone marrow (ABM). These comprise: (a) the British Childhood Cancer Survivor Study (BCCSS);[14] (b) two parallel French datasets, the Société Française d'Oncologie Pédiatrique (SFOP) dataset,[19,20] and the Euro2K dataset, which recently became the French Childhood Cancer Survivor Study (FCCSS);[12,13] and (c) the International Late Effects Study Group (LESG) study.[16] This current pooled analysis, with information on 147 cases and 522 matched controls, offers a unique opportunity to more

thoroughly investigate the respective roles of chemotherapy and radiotherapy in the occurrence of SPL after childhood cancer.

Materials and Methods

Selection criteria and data inclusion

We included all studies on SPL after childhood cancer published during 1987-2015 that collected information on chemotherapy and radiation dose to ABM in the present collaborative international study. Four case–control studies including patients from six countries (France, United Kingdom, United States, Canada, Italy, Netherlands) contributed data (Supplementary Table A1, online only).[13,14,16,19] Each study was a nested case–control study of SPL occurring within respective cohorts of childhood cancer survivors. Three to five controls were matched by basic demographic characteristics (e.g., age at first treatment, sex) and survival time at least as long as the index matched case's interval from childhood cancer to SPL diagnosis (Supplementary Table A1, online only). The leukemia subtype was classified according to the International Classification of Diseases for Oncology [ICD-O] (Supplementary Table A2, online only).[21–23]

Chemotherapy (CT) and Radiotherapy (RT) Data

In each study, radiotherapy and chemotherapy exposures were ascertained from the start of childhood cancer treatment until the development of SPL for each case or the corresponding interval for each matched control. Individual-level data on radiotherapy were utilized to reconstruct the mean radiation dose to the main bones containing ABM, and then, using age-dependent coefficients, to the whole ABM.[12–14,16,19,20,24–26] Each study also abstracted detailed data from medical records regarding chemotherapy exposures for both initial and subsequent therapy for the first cancer. Data collected included drug name, dates of administration, and total dose per unit of body surface area measured as milligrams per square meter (mg/m^2). We assessed SPL risk according to class of chemotherapy drugs, defined as follows: (a) alkylating agents, (b) topoisomerase II inhibitors including both anthracyclines and epipodophyllotoxins, (c) platinum compounds, (d) vinca-alkaloids and (e) antimetabolites (Supplementary Tables A3 and A4, online only). Except for the alkylating agents, the sum of cumulative doses of different chemotherapy agents within specific groups was performed, based on the assumption that all agents within a particular class had equal leukemogenic potency per unit dose. To sum the alkylating agent doses, we used the cyclophosphamide equivalent dose (CED) for toxicity proposed by Green et al.[27] using the following formula: CED (mg/m^2)=1.0*(cumulative cyclophosphamide dose [mg/m^2]) + 0.2440*(cumulative ifosfamide dose [mg/m^2]) + 0.857*(cumulative procarbazine dose [mg/m^2]) + 14.286*(cumulative chlorambucil dose [mg/m^2]) + 15.0*(cumulative BCNU dose [mg/m^2]) + 16.0*(cumulative CCNU dose [mg/m^2]) + 40.0*(cumulative melphalan dose [mg/m^2]) + 50.0*(cumulative thiotepa dose [mg/m^2]) + 100.0*(cumulative mechlorethamine dose [mg/m^2]) + 8.823*(cumulative busulfan dose [mg/m^2]) + 3.770*(cumulative dacarbazine dose [mg/m^2]). The 33^{rd} and 66^{th} percentiles and quartiles of the distribution among cases exposed were used to define the dose intervals for the classes of chemotherapy drugs and for whole ABM dose respectively (Supplementary Fig A1, online only). We were unable to group chemotherapy drugs together into regimens administered in

cycles since these data were not collected in some studies. Therefore we analysed SPL risk according to broad combinations of agents across different classes.

Statistical analysis

Conditional logistic regression analysis was conducted to derive estimated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of SPL associated with specific treatments.[28,29] We first ran univariate models including each chemotherapy drug or each class of chemotherapy drugs and radiotherapy as indicator variables (no vs. yes) (Supplementary Table A5, online only). Similar models were employed in which the chemotherapeutic doses per class and ABM radiation doses were divided into categories (using the quartiles of the distribution of the whole ABM dose and the 33rd and 66th percentiles in the distribution of each cumulative dose of chemotherapy in the combined cases group) (Supplementary Fig A1 and A2, online only). We then constructed multivariable models to estimate adjusted ORs for treatment-related variables. Tests of heterogeneity and trend were based on the likelihood ratio, comparing model fit with and without the variable of interest. For trend tests, ordinal variables were treated as continuous. Additionally, the excess OR per Gy (EOR/Gy) for the ABM dose from radiotherapy was estimated using a linear radiation dose-response model, with additional analyses also assessing departure from a multiplicative interaction between ABM radiation (continuous dose) and chemotherapy (yes/no).

Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA)[30] and Epicure.[31] A two-sided type I error of 0.05 was assumed to determine significance, and 95% CIs were likelihood-based.[32]

Results

Most (N=101, 68.7%) of the cases were diagnosed with AML; the remaining cases included acute lymphoblastic leukemia (N=18, 12.2%), chronic myeloid leukemia (N=6, 4.1), myelodysplastic syndromes (N=17, 11.6%) and other leukemias (N=5, 3.4%). The median age at first childhood cancer diagnosis overall was 8.0 years, and the median interval before SPL diagnosis was 4.4 years (Table 1). 119 SPL cases (81%) occurred within the decade following childhood cancer treatment initiation. Lymphoma accounted for approximately one-quarter of the childhood cancer diagnoses (27.9% for cases, 20.7% for controls), with lesser proportions associated with brain tumor (17.0% for cases, 18.0% for controls) and osteosarcoma (10.2% for cases, 6.5% for controls). Only 2 cases of SPL occurred in patients who received neither radiotherapy nor chemotherapy.

The characteristics of the 147 cases who developed a SPL are summarized in supplementary Table A6 (online only) by type of primary childhood cancer. Among these, 59 (40.1%) were diagnosed with their primary cancer under the age of five years; specifically, 93.3% (14/15) and 78.6% (11/14) of SPL cases occurring among neuroblastoma or kidney tumor survivors were originally diagnosed before age five, respectively. Of the 25 cases of SPL in brain tumor survivors, 18 were women (72.0%), whereas 11 among 15 cases of SPL in osteosarcoma survivors, were men (73.3%). The median attained age at the development of

SPL was highest for lymphoma (17.0 years) and lowest for neuroblastoma (8.0 years) (Supplementary Table A6, online only).

Radiotherapy

Radiation therapy was associated at borderline levels of significance with increased SPL risk whether adjusted for chemotherapy (OR=1.5, 95%CI:0.99-2.3; P=0.06) or unadjusted (OR=1.6, 95%CI:1.0-2.4; P=0.03) (Table 2). Risk associated with radiotherapy was much higher (OR=6.4, 95%CI:1.3-30.3) among patients who did not receive chemotherapy (Table 2). Likewise SPL risk modestly increased with increasing mean ABM radiation doses unadjusted for chemotherapy (OR for the highest quartile (>12 Gy)=2.3, 95%CI:1.1-4.6; P-trend=0.02), but this was not the case when adjusted for chemotherapy (OR for the highest quartile (>12 Gy)=1.5, 95%CI:0.66-3.13; P-trend=0.3) (Table 3), with a significant negative interaction with chemotherapy (P for interaction=0.006, Table 4). Using a linear excess OR model, the EOR/Gy of SPL was equal to 0.02 (95%CI:-0.01-0.09) among patients who received chemotherapy and 1.55 (95%CI:0.14-14.3) among patients who did not (Table 4). Again, much higher radiation-associated risks were seen among patients not receiving chemotherapy (OR [>0-12 Gy]=7.7, 95%IC:1.7-36.2 and OR [>12 Gy]=3.7, 95%IC:0.28-49.9) (Table 5).

The association between radiotherapy and SPL risk strongly varied with time after childhood cancer treatment (Supplementary Table A7, online only). Indeed, 78 (66%) of SPL occurring in the first decade following childhood cancer treatment were treated with radiotherapy, which was associated with 34.8-fold (95%CI:10.8-111.8) increased SPL risk, but there was no significant radiation-associated SPL risk after the first decade.

Chemotherapy

Overall, SPL was significantly associated with chemotherapy (OR=6.2, 95%CI:2.9-13.3; P<0.0001), and was close (OR=5.5, 95%CI:2.6-12.0; P<0.0001) after adjustment for radiotherapy and year of diagnosis (Table 2). Patients who received chemotherapy alone had a markedly elevated risk of SPL (OR=19.0, 95%CI:3.8-94.7) compared with those not receiving chemotherapy or radiotherapy (p<0.001).

In univariate analyses, topoisomerase II inhibitors (P<0.0001), alkylating agents (P<0.0001), platinum compounds (P=0.007) and vinca-alkaloids (P<0.0001) administration were found to increase the risk of SPL (Table 3), but in a multivariable analysis the association with alkylating agents and platinum compounds disappeared. Topoisomerase II inhibitors were independently associated with an increased SPL risk (Table 3). The risk of SPL associated with topoisomerase-II inhibitors increased in a strongly dose-dependent manner, with OR=3.6 (95%CI:1.8-7.3), 3.2 (95%CI:1.5-6.9), and 10.0 (95%CI:3.7-27.3) for cumulative doses of >0- to 600, >600 to 2500, and >2500 mg/m^2, respectively, compared with patients not receiving topisomerase-II inhibitors. Likewise, patients who received both radiotherapy and high-dose topoisomerase II inhibitors (>2500 mg/m^2) had strikingly elevated SPL risk (OR=16.1, 95%CI:5.0-51.4) compared with those who did not receive radiotherapy and topoisomerase II inhibitors (Table 6). Our results with respect to SPL risk for topoisomerase

II inhibitors varied little according to the calendar period of diagnosis of first primary childhood cancer (Supplementary Table A8, online only).

There was no clear association between SPL risk and alkylating agents (P=0.9; Supplementary Table A5, online only) but a significant dose response for cyclophosphamide-equivalent dose (CED) overall was found (P-trend=0.04) (Table 3). There was high evidence of increased risk of SPL associated with alkylating agents for the high-dose of CED (>22000 mg/m^2) (OR=2.8, 95%CI:1.2-6.6) vs no alkylating agents after adjusting for ABM radiation dose, topoisomerase II inhibitors and platinum compounds (Table 3). This risk of SPL with alkylating agents for the high-dose of CED (>22000 mg/m^2) (OR=2.2, 95%CI:0.54-9.1) was slightly reduced in patients who did not receive radiotherapy (Table 6).

The association between topoisomerase II inhibitors or alkylating agents and SPL risk was also dependent on the latency period following childhood cancer treatment (Supplementary Table A7, online only). Indeed, 97 (81%) of SPL occurred in the first decade following childhood cancer treatment with topoisomerase II inhibitors 16 (13%) or alkylating agents 15 (13%) or both 66 (55%).

Receiving both topoisomerase II inhibitors and alkylating agents, or both topoisomerase II inhibitors and vinca-alkaloids were associated with OR of 14.8 (95%CI:5.2-42.3), and 9.6 (95%CI:3.2-29.2), respectively, compared to those having no chemotherapy, after adjustment for ABM dose and year of diagnosis (Supplementary Table A9, online only). Those who received only alkylating agents and vinca-alkaloids had a lower risk (OR=2.6, 95%CI:0.98-6.8).

Type of SPL

When restricting the analysis to AML, the effect of ABM radiation dose (OR [>0-12 Gy]=4.9, 95%CI:0.95-25.6) in patients who did not receive chemotherapy was lower than when considering all types of leukemias (Table 5). There was modest and non-significant risk of high ABM radiation dose (>12 Gy) among patients who had received chemotherapy (OR=2.2, 95%CI:0.94-5.0) vs patients who had received chemotherapy without no radiotherapy. Small numbers did not permit specific investigations for other types of leukemias.

Type of first cancer

No independent effect of the first cancer type on risk of SPL was observed (p=0.2), and the findings for the dose-related SPL risks for radiation dose, topoisomerase II inhibitors and alkylating agents were little changed with adjustment for the first cancer type.

Discussion

This pooled analysis of all studies that had individual ABM dose estimates and information on chemotherapy,[13,14,16,20] is to the best of our knowledge the largest to assess the risk of SPL among childhood cancer survivors, with 147 SPL cases. By combining data from individual studies conducted over several decades, we increased power to assess SPL risk

associated with childhood cancer treatment. We showed that topoisomerase II inhibitors (anthracyclines and epipodophyllotoxins) increased the risk of SPL independently of other treatments, whereas the increase in risk associated with increasing ABM radiation dose was observed only in patients who did not receive chemotherapy. Our results for topoisomerase II inhibitors and ABM radiation dose are particularly important given their role in current treatment approaches.[33,34]

Analyses of treatment patterns over time revealed a shift from the predominant use of radiation before the 1960s to increasing using of a combination of radiotherapy and chemotherapy by the 1970s. In the 1980s, treatment mainly by poly-chemotherapy with alkylating agents, topoisomerase II inhibitors, vinca-alkaloids, or antimetabolites, added to the treatment modalities. From this period to 1990s and for the most recent periods, the use of multidrug therapy has greatly increased, and new therapeutic agents such as platinum compounds have been used. However, this pooled analysis was based on case-control studies, which could not fully describe changes in treatment regimens of childhood cancers.

Our results extend those of previous studies based on substantially smaller numbers of childhood cancer survivors that reported an increased risk of SPL from topoisomerase II inhibitors (anthracyclines and epipodophyllotoxins).[12–14,19] We were unable to investigate the role of the schedule of administration.[35] Nevertheless, our study confirmed that after controlling for radiotherapy and other chemotherapy classes, patients with topoisomerase II inhibitors had increased risk of SPL (OR=3.9, 95%CI:2.1-7.4; P<0.0001; Supplementary Table A5, online only) compared with patients who had received none of these drugs, in line with previous findings,[12–14,19,35] and showed that this remains when adjusting for other types of treatment.

The first broad class of cytotoxic drugs to be linked to SPL was the alkylating agents.[34–38] In the present study, the risk associated with this class of drugs was markedly reduced when adjusting for use of topoisomerase II inhibitors, and contrasts with some previous studies.[34–38] This could be explained in part by decreases in use of alkylating agents over time and/or the close association between exposure to alkylating agents and exposure to topoisomerase II inhibitors (Cramer's V=0.6). Although there was a trend for increased risk of SPL with platinum compounds, this trend disappeared when adjusting for use of other drugs, in contrast with the finding of a recent study.[39] Our findings also confirmed that treatment with topoisomerase II inhibitors in combination with alkylating agents increases the probability of SPL, as others have found;[35] other studies have suggested that this risk may be affected by genetic predisposition, genetic variations in drug metabolism, and cytogenetic and molecular features.[40,41]

Leukemia induced by therapeutic radiation alone among childhood cancer survivors is rare.[12,13,16,19,42,43] The EOR/Gy that we estimated among patients who did not receive chemotherapy, 1.55 (95%CI:0.14-14.3), has a wide range and is slightly lower, with what was expected from BEIR VII model for the same age at irradiation. This risk coefficient contrasts with the large risks seen for myeloid malignancies and acute lymphocytic leukemia after low doses (<100 mGy) of radiation.[8] We did not observe an additional increase in SPL risk associated with radiation in patients who received chemotherapy (Tables 4). This may

be due to the strongly elevated risks associated with chemotherapy, and possible ablative effects of high-dose radiotherapy on the ABM.[11,44,45]

Among the strengths of our study is the inclusion of all studies on SPL after childhood cancer with information on chemotherapy and radiation dose to ABM published in the interval 1987 – 2015, among childhood cancer survivors diagnosed from 1930 through 2000, covering several decades of treatment regimens. Previous studies have been generally limited by smaller sample sizes, which prevented more detailed investigation associated with specific classes of chemotherapy agents.[13,14,16,20] In our pooled dataset, we were better able to evaluate the risk of SPL associated with radiotherapy and/or chemotherapy treatments, but the analyses were limited by the differential data on chemotherapy regimens and drug doses available among the included studies.

Although rare, SPL has poor survival, therefore, identifying patients at highest risk has important implications for clinical approaches to childhood cancer treatment. Cancer survival rates are expected to increase further with improved diagnosis, treatment and followup.[46,47] Additional attention must be paid to reduce the incidence of treatment-related morbidity, such as SPL. Our results provide SPL risks that may have implications both for the planning of new treatments and highlight the need for awareness by survivors and their healthcare providers for potential risk related to SPL several decades after childhood cancer treatment.[48]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We are very grateful to the childhood cancer survivors from the Late Effects Study Group (LESG), Société Française d'Oncologie Pédiatrique (SFOP), French Childhood Cancer Survivor Study (FCCSS), and British Childhood Cancer Survivor Study (BrCCSS) whose information was used in the current study.

Funding:

This work was supported by the Ligue Nationale Contre le Cancer, the Fondation (FORCE) de recherche sur le cancer de l'enfant, the Intramural Research Program of the National Cancer Institute/National Institutes of Health, the PeriDoseQuality project (Grant Agreement Number C14017LS), The Fondation ARC (Grant PopHARC), and the Agence Nationale pour la Recherche (ANR).

Role of the Sponsor:

The funding agencies had no role in the design and conduct of the study; nor in the collection, management, analysis and interpretation of the data; nor in the preparation, review, and approval of the manuscript.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

ABM	Active Bone Marrow

AML	Acute Myeloid Leukemia
BCCSS	British Childhood Cancer Survivor Study
CED	Cyclophosphamide Equivalent Dose
CT	Chemotherapy
EOR/Gy	Excess Odds Ratio per Gray
FCCSS	French Childhood Cancer Survivor Study
LESG	Late Effects Study Group
OR	Odds Ratio
RT	Radiotherapy
SFOP	Société Française d'Oncologie Pédiatrique
SPL	Second Primary Leukemia

References

1. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010; 102: 1083–1095. doi: 10.1093/jnci/djq238. [PubMed: 20634481]
2. Trama A, Botta L, Foschi R, et al. Survival of European adolescents and young adults diagnosed with cancer in 2000–07: population-based data from EUROCARE-5. Lancet Oncol 2016; 17: 896–906. doi: 10.1016/S1470-2045(16)00162-5. [PubMed: 27237614]
3. Reulen RC, Frobisher C, Winter DL, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. J Am Med Assoc (JAMA) 2011; 305: 2311–2319. doi: 10.1001/jama.2011.747.
4. Allodji RS, Hawkins MM, Bright CJ, et al. Risk of subsequent primary leukaemias among 69,460 five-year survivors of childhood cancer diagnosed from 1940 to 2008 in Europe: A cohort study within PanCareSurFup. Eur J Cancer. 2019;117:71–83. doi: 10.1016/j.ejca.2019.05.013. [PubMed: 31260818]
5. Turcotte LM, Liu Q, Yasui Y, et al. Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015. J Am Med Assoc (JAMA) 2017; 317: 814–824. doi: 10.1001/jama.2017.0693.
6. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), UNSCEAR 2006 Report. Annex A. Epidemiological Studies of Radiation and Cancer. Place United Nations: United Nations; 2008.
7. Armstrong B, Brenner DJ, Baverstock K, Cardis E, Green A, Guilmette RA, et al., Radiation. Volume 100D. A review of human carcinogens. Lyon, France: International Agency for Research on Cancer; 2012.
8. Little MP, Wakeford R, Borrego D, et al. Leukaemia and myeloid malignancy among people exposed to low doses (<100 mSv) of ionising radiation during childhood: a pooled analysis of nine historical cohort studies. Lancet Haematol 2018; 5:e346–e358. doi: 10.1016/S2352-3026(18)30092-9. [PubMed: 30026010]
9. Kendall GM, Little MP, Wakeford R, et al. A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980–2006. Leukemia 2013; 27:3–9. doi: 10.1038/leu.2012.151. [PubMed: 22766784]

10. Spycher BD, Lupatsch JE, Zwahlen M, et al. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect 2015; 123:622–628. doi: 10.1289/ehp.1408548. [PubMed: 25707026]
11. Nottage K, Lanctot J, Li Z, Neglia JP, et al. Long-term risk for subsequent leukaemia after treatment for childhood cancer: a report from the Childhood Cancer Survivor Study. Blood 2011;117:6315–6318. [PubMed: 21498675]
12. Haddy N, Le Deley MC, Samand A, et al. Role of radiotherapy and chemotherapy in the risk of secondary leukaemia after a solid tumour in childhood. Eur J Cancer 2006; 42: 2757–2764. doi: 10.1182/blood-2011-02-335158. [PubMed: 16965909]
13. Allodji RS, Schwartz B, Veres C, et al. Risk of Subsequent Leukemia after a solid tumour in childhood: Impact of bone marrow radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys 2015; 93: 658–667. doi: 10.1016/j.ijrobp.2015.07.2270. [PubMed: 26461008]
14. Hawkins MM, Wilson LM, Stovall MA, et al. Epipodophyllotoxins, alkylating agents, and radiation and risk of secondary leukaemia after childhood cancer. BMJ 1992; 304: 951–958. doi: 10.1136/bmj.304.6832.951. [PubMed: 1581717]
15. Granfeldt Ostgard LS, Medeiros BC, Sengeløv H, et al. Epidemiology and Clinical Significance of Secondary and Secondary Acute Myeloid Leukemia: A National Population-Based Cohort Study. J Clin Oncol. 2015; 33: 3641–3649. doi: 10.1200/JCO.2014.60.0890. [PubMed: 26304885]
16. Tucker MA, Meadows AT, Boice JD Jr, et al. Leukaemia after therapy with alkylating agents for childhood cancer. J Natl Cancer Inst 1987; 78: 459–464. [PubMed: 3469460]
17. Ribera JM. Secondary acute lymphoblastic leukemia. Haematologica. 2018; 103: 1581–1583. doi: 10.3324/haematol.2018.200311. [PubMed: 30270204]
18. Nikkilä A, Raitanen J, Lohi O, et al. Radiation exposure from computerized tomography and risk of childhood leukemia: Finnish register-based case-control study of childhood leukemia (FRECCLE). Haematologica. 2018; 103: 1873–1880. doi: 10.3324/haematol.2018.187716. [PubMed: 29976736]
19. Le Deley MC, Leblanc T, Shamsaldin A, et al. Risk of secondary leukaemia after a solid tumour in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Société Française d'Oncologie Pédiatrique. J Clin Oncol 2003; 21: 1074–1081. doi: 10.1200/JCO.2003.04.100. [PubMed: 12637473]
20. Allard A, Haddy N, Le Deley MC, et al. Role of radiation dose in the risk of secondary leukemia after a solid tumor in childhood treated between 1980 and 1999. Int J Radiat Oncol Biol Phys 2010; 78: 1474–1482. doi: 10.1016/j.ijrobp.2009.09.032. [PubMed: 20303670]
21. International Classification of Diseases for Oncology, first edition. Geneva, World Health Organization 1976.
22. Percy C, Van Holten V, Muir CS, editors. International Classification of Diseases for Oncology, 2nd edition. Geneva, Switzerland: World Health Organization 1992.
23. Steliarova-Foucher E, Stiller C, Lacour B, et al. International Classification of Childhood Cancer, third edition. Cancer 2005; 103: 1457–67. doi: 10.1002/cncr.20910. [PubMed: 15712273]
24. Cristy M Active bone marrow distribution as a function of age in humans. Phys Med Biol. 1981; 26: 389–400. doi: 10.1088/0031-9155/26/3/003. [PubMed: 7243876]
25. Stovall M, Weathers R, Kasper C, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. Radiat Res. 2006; 166: 141–57. doi: 10.1667/RR3525.1. [PubMed: 16808603]
26. Veres C, Allodji RS, Llanas D, et al. A method for retrospective reconstructions of active bone marrow dose-volume metrics. Int J Radiat Oncol Biol Phys 2014; 90: 1216–1224. doi: 10.1016/j.ijrobp.2014.08.335. [PubMed: 25442047]
27. Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: A report from the childhood cancer survivor study. Pediatr Blood Cancer 2014; 61: 53–67. doi: 10.1002/pbc.24679. [PubMed: 23940101]
28. Blettner M, Boice JD Jr. Radiation dose and leukaemia risk: general relative risk techniques for dose-response models in a matched case-control study. Stat Med. 1991; 10: 1511–1526. doi: 10.1002/sim.4780101004. [PubMed: 1947508]

29. Breslow NE, Day NE. Statistical Methods in Cancer Research, Volume 1—The Analysis of Case-Control Studies. IARC: Lyon, 1980.
30. SAS Institute Inc. Base SAS® 9.3 Procedures Guide: Statistical Procedures. Cary, NC: SAS Institute Inc. 2011.
31. Preston DL, Lubin JH, Pierce DA. EPICURE User's Guide. Seattle: Hirosoft International Corporation, 1993.
32. Moolgavkar SH, Venzon DJ. A method for computing profile likelihood based confidence bounds. Ann Statist 1987; 15: 346–359. doi: 10.2307/2347496
33. Green DM, Kun LE, Matthay KK, et al. Relevance of historical therapeutic approaches to the contemporary treatment of pediatric solid tumors. Pediatr Blood Cancer. 2013; 60: 1083–94. doi: 10.1002/pbc.24487. [PubMed: 23418018]
34. Hudson MM, Neglia JP, Woods WG, et al. Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. Pediatr Blood Cancer. 2012; 58: 334–43. doi: 10.1002/pbc.23385. [PubMed: 22038641]
35. Hijiya N, Ness KK, Ribeiro RC, et al. Acute leukaemia as a secondary malignancy in children and adolescents: current findings and issues. Cancer 2009; 115: 23–35. doi: 10.1002/cncr.23988. [PubMed: 19072983]
36. Kyle RA, Pierre RV, Bayrd ED. Multiple myeloma and acute myelomonocytic leukemia: report of four cases possibly related to melphalan. N Engl J Med 1970; 283: 1121–1125. doi: 10.1056/NEJM197011192832101. [PubMed: 5273282]
37. Davies SM. Secondary leukemia associated with alkylating agents. Med Pediatr Oncol. 2001; 36: 536–40. doi: 10.1002/mpo.1126. [PubMed: 11340608]
38. Morton LM, Dores GM, Tucker MA, et al. Evolving risk of secondary acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood. 2013; 121: 2996–3004. doi: 10.1182/blood-2012-08-448068. [PubMed: 23412096]
39. Liang F, Zhang S, Xue H, et al. Risk of second primary cancers in cancer patients treated with cisplatin: a systematic review and meta-analysis of randomized studies. BMC Cancer. 2017; 17: 871. doi: 10.1186/s12885-017-3902-4. [PubMed: 29258467]
40. Pedersen-Bjergaard J, Andersen MK, Andersen MT, et al. Genetics of secondarymyelodysplasia and acute myeloid leukemia. Leukemia 2008; 22:240–8. doi: 10.1038/sj.leu.2405078. [PubMed: 18200041]
41. Bogni A, Cheng C, Liu W, et al. Genome-wide approach to identify risk factors for secondarymyeloid leukemia. Leukemia 2006; 20: 239–246. doi: 10.1038/sj.leu.2404059. [PubMed: 16341039]
42. Advani PG, Schonfeld SJ, Curtis RE, et al. Risk of therapy-related myelodysplastic syndrome/acute myeloid leukemia after childhood cancer: a population-based study. Leukemia 2019; 33:2947–2978. 10.1038/s41375-019-0520-y. [PubMed: 31341236]
43. Kaldor JM, Day NE, Clarke EA, et al. Leukemia following Hodgkin's disease. N Engl J Med 1990; 322: 7–13. doi: 10.1056/NEJM199001043220102. [PubMed: 2403650]
44. Radivoyevitch T, Sachs RK, Gale RP, et al. Defining AML and MDS second cancer risk dynamics after diagnoses of first cancers treated or not with radiation. Leukemia 2016;30:285–94. doi: 10.1038/leu.2015.258. [PubMed: 26460209]
45. Teepen JC, Curtis RE, Dores GM, et al. Risk of subsequent myeloid neoplasms after radiotherapy treatment for a solid cancer among adults in the United States, 2000-2014. Leukemia 2018;32:2580–2589. doi: 10.1038/s41375-018-0149-2. [PubMed: 29795414]
46. Newhauser WD, Berrington de Gonzalez A, Schulte R, et al. A Review of Radiotherapy-Induced Late Effects Research after Advanced Technology Treatments. Front Oncol 2016; 10: 6–13. doi: 10.3389/fonc.2016.00013.
47. Bright CJ, Reulen RC, Winter DL, et al. Risk of subsequent primary neoplasms in survivors of adolescent and young adult cancer (Teenage and Young Adult Cancer Survivor Study): a population-based, cohort study. Lancet Oncol 2019; 20: 531–545. doi: 10.1016/S1470-2045(18)30903-3. [PubMed: 30797674]

48. Gupta S. and Adolescents and young adults with cancer and the risk of subsequent primary neoplasms: not just big children. Lancet Oncol 2019; 20: 466–467. doi: 10.1016/S1470-2045(18)30941-0. [PubMed: 30797675]

Novelty and Impact

Although rare, secondary leukemia has poor survival, therefore, identifying patients at highest risk has important implications for clinical approaches to childhood cancer treatment. This study is the first with good statistical power to investigate the risk of leukemia and to assess the combination of mutagenic therapies (radiation therapy, topoisomerase II inhibitors, alkylating agents) contributing to risk. These results help inform surveillance guidelines for childhood cancer survivors and guide assessment of leukemia risks from certain contemporary treatment protocols.

Int J Cancer. Author manuscript; available in PMC 2022 May 01.

Table 1:

Patient and treatment characteristics of secondary leukemia cases and controls, by study and in the pooled analysis

Characteristics	LESG[†]		SFOP[¥]		FCCSS[£]		BCCSS[§]		Pooled	
	Cases (n = 25)	Controls (n = 90)	Cases (n = 61)	Controls (n = 196)	Cases (n = 35)	Controls (n = 140)	Cases (n = 26)	Controls (n = 96)	Cases (n = 147)	Controls (n = 522)
Gender										
Female (%)	15 (60.0)	52 (57.8)	32 (52.5)	103 (52.6)	14 (40.0)	56 (40.0)	14 (53.8)	50 (52.1)	75 (51.0)	261 (50.0)
Male (%)	10 (40.0)	38 (42.2)	29 (47.5)	93 (47.4)	21 (60.0)	84 (60.0)	12 (46.2)	46 (47.9)	72 (49.0)	261 (50.0)
Age at childhood cancer diagnosis										
Median (range), years	9.1 (0–16.0)	7.0 (0–16.0)	8.0 (0–17.0)	8.0 (0–17.0)	5.1 (0–15.9)	5.5 (0–17.0)	8.5 (2–15.0)	8.0 (0–15.0)	8.0 (0–17.0)	7.0 (0–17.0)
Year of childhood cancer diagnosis										
Median (range), years	1971 (1950–1977)	1966 (1930–1977)	1991 (1980–1996)	1991 (1980–1997)	1986 (1966–1999)	1986 (1964–2000)	1978 (1945–1983)	1975 (1951–1983)	1985 (1945–1999)	1985 (1930–2000)
First primary childhood cancer type										
Brain tumor (%)	3 (12.0)	12 (13.3)	9 (14.8)	34 (17.3)	6 (17.1)	25 (17.9)	7 (26.9)	23 (24.0)	25 (17.0)	94 (18.0)
Lymphoma (%)	12 (48.0)	32 (35.6)	10 (16.4)	14 (7.1)	10 (28.6)	27 (19.3)	9 (34.6)	35 (36.5)	41 (27.9)	108 (20.7)
Kidney tumor (%)	4 (16.0)	29 (32.2)	3 (4.9)	21 (10.7)	6 (17.1)	18 (12.9)	1 (3.8)	3 (3.1)	14 (9.5)	71 (13.6)
Neuroblastoma (%)	1 (4.0)	6 (6.7)	9 (14.8)	21 (10.7)	3 (8.6)	15 (10.7)	2 (7.7)	8 (8.3)	15 (10.2)	50 (9.6)
Osteosarcoma (%)	3 (12.0)	6 (6.7)	8 (13.1)	10 (5.1)	2 (5.7)	11 (7.9)	2 (7.7)	7 (7.3)	15 (10.2)	34 (6.5)
Other cancers (%)	2 (8.0)	5 (5.6)	22 (36.1)	96 (49)	8 (22.9)	44 (31.4)	5 (19.2)	20 (20.8)	37 (25.2)	165 (31.6)
Radiotherapy										
No	5 (20.0)	12 (13.3)	27 (44.3)	111 (56.6)	14 (40.0)	71 (50.7)	4 (15.4)	30 (31.3)	50 (34.0)	224 (42.9)
Yes	20 (80.0)	78 (86.7)	34 (55.7)	85 (43.4)	21 (60.0)	69 (49.3)	22 (84.6)	66 (68.7)	97 (66.0)	298 (57.1)
Chemotherapy										
No	5 (20.0)	34 (37.8)	1 (1.6)	37 (18.9)	1 (2.9)	37 (26.4)	8 (30.8)	43 (44.8)	15 (10.2)	151 (28.9)
Yes	20 (80.0)	56 (62.2)	60 (98.4)	159 (81.1)	34 (97.1)	103 (73.6)	18 (69.2)	53 (55.2)	132 (89.8)	371 (71.1)
Treatment combination										
Neither radiotherapy nor chemotherapy	-	6 (6.7)	-	24 (12.2)	1 (2.9)	19 (13.6)	1 (3.8)	16 (16.7)	2 (1.4)	65 (12.5)
Radiotherapy only	5 (20)	6 (6.7)	27 (44.3)	87 (44.4)	13 (37.1)	52 (37.1)	3 (11.5)	14 (14.6)	48 (32.7)	159 (30.5)

Characteristics	LESG†		SFOP¥		FCCSS£		BCCSS§		Pooled	
	Cases (n = 25)	Controls (n = 90)	Cases (n = 61)	Controls (n = 196)	Cases (n = 35)	Controls (n = 140)	Cases (n = 26)	Controls (n = 96)	Cases (n = 147)	Controls (n = 522)
Chemotherapy only	5 (20)	28 (31.1)	1 (1.6)	13 (6.6)	-	18 (12.9)	7 (26.9)	27 (28.1)	13 (8.8)	86 (16.5)
Both radiotherapy and chemotherapy	15 (60)	50 (55.6)	33 (54.1)	72 (36.7)	21 (60)	51 (36.4)	15 (57.7)	39 (40.6)	84 (57.1)	212 (40.6)
Interval from childhood cancer to leukemia Ψ										
Median (range), years	6.0 (2.0–18.0)		4.0 (2.0–14.0)		6.2 (2–35.7)		4.0 (1.0–27.0)		4.4 (1.0-35.7)	
Leukemia subtypes										
Acute myeloblastic leukemia (%)	20 (80.0)		34 (55.7)		28 (80.0)		19 (73.1)		101 (68.7)	
Acute lymphoblastic leukemia (%)	3 (12.0)		8 (13.1)		3 (8.6)		4 (15.4)		18 (12.2)	
Chronic myeloid leukemia (%)	2 (8.0)		1 (1.6)		3 (8.6)		-		6 (4.1)	
Myelodysplastic syndromes (%)	-		17 (28.0)		-		-		17 (11.6)	
Other (%)	-		1 (1.6)		1 (2.8)		3 (11.5)		5 (3.4)	

† LESG = Late Effects Study Group (Tucker et al);

¥ SFOP = Société Française d'Oncologie Pédiatrique (Le Deley et al);

£ FCCSS = French Childhood Cancer Survivor Study (Allodji et al);

§ BrCCSS = British Childhood Cancer Survivor Study (Hawkins et al);

† Data presented as n (%), unless otherwise noted.

Ψ Matched time period for control.

Int J Cancer. Author manuscript; available in PMC 2022 May 01.

Table 2:

Risk of secondary leukemia in relation to radiotherapy or/and chemotherapy.

Treatment characteristics	Cases / Controls	Univariate analyses	Multivariable analysis
		Odds ratio[$] (95% CI)	Odds ratio[$] (95% CI)
Radiotherapy			
No	50/224	**1.0 (Reference)**	**1.0 (Reference)**
Yes	97/298	1.6 (1.0-2.4)	1.5 (0.99-2.3)
P-value for heterogeneity		*0.03*	*0.06*
Chemotherapy			
No	15/151	**1.0 (Reference)**	**1.0 (Reference)**
Yes	132/371	6.2 (2.9-13.3)	5.5 (2.6-12.0)
P-value for heterogeneity		*<0.0001*	*<0.0001*
Treatment combination			
Nor radiotherapy nor chemotherapy	2/65	**1.0 (Reference)**	
Radiotherapy alone	13/86	6.4 (1.3-30.3)	
Chemotherapy alone	48/159	19.0 (3.8-94.7)	
Radiotherapy and chemotherapy	84/212	24.6 (5.0-120.8)	
P-value for heterogeneity		*0.0001*	

Abbreviations: 95% CI = 95% confidence interval.

[$]Conditional logistic regression matched on gender, age at childhood cancer diagnosis and follow-up, and the multivariable analysis, adjusted for radiotherapy, chemotherapy and year of diagnosis.

Table 3:

Risk of secondary leukemia in relation to cumulative dose of radiation dose to active bone marrow (ABM) and selected chemotherapy drugs.

Treatment characteristics	Dose category[¥]	Cases / Controls	Univariate analyses	Multivariable analysis
			Odds ratio[$] (95% CI)	Odds ratio[$] (95% CI)
Radiotherapy (whole active bone marrow dose)	**0 Gy**	51/230	**1.0 (Reference)**	**1.0 (Reference)**
	>0-2	24/79	1.5 (0.85-2.6)	1.6 (0.87-3)
	>2-5	24/76	1.6 (0.87-2.9)	1.4 (0.73-2.7)
	>5-12	24/82	1.5 (0.83-2.6)	1.3 (0.69-2.5)
	>12	24/55	2.3 (1.1-4.6)	1.5 (0.66-3.3)
P-value for trend			*0.02*	*0.3*
Alkylating agents	**0 mg/m^2**	48/246	**1.0 (Reference)**	**1.0 (Reference)**
	>0-10400	33/159	1.1 (0.67-2)	0.7 (0.35-1.2)
	>10400-22000	33/84	2.2 (1.2-3.9)	0.9 (0.43-1.8)
	>22000	33/33	7.2 (3.5-14.7)	2.8 (1.2-6.6)
P-value for trend			*<0.0001*	*0.04*
Topoisomerase II inhibitors[§]	**0 mg/m^2**	50/295	**1.0 (Reference)**	**1.0 (Reference)**
	>0-250	32/97	3.4 (1.8-6.4)	3.6 (1.8-7.3)
	>250-2500	33/99	3.5 (1.9-6.6)	3.2 (1.5-6.9)
	>2500	32/31	13.1 (6.0-28.5)	10.0 (3.7-27.3)
P-value for trend			*<0.0001*	*0.0002*
Platinum compounds	**0 mg/m^2**	108/426	**1.0 (Reference)**	**1.0 (Reference)**
	>0-600	13/34	1.5 (0.74-3)	1.2 (0.56-2.6)
	>600-2500	13/46	1.3 (0.64-2.5)	0.5 (0.23-1.3)
	>2500	13/16	4.6 (1.8-11.9)	1.8 (0.54-5.8)
P-value for trend			*0.007*	*0.6*
Vinca-alkaloids	**0 mg/m^2**	50/227	**1.0 (Reference)**	
	>0-20	32/170	0.9 (0.5-1.5)	
	>20-50	32/76	1.9 (1.1-3.4)	
	>50	33/49	4.4 (2.2-8.6)	
P-value for trend			*<0.0001*	
Antimetabolites	**0 mg/m^2**	109/404	**1.0 (Reference)**	
	>0-1100	12/42	1.0 (0.51-2.1)	
	>1100-9000	13/34	1.7 (0.78-3.9)	
	>9000	13/42	1.3 (0.66-2.7)	
P-value for trend			*0.3*	

Abbreviations: 95% CI = 95% confidence interval.

[$]Conditional logistic regression matched on gender, age at childhood cancer diagnosis and follow-up, and for the multivariable analysis, adjusted for all the other variables in the table and year of diagnosis. Antimetabolites aren't included in the multivariable model, because they were not

statistically significant in univariate analysis. Also, due to a high (71.2%) Phi correlation coefficient between categories of vinca-alkaloids dose with those of alkylating agents, therefore they aren't included in the multivariable model.

[§] Topoisomerase II inhibitors include both anthracyclines and epipodophyllotoxins.

[¥] The categories of mean whole ABM dose are defined by the quartiles of the distribution in the pooled cases group. The categories of doses for chemotherapy groups are defined by the percentiles (33% and 66%) of the distribution in the cases group.

Table 4:

Excess odds ratio of secondary leukemia per Gy of weighted average radiation dose to the active bone marrow (EOR/Gy) in a linear multiplicative model, according to chemotherapy status

	Patients without chemotherapy	Patients receiving chemotherapy	P-values
EOR/Gy (95% CI)	1.55 (0.14-14.3)	0.02 (−0.01-0.09)	0.006[¥]

EOR/Gy: Excess odds ratio of secondary leukemia per Gy of weighted average radiation dose to the active bone marrow; 95% CI = 95% confidence interval;

[¥]P-value from likelihood ratio test (comparison of two nested models – i.e. the first one including radiotherapy dose to ABM and chemotherapy vs the second one with adding an interaction term of dose to ABM x chemotherapy to the first model).

Table 5:

Risk of secondary leukemia according to the age weighted average radiation dose to active bone marrow (ABM) and to chemotherapy (CT)

Treatment characteristics	Cases/controls	Reference: No CT, no RT	Reference: CT, no RT
		Odds ratio[$] (95% CI)	Odds ratio[$] (95% CI)
All leukemias	**147/522**		
No CT and 0 Gy[*]	**2/69**	**1.0 (Reference)**	0.0 (0.01-0.3)
No CT and >0-12	11/66	7.7 (1.7-36.2)	0.4 (0.16-1.0)
No CT and >12	2/16	3.7 (0.28-49.9)	0.2 (0.02-1.7)
CT and 0 Gy	**49/161**	18.8 (3.9-92)	**1.0 (Reference)**
CT and >0-12	61/171	22.3 (4.6-108)	1.2 (0.75-1.9)
CT and >12	22/39	33.0 (6.3-173.9)	1.8 (0.85-3.6)
[§] *P-value for interaction*		*0.01*	*0.01*
AML	**101/356**		
No CT and 0 Gy[*]	**2/41**	**1.0 (Reference)**	0.1 (0.02-0.6)
No CT and >0-12	7/45	4.9 (0.95-25.6)	0.6 (0.20-1.6)
No CT and >12	1/12	-	-
CT and 0 Gy	**30/107**	8.6 (1.7-44)	**1.0 (Reference)**
CT and >0-12	43/120	11.8 (2.3-59.8)	1.4 (0.77-2.4)
CT and >12	18/31	18.8 (3.3-105.7)	2.2 (0.94-5.0)
[§] *P-value for interaction*		*0.03*	*0.03*

Abbreviations: 95% CI = 95% confidence interval; CT = chemotherapy; RT = radiotherapy; AML= Acute myeloid leukemia.

[$]Conditional logistic regression matched on gender, age at childhood cancer diagnosis and follow-up and adjusted for year of diagnosis.

[*]The classes of whole active bone marrow radiation dose (Gy) were grouped as 0, >0-12 (highest quartile) and >12 Gy for the analysis in table 3.

[§]P-value for interaction between chemotherapy and active bone marrow radiation dose was calculated using a likelihood ratio test under the multiplicative model.

Table 6:

Risk of secondary leukemia according to the dose of alkylating agents or topoisomerase II inhibitors and radiotherapy (RT)

Treatment characteristics	Cases/controls	Reference: No RT, no studied drug category	Reference: RT, no studied drug category
		Odds ratio[$] (95% CI)	Odds ratio[$] (95% CI)
All leukemias	**147/522**		
Alkylating agents			
No RT and 0 mg/m^2	**13/102**	**1.0 (Reference)**	0.6 (0.27-1.3)
No RT and >0-22000	30/113	0.9 (0.38-2.1)	0.5 (0.26-1.1)
No RT and >22000	7/9	2.2 (0.54-9.1)	1.3 (0.37-4.7)
RT and 0 mg/m^2	**35/144**	1.7 (0.76-3.7)	**1.0 (Reference)**
RT and >0-22000	36/130	1.0 (0.44-2.5)	0.6 (0.32-1.2)
RT and >22000	26/24	4.8 (1.6-14.6)	2.9 (1.1-7.2)
[§] *P-value for interaction*		*0.1*	*0.1*
Topoisomerase II inhibitors			
No RT and 0 mg/m^2	**12/113**	**1.0 (Reference)**	0.6 (0.26-1.3)
No RT and >0-2500	27/99	4.1 (1.7-10.2)	2.4 (1.0-5.5)
No RT and >2500	11/12	12.5 (3.4-45.6)	7.1 (2.1-24.6)
RT and 0 mg/m^2	38/182	1.8 (0.79-3.9)	**1.0 (Reference)**
RT and >0-2500	38/97	5.2 (2.2-12.3)	3.0 (1.4-6.4)
RT and >2500	21/19	16.1 (5.0-51.4)	9.2 (3.0-28.1)
[§] *P-value for interaction*		*0.8*	*0.8*
AML	**101/356**		
Alkylating agents			
No RT and 0 mg/m^2	**9/68**	**1.0 (Reference)**	0.5 (0.19-1.3)
No RT and >0-22000	17/72	0.8 (0.30-2.4)	0.4 (0.18-1)
No RT and >22000	5/4	5.7 (0.91-36.1)	2.8 (0.55-14.6)
RT and 0 mg/m^2	**27/104**	2.0 (0.77-5.4)	**1.0 (Reference)**
RT and >0-20000	23/89	1.3 (0.45-3.7)	0.6 (0.29-1.4)
RT and >20000	20/19	6.2 (1.5-25.4)	3.1 (0.96-9.8)
[§] *P-value for interaction*		*0. 2*	*0. 2*
Topoisomerase II inhibitors			
No RT and 0 mg/m^2	**9/72**	**1.0 (Reference)**	0.6 (0.23-1.7)
No RT and >0-2500	15/64	2.6 (0.89-7.7)	1.6 (0.57-4.7)
No RT and >2500	7/8	14.3 (2.7-75.1)	9.0 (1.8-43.9)

Treatment characteristics	Cases/controls	Reference: No RT, no studied drug category	Reference: RT, no studied drug category
		Odds ratio[$] (95% CI)	Odds ratio[$] (95% CI)
RT and 0 mg/m^2	26/135	1.6 (0.60-4.3)	**1.0 (Reference)**
RT and >0-2500	30/65	6.1 (2.2-16.9)	3.8 (1.5-9.5)
RT and >2500	14/12	10.2 (2.5-42)	6.4 (1.6-25.5)
[§] *P-value for interaction*		*0.2*	*0.2*

Abbreviations: 95% CI = 95% confidence interval; RT = radiotherapy; AML= Acute myeloid leukemia.

[$]Conditional logistic regression matched on gender, age at childhood cancer diagnosis and follow-up, and adjusted for all the other drugs (platinum compounds and topoisomerase II inhibitors or alkylating agents) and year of diagnosis. The categories of doses of alkylating agents or topoisomerase II inhibitors were defined by the percentile (66%) of the distribution in the cases group.

[§]P-value for interaction between radiotherapy and Alkylating agents or Topoisomerase II inhibitors was calculated using a likelihood ratio test under the multiplicative model.