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Role of radiotherapy and chemotherapy in the risk of secondary leukaemia after a solid tumour in childhood

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ABSTRACT

The aim of this study was to determine the therapy-related risk factors for the occurrence of leukaemia after childhood solid cancer. Among 4204 3-year survivors of a childhood cancer treated in eight French and British centres before 1986, 11 patients developed leukaemia as a second malignant neoplasm (SMN). Compared with the leukaemia incidence in the general French and British populations, the standardised incidence ratio (SIR) of leukaemia was 7.8 (95% CI 4.0–13.4). It decreased from 20.3 (95% CI 8.3–41.2) during the first years of follow-up, to 2.2 (95% CI 0.1–9.7) between 10 and 20 years, but rose again to 14.8 (95% CI 3.7–38.3) 20 or more years after the first cancer. Radiotherapy appeared to increase the risk of leukaemia at moderate weighted doses to active bone marrow; the relative risk (RR) was 4.2 (95% CI 0.8–20.7) for doses ranging from 3 to 6.6 Gy. A greater RR was observed for epipodophyllotoxins and for vinca alkaloids. No specific type of first malignant neoplasm (FMN) was found to lead to a higher risk of secondary leukaemia. Epipodophyllotoxins and vinca alkaloids at high doses and moderate weighted radiation doses to active bone marrow may contribute independently to an increased risk of leukaemia for patients treated for childhood cancer. Our results suggest that the long-term risk of secondary leukaemia could be higher than previously reported.

1. Introduction

It is now apparent that the incidence of a second cancer is higher than expected in successfully treated childhood cancer patients. Several studies have addressed the role of radiotherapy and chemotherapy in the development of secondary malignant neoplasms (SMN)[1–6] and the importance of genetic factors.[7]

Risk factors for leukaemia after treatment of a childhood cancer have been studied mainly in case-control studies. These studies showed an increased risk of secondary leukaemia in patients treated with alkylating agents before 1980.[1,8]

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With the advent of epipodophyllotoxins between 1975 and 1980[9,10] their administration became the major risk factor for leukaemia after a childhood cancer. In 2003, Le Deley and colleagues[11] found that the risk of secondary leukaemia following treatment for a primary solid tumour was dependent both on the type of first cancer and on exposure to topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines).

After single whole-body irradiation, like that sustained by the survivors of the Hiroshima and Nagasaki atomic bombs, the relationship between the radiation dose and the risk of leukaemia was found to be linear from about 150 mSv to a few Sieverts.[12] Both animal experiments[13,14] and human data[15] show that the risk of radiation-induced leukaemia decreases when doses are high. The temporal pattern of leukaemia incidence following irradiation in childhood is known to follow a wave-like pattern; the maximum risk occurs about 5 years following irradiation.[12]

A few studies have addressed the role of radiotherapy in the development of leukaemia after cancer in childhood[1,4,15–17] using the radiation dose received at different bone marrow sites.

We report here the results of a hospital-based cohort study designed to estimate the long-term excess leukaemia incidence after a childhood cancer among French and British patients and to evaluate the risk associated with chemotherapy and with radiotherapy as a function of the dose received by bone marrow.

2. Patients and methods

2.1. *Patients*

The study was performed in a cohort of 4400 patients, 3-year survivors of childhood cancer. The patients were treated before 16 years of age, between 1947 and 1986, in eight treatment centres in France and Great Britain, for all types of solid tumours, except retinoblastoma in the United Kingdom (UK).

In the present study, we excluded 196 subjects whose radiotherapy and chemotherapy doses could not be evaluated. The remaining 4204 persons were included in the analysis. The main characteristics of the present study cohort are described in Table 1. First malignant neoplasms (FMN) were grouped together according to the International Classification of Childhood Cancer (ICCC),[18] while second malignancies were classified according to the ICD-O.[19] The present study focused on the risk of leukaemia, including acute myelocytic and lymphoblastic leukaemia; no chronic leukaemia was observed. Myelodysplastic syndromes were outside the scope of this study.

The study period started 3 years after the diagnosis of the FMN and ended at the onset of secondary leukaemia for leukaemia patients. For the others, the end of the period at risk was the date of the last contact or the date of death for deceased patients. We obtained follow-up data concerning British patients from hospital records and from the National Registry of Childhood Tumours. In the French centres, follow-up data were extracted from clinical records. In all centres, patients were regularly contacted for a follow-up visit;

Table 1 – General characteristics of the cohort of 4204 3-year survivors of a first cancer in childhood

First cancer	Number	Median year of first cancer treatment	British (%)	Females (%)	Median age at first cancer (min–max)	Median follow-up (min–max)	Type of treatment for first cancer (% per row)			
							No RT & no CT	RT no CT	CT no RT	RT & CT
Wilms' tumour	796	1975	26	47	3 (<1–15)	15 (3–44)	2.9	10.5	24.3	62.3
Neuroblastoma	549	1977	25.5	50	1 (<1–17)	13 (3–38)	13.7	15.1	31.5	39.7
Lymphoma*	799	1978	34	31	9 (<1–16)	12 (3–41)	0.8	14.9	25.8	58.6
Soft tissue sarcoma	543	1976	31	44	5 (<1–17)	14 (3–42)	12.7	15.8	23.6	47.9
Bone sarcoma	256	1978	17	37	11 (1–17)	10 (3–38)	6.3	14.4	23.4	55.9
Central nervous system	700	1973	35	50	7 (<1–17)	14 (3–43)	16.3	57.9	0.6	25.3
Gonadal tumour	143	1976	16	51	6 (<1–17)	15 (3–46)	19.6	23.8	39.9	16.8
Thyroid	34	1967	3	79	11 (3–15)	28 (8–45)	58.8	35.3	2.9	2.9
Bilateral retinoblastoma	81	1980	0	48	1 (<1–5)	11 (3–39)	2.5	26	1	70.5
Unilateral retinoblastoma	55	1978	0	44	2 (<1–12)	13 (5–32)	20	25.4	18.2	36.4
Other	245	1978	15.5	47	6 (<1–17)	11 (3–38)	13.5	25.3	22.0	39.2
Total	4204	1976	27	44	5 (<1–17)	13 (3–46)	9.5	22.8	21.1	46.6

RT, radiotherapy; CT, chemotherapy.
* Lymphomas include 352 patients with Hodgkin's disease.

the follow-up schedule varied according to the type of first tumour. Additionally in the French centres, all members of the *Fédération Nationale des Centres de Lutte Contre le Cancer* (National Federation of Anticancer Centers), conducted active follow-up by writing to the patients and linking their database with national death certificate data. The cut-off date for the analysis was 1st January 1991 for patients treated in the UK centres and 1st January 1993 for those treated in French centres.

The median follow-up of the cohort was 13 years (range 3–46 years), varying according to the type of FMN (Table 1). A total of 1095 persons (25%) were followed up for 20 or more years.

2.2. Data collected from medical records

Clinical and pathological characteristics of the first and second malignancies, detailed information on chemotherapy administered for the first cancer, as first-line or salvage treatment and follow-up data were recorded from hospital clinical files. The histopathological and cytological reports were reviewed to confirm the diagnoses of the FMN and SMN. The diagnoses of FMN and SMN were coded for the morphological type and the site.

Radiotherapy data were obtained from hospital radiotherapy technical records. The treatments administered to patients for each type of first cancer are detailed in Table 1.

2.3. Radiotherapy

The beam qualities used for the treatment were Cobalt-60 gamma rays, X-rays with energies ranging from 200 to 250 kV produced by low energy X-rays machines, and photons with energies ranging from 4 to 25 MV or electrons beam energies ranging from 6 to 25 MeV produced by medical linear accelerators. The software package Dos_EG used for dose estimations has previously been described in detail.[20–22] Dos_EG generates a mathematical phantom based on the sex and age of the patient at delivery of radiotherapy. The primary and the main scattered radiation sources, such as the collimator and beam modifying devices and leakage radiation, are taken into account. Corrections for lung heterogeneity are included, but the bone and all the other structures inside the patient are considered to be water equivalent.

The phantom was subdivided into 14 regions according to Hawkins and colleagues,[4] then the mean dose of radiation received by the active bone marrow was computed as the average weighted sum of the doses to the 91 points of the skeleton, using published age-dependent weights among the 151 points of anatomical interest available.[23]

2.4. Chemotherapy

Chemotherapy agents were classified into five drug categories according to their known mechanism of action in the cell: alkylating agents, platinum compounds, vinca alkaloids, anti-metabolites and topoisomerase II inhibitors. Among the topoisomerase II inhibitors, epipodophyllotoxins, anthracyclines and actinomycin D were considered separately due to differences in their leukaemogenicity.

In order to quantify the total amount of drug in each treatment category, the dose of each chemotherapy agent, which was in milligrams per square metre, was converted to moles per square metre. We then added the number of moles/m^2 for each drug category. This was done because a molecule of a given drug generally has one active site, whatever its weight. Even if a particular drug may have more than one active site per molecule, the error introduced by this hypothesis is probably lower than that introduced when summing the weights. For example, the molecular weight among electrophil agents varies from 182 (dacarbazine) to 1407 (bleomycin).

2.5. Statistical analysis

The expected number of cancers was obtained for each sex, by 5-year age groups and 5-year calendar periods, by multiplying the reference incidence rates by the number of person-years at risk (PYR). Estimations published by the French Cancer Registries were used as reference rates for leukaemia incidence for patients treated in French centres.[24] The UK national cancer incidence rates were used for patients treated in Great Britain.[25]

The standardised incidence ratio (SIR), i.e. the observed number divided by the expected number of leukaemias was modelled assuming that the number of leukaemias followed a Poisson distribution.[26] Parameter 95% confidence intervals (95% CI) were estimated using maximum likelihood methods.[27] Because of the small number of cases in our cohort, we did not study the extra-Poisson variation of the distribution.

A within-cohort analysis was also performed using the actuarial method to estimate the cumulative incidence of leukaemia. A Cox regression model was performed to estimate the relative risk (RR) of developing leukaemia associated with radiotherapy and chemotherapy using the PHREG procedure of the SAS software system (SAS Institute, Cary, NC, United States of America (USA)). The dose-effect relationship between the dose of chemotherapy or the dose of radiation and the risk of leukaemia was studied by calculating the RR of leukaemia in each tertile of dose distribution taking patients who had not been exposed as the reference category.

In order to evaluate the dose-effect relationship between the bone marrow radiation dose and the RR of leukaemia, we tested linear (2) and linear exponential (3) models, adjusted on chemotherapy, by comparing nested models. Tests were based on a comparison of the deviance of the models. The AMFIT epidemiological Software was used for these analyses.[28]

- basic: $RR = \exp(\alpha_1 CT)$
- linear: $RR = \exp(\alpha_1 CT)[1 + \beta_1 dose]$
- linear-exponential: $RR = \exp(\alpha_1 CT) \times [1 + \beta_1 dose * \exp \gamma dose]$

where:

CT = chemotherapy is coded as yes/no
α_1, β_1, γ = coefficients
dose = bone marrow radiation dose.

3. Results

Between 1947 and 1986, 4204 patients younger than 16 years received treatment for a FMN. During the follow-up period, 11 patients developed leukaemia whose type was acute myeloblastic leukaemia in 6 patients, acute lymphoblastic leukaemia in 3 patients and acute leukaemia of unspecified cell type in 2 cases (Table 2). Chronic myelocytic leukaemia did not occur.

The cumulative incidence of leukaemia after a 15-year follow-up was 0.21% (95% CI 0.10–0.42%) and 0.76% (95% CI 0.3–2.0%) after 40 years. Fig. 1 depicts the cumulative incidence by years since the diagnosis for the whole cohort.

Compared with the leukaemia incidence in the general French and British populations, the expected number of leukaemias was 1.4 and the SIR was 7.8 (95% CI 4.0–13.4). The SIR did not vary according to attained age. It decreased from 20.3 (95% CI 8.3–41.2) during the 3–5-year follow-up period, to 2.2 (95% CI 0.1–9.7) during the 10–20 year period, but rose again to 14.8 (95% CI 3.7–38.3) 20 or more years after the first cancer (Table 3).

Table 4 summarises the results of the univariate analysis within cohort for the type of first cancer and treatment characteristics. Lymphoma, neuroblastoma and Wilms' tumour were the most frequent FMN among leukaemia cases. However, none of these tumours were significantly associated with an increased risk of leukaemia. Eight cases of leukaemia occurred in patients who had been treated with radiotherapy and chemotherapy, one after radiotherapy alone and two after chemotherapy alone (Table 2). In the univariate analysis, radiotherapy, coded as yes/no, was not associated with an increased risk of leukaemia: RR = 1.8 (95% CI 0.4–8.4). Chemotherapy, coded as yes/no, was significantly associated with an increased risk of leukaemia, RR of 9.5 (95% CI 1.1–81.5, $P = 0.04$). The risk of leukaemia for patients who had received chemotherapy alone and for patients who had received chemotherapy plus radiotherapy was 6.8-fold (95% CI 0.6–84) and 10.3-fold (95% CI 1.2–90) respectively compared with the risk for patients who had not received chemotherapy (c.f. Table 4).

When we examined the role of the different categories of chemotherapeutic agents in the univariate analysis, we found that epipodophyllotoxins, vinca alkaloids and platinum compounds were significantly associated with an increased risk of leukaemia (Table 4). The risk was significantly higher in the third tertile of the dose of vinca alkaloids than in lower doses ($P = 0.03$). The dose-effect relationship for epipodophyllotoxins could not be studied because a limited number of patients received these drugs. When these drugs were considered simultaneously in the multivariate analysis, the risk of leukaemia was found to be only significantly associated with treatment with epipodophyllotoxins (RR = 5.6, 95% CI 1.1–28.2 $P = 0.03$) and high doses of vinca alkaloids (RR = 7.3, 95% CI 2.0–26.3 $P = 0.002$). After controlling for other chemotherapy drugs, platinum compounds were not found to be significantly associated with the risk of leukaemia. Results concerning chemotherapy-related risks were stable after controlling for radiotherapy doses (data not shown).

The dose received by the bone marrow was moderate (between 3 and 6.6 Gy defining the second tertile) in 6 of the 9 leukaemia patients who were treated with radiotherapy. In

Table 2 – Characteristics of the 11 leukaemia patients

First cancer				Treatment used for first cancer			Leukaemia			
	Year of diagnosis	Age 2(years)	Country	Chemotherapy	Radiotherapy	Radiation dose at the bone morrow (Gy)	Leukaemia type	Year of diagnosis	Age (years)	Time to leukaemia (years)
Neuroblastoma	1961	2	France	No	Yes	3.31	AML	1991	31	29
Wilms' tumour	1963	<1	France	Yes	Yes	3.37	ALL	1985	22	22
Wilms' tumour	1967	2	France	Yes	Yes	6.12	AL	1989	23	21
Lymphoma	1968	10	France	Yes	No	0.00	AML	1978	20	10
Lymphoma	1979	7	France	Yes	Yes	4.37	AML	1985	13	6
Neuroblastoma	1978	2	UK	Yes	No	0.00	ALL	1984	7	5
Bone sarcoma	1976	11	UK	Yes	Yes	10.32	ALL	1981	15	4
Lymphoma	1983	10	UK	Yes	Yes	5.99	AML	1987	13	4
Wilms' tumour	1973	3	France	Yes	Yes	2.29	AML	1977	6	3
Central nervous system	1976	7	France	Yes	Yes	14.99	AL	1979	10	3
Wilms' tumour	1978	3	France	Yes	Yes	4.21	AML	1981	6	3

AML, acute myelocytic leukaemia; ALL, acute lymphoblastic leukaemia; AL, acute leukaemia.

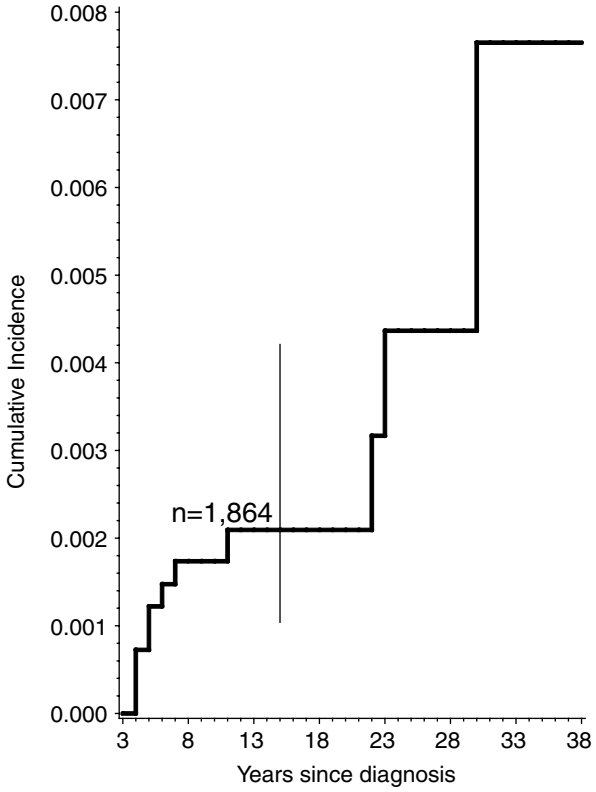

Fig. 1 – Cumulative incidence of leukaemia according to follow-up of the 3-year survivors.

the univariate analysis, the risk was increased, albeit of borderline significance, exclusively in the second tertile of the radiation doses compared with that found in patients who had not received radiotherapy (Table 4). Results did not vary after controlling for chemotherapy (data not shown).

Different dose-response relationships were considered (Table 5).

In the linear model, the coefficient was 0.31 and increased to 0.96 (95% CI −1.6–3.5) if a negative exponential term was taken into account. Adding a negative exponential term to the linear model did not significantly reduce the deviance of the model ($P = 0.3$). The value of the negative exponential coefficient was −0.08 (95% CI −0.26–0.1). When the negative exponential term was taken into account, both coefficients led to an excess RR of 0.87 for 1 Gy.

4. Discussion

This study on the incidence of leukaemia in a cohort of 4204 patients treated for a first cancer during childhood (1942–1986) demonstrated that the risk of developing leukaemia after a childhood cancer is 7.8-fold higher in this cohort (95% CI 4.0–13.4) than in the general population. The major finding in this study was the unexpected increase in the SIR observed 20 or more years after the diagnosis of the FMN, SIR = 14.8 (95% CI 3.7–38.3). The risk of secondary leukaemia was found to increase with both epipodophyllotoxins and vinca alkaloids. A trend was observed for moderate radiation doses received by active bone marrow.

In spite of the large size of the cohort and the duration and quality of the follow-up, the main limitation of our study is the small number of leukaemia cases (11 cases) which limits the analysis of risk factors.

The overall SIR is higher than that observed in other population-based paediatric cohorts including patients diagnosed up to 1976 (SIR = 4.5)[29] or between 1943 and 1987 (SIR = 2.8).[30] It is similar to that published by Neglia on a hospital-based cohort of patients treated more recently (SIR = 6.86).[31]

Two peaks of leukaemia incidence were observed during the follow-up. An early peak, which occurred during the first years of follow-up, is in good agreement with that reported in the Nordic cohort[30] and in the American cohort.[31] A later peak was also observed 20–30 years after the FMN, with a large confidence interval due to the small number of cases.

Table 3 – Occurrence of leukaemia according to attained age and to follow-up in a cohort of children treated for a first paediatric cancer

Attained age	Persons Years	O	E	Annual incidence $\times 10^{-5}$ (95% CI)	Annual excess incidence $\times 10^{-5}$ (95% CI)	Standardised incidence ratio (95% CI)
3–9	10,177	3	0.33	29 (7–76)	27 (5–74)	8.7 (2.0–21.3)
10–19	24,188	4	0.60	17 (5–38)	14 (2–36)	6.7 (2.1–15.6)
20–29	13,592	3	0.31	22 (5–57)	20 (3–55)	9.6 (2.4–25.0)
⩾ 30	4426	1	0.14	23 (1–99)	21 (<0–97)	7.4 (0.4–32.6)
Period of follow-up						
3–5	8155	6	0.27	73 (29–149)	70 (26–146)	20.3 (8.1–41.2)
5–10	17,723	1	0.45	5.6 (0.3–24)	3 (8.10^{-2}–112)	2.2 (0.1–9.7)
10–20	19,054	1	0.45	5.2 (0.3–23)	2.7 (7.10^{-2}–126)	2.2 (0.1–9.7)
20–46	7450	3	0.20	40 (10–104)	37 (7.5–102)	14.8 (3.7–38.3)

O, observed number of leukaemia cases; E, Expected number of leukaemia cases, compared with general population; 95% CI, 95% confidence interval.

Table 4 – Risks of secondary leukaemia after a childhood cancer according to type of first cancer and treatment characteristics (univariate analysis, Cox regression model)

Characteristics	Number of patients	Number of patients with leukaemia	RR (95% CI)	P-value
Type of first cancer				
Other	2060	2	1*	0.20
Neuroblastoma	549	2	3.7 (0.5–26)	
Wilms' tumour	796	4	4.6 (0.8–25)	
Lymphoma	799	3	4.4 (0.7–27)	
Treatment				
No RT, no CT	399	0	1*	0.03
RT alone	958	1	–	
CT alone	887	2	6.8 (0.6–84)	
CT and RT	1960	8	10.3 (1.2–90)	
Alkylating agents				
No	2339	6	1*	NS
Yes	1865	5	1.6 (0.5–5.7)	
Platinum compounds				
No	3902	9	1*	0.05
Yes	302	2	5.0 (1–25)	
Vinca alkaloids				
No	1805	3	1*	0.05
Yes	2399	8	4.9 (1–24)	
Dose of vinca alkaloids				
0	1846	3	1*	0.01
[0–0.01]	697	1	2.0 (0.2–22)	
[0.01–0.03]	864	1	1.7 (0.1–19)	
> 0.03	797	6	10.9 (2.2–53)	
Anti-metabolites				
No	3590	10	1*	NS
Yes	614	1	0.8 (0.1–6.3)	
Epipodophyllotoxins				
No	3950	8	1*	0.001
Yes	254	3	10.8 (2.6–45)	
Anthracyclines				
No	2929	8	1*	NS
Yes	1275	3	1.4 (0.3–6)	
Actinomycin D				
No	2869	6	1*	0.2
Yes	1335	5	2.2 (0.7–7.5)	
Radiation dose (Gy)				
0 (referent)	1378	2	1*	0.1
[0–3]	973	1	0.6 (0.05–6.3)	
[3–6.6]	900	6	4.2 (0.8–21)	
>6.6	953	2	1.6 (0.2–11)	

95% CI, 95% confidence interval; RT, radiotherapy; CT, chemotherapy; NS, not significant.
* Referent group. For treatment variable, the referent group include both groups: no RT no CT and RT alone.

Table 5 – RR models and regression coefficients of second cancer for the active bone marrow radiation dose in Gy, adjusted for chemotherapy administration (yes/no)

Models	Parameter estimates (95% CI)		
Radiation adjusted for chemotherapy (CT)*	Dose	e^{dose}	Deviance
Basic: RR = exp (α_1CT)	–	–	115.9
Linear: RR = exp (α_1CT) [1 + $\beta_1$dose]	0.31 (−0.32–0.94)	–	113.1
Linear-exponential: RR = exp (α_1CT) × [1 + $\beta_1$dose * exp γdose]	0.96 (−1.6–3.5)	−0.08(−0.26–0.1)	112.0

95% CI, 95% confidence interval; RR, relative risk; CT, chemotherapy.
* Chemotherapy is coded as yes/no.

Considering as followed-up until the end-point date the known to be alive lost-to-follow-up subjects, thus increasing the denominator of the SIR, does not modify the SIR value (13.0 (4.2–40.2) versus 14.8 (3.7–38.3)).

A treatment received for recurrence or metastasis of the initial cancer, particularly if such a treatment has occurred in a different hospital, could be a bias if this occurred among the observed cases accounting for the second peak. But among these, no such treatment has been administered since they have had no recurrence or metastasis.

To date, the occurrence of such a second peak has never been reported, probably because population-based studies on the risk of this SMN are quite scarce due to difficulties in following up paediatric patients through to adulthood. An additional explanation is that the mean follow-up in all but one previously reported study,[31] is shorter than ours (15 years). In Neglia's study[31] the longer follow-up was 28 years, while, 25% of the patients in our study were followed up for 20 or more years (maximum 46 years).

The first and major limitation of our study, which included only 11 leukaemia cases, is the small number of cases, so these new results have to be read with caution and need to be confirmed by studies with a higher number of secondary leukaemia cases.

In our study, radiotherapy (coded yes/no in the analysis), did not increase the risk of secondary leukaemia, which is in accordance with several previous studies.[32–34] No relation was observed between the risk and the weighted radiation dose as a continuous variable.[11,35,36] In contrast, a trend was observed between the weighted radiation dose to active bone marrow and the risk of secondary leukaemia for doses ranging from 3 to 6.6 Gy (RR = 4.2, 95% CI 0.8–20.7). Doses lower than 3 Gy and those higher than 6.6 Gy had no significant effect on the risk of secondary leukaemia, as found in previous studies in both animals[13,14] and humans,[15] in which the risk of radiation-induced leukaemia was found to decline for the highest doses (4 Gy). A significant dose-effect relationship between the risk of leukaemia and radiation has been evidenced[16,17] and particularly in a British case-control study[4] including 26 cases of secondary leukaemia among survivors of childhood cancer diagnosed between 1940 and 1983 and 96 controls. Hawkins and colleagues[4] evidenced a significantly increased RR of secondary leukaemia increasing with the radiation dose averaged over the patient's active bone marrow (RR = 2.0, 4.0, 8.1 and 16.3 after exposure respectively to 1–4.9, 5–10, 10–15 and >15 Gy). The findings in this previous study are not in keeping with the dose-effect relationship between radiation and the risk of leukaemia usually described, namely an increase for low and moderate doses up to a maximum followed by a decrease for the highest doses.[37] In fact, this relationship was found to be complex due to competing processes of cell killing, cell transformation and DNA repair. At very high doses delivered at high rates, cell destruction is probably predominant, and the risk per dose unit is low.[38]

Epipodophyllotoxins were significantly associated with an increased risk of leukaemia. An association between epipodophyllotoxins and secondary leukaemia has been demonstrated by numerous studies[4,11,31] covering a later period than ours. The number of patients who had been treated with epipodophyllotoxins in our study was small due to the study period: only 6.6% of the total cohort (3 leukaemia cases), which prohibits a more detailed analysis. However, although the administration of epipodophyllotoxins was not generalised at the time of the study period, which explains why a small number of patients received these drugs, we nonetheless demonstrate an independent effect of these drugs.

Exposure to high doses of vinca alkaloids (>0.03 moles/m^2) was significantly associated with an increased risk of leukaemia; the RR attained 7.3 for patients who had received more than 0.03 moles/m^2 of the drug. This is in agreement with one study in which the drug was simply coded yes/no in the analysis.[36] This increased risk with increasing doses of vinca alkaloids was identified in another study, but it vanished after controlling for exposure to other treatments.[4]

We found no excess risk associated with alkylating agents, despite their recognised leukaemogenicity.[1,4,39] This could partly be explained by the fact that few patients had been treated with the most leukaemogenic alkylating agents, namely melphalan (1.8% of the cohort) and caryolysin (4.7% of the cohort).

One of the advantages of our cohort of patients treated between 1945 and 1986 is that it probably allows us to evaluate the effect of weaker risk factors such as radiotherapy and vinca alkaloids which, otherwise, might have been masked by the strong effect of the epipodophyllotoxins if a greater number of patients had received these drugs. A further advantage is that the follow-up spans a longer period than in most published studies and the oldest patients are only almost 60 years old. However, a limitation of the study is the small number of secondary leukaemia cases (11) that occurred during the follow-up period, restricting the analysis of risk factors.

In conclusion, our results confirm an increased risk of secondary leukaemia occurring during the first years of follow-up after a childhood cancer and suggest that the long-term risk (over 20 years of follow-up) could be higher than reported previously. The main results concerning treatment-related risks are that both high doses of epipodophyllotoxins and vinca alkaloids and moderate weighted radiation doses to active bone marrow may contribute to an increased risk of leukaemia for patients treated for a childhood cancer before 1986.

Conflict of interest statement

None declared.

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