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Second Malignant Neoplasms in Patients Treated for Childhood Leukemia

A Population-based Cohort Study from the Nordic Countries

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ABSTRACT. Nygaard R, Garwicz S, Haldorsen T, Jonmundsson GK, Lanning M, Moe PJ. For the Nordic Society of Pediatric Oncology and Hematology (NOPHO). (Department of Paediatrics, University Hospital of Trondheim, Trondheim, Norway, Department of Paediatrics, University Hospital of Lund, Lund, Sweden, the Cancer Registry of Norway, Oslo, Norway, Department of Paediatrics, University Hospital of Copenhagen, Copenhagen, Denmark, Department of Paediatrics, University Hospital of Reykjavik, Reykjavik, Iceland, Department of Paediatrics, University Hospital of Oulu, Oulu, Finland). Second malignant neoplasms in patients treated for childhood leukemias. A population-based study from the Nordic countries. Acta Paediatr Scand 80: 1220, 1991.

Among a cohort of 981 children who were followed up 4.3–26.5 years after cessation of antileukemic therapy, eight patients in remission of acute lymphoblastic leukemia (ALL) developed a distinctively new malignant disease. The second malignant neoplasms (SMN) included brain tumors, basal cell carcinomas, thyroid cancer, leiomyosarcoma and finally rhabdomyosarcoma in a patient who also had suffered from Hodgkin's disease while still on antileukemic treatment. Cranial radiation had been given to 58.4 % of the patients in the study group, which consisted of 895 ALL patients who had completed various chemotherapy protocols. With one exception, the SMN appeared after 7.5–16.5 years at a location previously exposed to radiotherapy (RT). The estimated cumulative risk of SMN appearing within 20 years after diagnosis was 2.9 %, and the corresponding risk for cases with RT was 8.1 % compared to 0.3 % for those without ($p=0.05$). In a Cox regression analysis, the incidence rate ratio of SMN between patients with and without RT was 6.7 (95 % CI=0.8, 57.7). Based on age-, year- and sex-specific cancer incidence figures for Norway, the overall standardized incidence rate ratio (SIR) of SMN after treatment for ALL was 5.9 (95 % CI=2.2, 12.9). The number of brain tumors among patients who had received cranial radiation was nearly 27 times greater than expected, whereas no such tumors were seen after chemotherapy. Individuals treated for childhood ALL are at increased risk of a new malignancy, and this seems mainly to be associated with previous irradiation.
Key words: brain neoplasms; chemotherapy, adverse effects; multiple primary neoplasms; radiation-induced neoplasms; risk factors; radiotherapy, adverse effects.

Survivors of acute leukemias comprise the largest proportion of patients successfully treated for childhood malignancies. During the last 2 to 3 decades, improved survival after antileukemic therapy has allowed time for the appearance of late adverse effects, including new malignant diseases. Malignancies due to chemical and radiation carcinogenesis have latency periods ranging from a few years to several decades, during which the patients are easily lost to follow-up. Large

numbers are required to evaluate the risk of SMN related to specific diseases and the treatment given. We contribute to the aggregation of data by reporting the new malignant neoplasms registered so far in a population-based cohort of 981 patients who had been observed after apparently successful antileukemic therapy. The study also analyzes the risk of SMN subsequent to treatment for ALL. Slightly more than half of the ALL patients had received radiation in addition to chemotherapy, and the role of radiation as a risk factor is evaluated.

PATIENTS AND METHODS

Patients. In the five Nordic countries of Denmark, Finland, Iceland, Norway and Sweden with about 23 million inhabitants, approximately 200 new cases of childhood leukemia are diagnosed each year. Our cohort, consisting of 981 individuals, includes all leukemia cases under 15 years of age at diagnosis, who had discontinued therapy in remission before 1985 (Table 1). Five of the originally reported patients (1) were excluded due to non-eligibility. Whereas new malignancies were registered in the complete cohort, the risk of SMN was analyzed only among ALL survivors, restricted to those who had received traditional therapy. Thus, patients with bone marrow transplantation were excluded, leaving 895 cases in the study group (Table 1). The majority of them ($n=877$) were in complete continuous remission (CCR) when therapy was stopped after a mean duration of 3.4 years. The patients had been treated according to a variety of contemporaneous protocols in Denmark, Finland, Iceland, Norway and Sweden during the period 1958–85 (2–6). Prophylaxis against CNS-involvement had gradually been introduced in 1972–73 in the form of methotrexate (intrathecal and later also intravenous) and/or cranial radiation, depending only on regional preferences. In the study group, cranial radiation had been given to 58.4% of the patients, of whom 519 had received it as prophylaxis (18 or 24 Gy) and 4 had been radiated for CNS leukemia. The investigation was closed 4.3 to 26.5 years after the patients had discontinued therapy. Median observation time till death or last follow-up was 10.5 years from diagnosis and 7.2 years from cessation of therapy.

Methods. Information was obtained directly from physicians in all departments treating and controlling the patients (1). Cases were followed up annually after the end of therapy until April 1, 1989. Well organized national health systems and cooperation within the Nordic Society of Pediatric Oncology and Hematology (NOPHO) facilitated obtaining complete surveys of the cohort. The medical records for all cases with second malignancies were reviewed by NOPHO's national representatives. New malignant diseases were registered as diagnosed at the local hospital and were histologically confirmed or, in one case, clinically agreed on. They were classifed as SMN and considered possibly secondary to treatment only when occurring after cessation of antileukemic therapy and more than 3 years from diagnosis. Certain new malignancies were considered to be a relapse of the original disease rather than a true SMN and were therefore registered separately. This included late recurrences (more than 5 years after cessation of therapy), new types of leukemia, non-Hodgkin's lymphomas, and reticulosarcomas ("microgliomas").

Table 1. *Complete patient cohort according to diagnosis and treatment category*

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, BMT = bone marrow transplantation, CML = chronic myeloid leukemia, CT = chemotherapy, RT = radiotherapy

	Treatment category		
Diagnosis ($n=$)	BMT	CT	CT+RT
CML (3)	3	0	0
AML (70)	14	45	11
ALL (908)	13	372	523
Total (981)			

Box indicates study group ($n=895$).

The risk of SMN was estimated as a cumulative probability according to the Kaplan-Meier method (7), and was calculated from time of initial diagnosis until time of SMN or study termination. Cases were censored at date of relapse ($n=198$), death ($n=4$), or last observation ($n=39$). Estimates for different subsets were compared with the log rank test (8). The Cox regression model (9) was used to compare patients with and without radiation, estimating incidence rate ratios while controlling for sex as well as age and calendar year of treatment start (3 and 4 categories, respectively). In addition, standardized incidence rate ratios (SIR) were computed as the ratio of the number of observed (O) divided by the number of expected (E) cancers and were used as measures of relative risk between the study group and the general population (10). Age, sex, and calendar year specific rates from the Norwegian population, available from the Cancer Registry of Norway, were applied to the appropriate number of person-years of observation from date of ended therapy till date of SMN, relapse, death, study termination or last observation. The incidence of childhood cancer shows no significant variations among the Nordic countries. Basal cell skin carcinomas were not evaluated in this analysis, as population-based incidence rates for part of the period were lacking. The 95% confidence intervals (CI) and tests of significance for the SIR were determined by assuming a Poisson distribution for the observed number of cancers (10). Statistical tests were 2-tailed, with a significance level at 5%.

RESULTS

New malignant disease. Nine new malignancies developed in 8 patients, in all but one after cessation of therapy. No new malignancies were registered in patients treated for myeloid leukemias. Clinical and demographic characteristics are summarized in Table 2. There was no family history suggesting cancer susceptibility and only case 2 had received alkylating agents (cyclophosphamide) during treatment for ALL. One patient (case 8) developed a pulmonary leiomyosarcoma with brain and abdominal metastases. All remaining neoplasms were observed in patients who had received cranial radiation early during the first year of treatment. Two of the 3 brain tumors were histologically confirmed. One was an anaplastic ganglioglioma and the other a primitive neuroectodermal tumor (anaplastic medulloblastoma or neuroblastoma). In the third patient biopsy was not performed due to inoperable location in the brain stem, and autopsy was later refused. This patient (case 2) had received a radiation dose of altogether 44 Gy for neuroleukemia during the initial treatment

Table 2. *Second malignant neoplasms in patients treated for childhood leukemia*

Latency periods after diagnosis and completed therapy. ALL = acute lymphoblastic leukemia, C = cranial, C-S = cranio-spinal, Dx = diagnosis, SMN = second malignant neoplasm. Time intervals in years

Case/ sex	SMN	Radiation	Dx of ALL		Dx of SMN	Latency of SMN from	
			Year	Age	Age	Dx of ALL	end of therapy
1 F	Brain tumor	C: 24 Gy	1973	9.2	18.9		
2 F	Brain tumor	C: 24+20 Gy	1976	9.8	22.1	9.1–12.3	6.1–8.3
3 M	Brain tumor	C: 24 Gy	1976	1.9	11.0		
4 M	Basal cell carcinoma	C-S: 25 Gy	1971	2.2	18.7		
5 M	Basal cell carcinoma	C: 24 Gy	1976	4.0	11.5	7.5–16.7	4.5–12.7
6 F	Thyroid carcinoma	C: 22.5 Gy	1976	2.7	13.4	10.7	7.4
7 M	(Hodgkin's disease	C: 24 Gy	1975	4.4	6.1	1.8	−1.2)
	Rhabdomyosarcoma	Mantle: 40 Gy			13.2	8.8	5.8
8 F	Leiomyosarcoma	None	1978	2.9	6.3	3.4	0.5

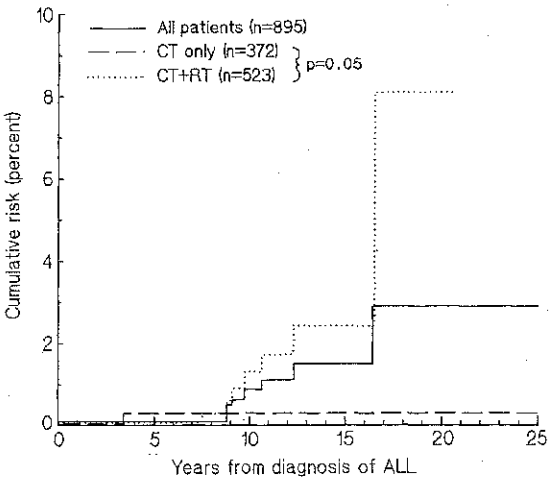

Fig. 1. Cumulative risk of SMN for patients in remission after treatment for acute lymphoblastic leukemia (ALL). Treatment groups: Chemotherapy (CT) with or without addition of radiotherapy (RT). The numbers of patients at risk initially and at 5-year intervals were: CT 372, 330, 172, 73, 32, 7 and RT 523, 429, 258, 52, 2, 0.

course and did not have evidence of CNS relapse later. The brain tumor was diagnosed 8 years after ended chemotherapy and one year after the patient had delivered her first child.

The basal cell carcinomas in cases 4 and 5 appeared on the scalp. The patient with thyroid carcinoma (case 6) had received 4 MV photone radiation through standard lateral cranial fields (11). Case 7 was diagnosed with Hodgkin's disease stadium IA (mixed cellularity) in a cervical lymph node while still on antileukemic therapy. The same individual developed an embryonal rhabdomyosarcoma on the thorax 6.7 years after mantle irradiation.

Absolute risk of SMN. The cumulative risk of SMN was 2.9% (SE=1.4%) by 20 years after diagnosis. As illustrated in Fig. 1, the risk was higher for ALL patients who had received radiation than for patients who had been given chemotherapy only; 8.1% compared to 0.3% ($p=0.05$).

Relative risk of SMN. The unadjusted incidence rate ratio between patients with and without radiation was 6.7 (95% CI=0.8, 57.7). It was not materially altered after adjustment for sex, calendar year of treatment start, or age at diagnosis. Based on population rates, one new malignant neoplasm (excluding basal cell carcinomas) was expected during the 6295 person-years accumulated (Table 3). In contrast, 6 were observed, yielding an SIR of 5.9 (95% CI=2.2, 12.9, $p<0.05$). For irradiated patients, with 3486 person-years, the SIR of a new cancer in general was 9.8 (95% CI=3.2, 22.9, $p<0.05$) and of a CNS-tumor 26.7 (95% CI=5.5, 78.1, $p<0.05$). In contrast, patients without radiation (2809 person-years) did not differ from the general population.

Malignant lymphomas and myeloproliferative diseases. Five cases in the study group were diagnosed with non-Hodgkin's lymphomas 0.03–10.9 years after ended therapy. None of them had concurrent leukemia relapse, but 3 cases had suffered a hematologic recurrence prior to the lymphoma, or relapsed afterwards. Within months after ended therapy, two other cases developed intracerebral expansions which were classified as reticulocellsarcoma/microglioma. Both patients had received prophylactic cranial radiation. One of them had simultaneous evidence of CNS-leukemia and the other had suffered a CNS relapse earlier.

In the ALL study group, disease-free survival after cessation of therapy was 75% at 15 years. Eighty percent of the 198 patients with relapse had their recurrence within two years. Seven patients had a very late first recurrence; 5.1–12.3 years after cessation of therapy and 8.1–17.3 years after diagnosis. For ALL patients in CCR 5 years after cessation, the cumulative proportion who were again diagnosed with leukemia within another 10 years was 3.1% (SE = 1.4%).

Among AML patients in the cohort, isolated lymphoma was seen in one and late relapse in two cases. Two patients with AML and two with ALL had phenotypic switch at relapse. All switch-overs occurred within 4 years after completed therapy.

DISCUSSION

The risk of a new malignancy in childhood cancer survivors may be influenced by genetic and other predisposing factors, as well as by the primary disease and the treatment given. Our study provides evidence of an elevated risk after ALL when the treatment had included irradiation.

In a study from 1975 of 5-year survivors, Li et al. found the relative risk of a new primary after childhood cancers to be over 20 (12). The cumulative probability was 12% by 20 years after 5-year survival and the corresponding probability of a new malignancy developing within an orthovoltage radiation field was 17%. In the latest report from the Late Effects Study Group, the relative risk was over 10 and the cumulative probability 8% within 20 years from diagnosis (13, 14). These investigations included patients with known hereditary/constitutional disorders predisposing for malignancies, and new leukemias/lymphomas were regarded as SMN also after leukemia. A population-based British study of childhood cancer survivors observed 6-fold the expected number of new malignancies and a cumulative probability of about 4% within 25 years of 3-year survival (15). Attempts have also been made to separate diagnostic and therapeutic groups to find a possible relationship between SMN and the specific diseases and treatment modalities.

SMN related to therapy. Some studies of cancers secondary to treatment include all new malignancies subsequent to the first diagnosis. Other studies are restricted to new cancers occurring after a latency period, when therapeutic influences are considered less likely to contribute towards the development of a subsequent tumor. With a median treatment length of slightly above 3 years among the patients, our investigation is comparable to studies of 3-year survivors beyond diagnosis (15, 16).

Table 3. *Incidence of second malignant neoplasms after cessation of therapy for ALL*

Observed versus expected numbers, and standardized incidence rate ratios. CI = 95% confidence interval, CNS = central nervous system, E = expected, F = females, M = males, O = observed, P-years = person-years of observation, RT = radiotherapy, SIR = standardized incidence rate ratio

Treatment (n=)	P-years	CNS		Thyroid		Soft tissue		All sites	
		O	E	O	E	O	E	O	E
RT+(523; 259 F, 265 M)	3 486	3	0.1124	1	0.0220	1	0.0167	5	0.5086
RT−(372; 190 F, 182 M)	2 809	0	0.0951	0	0.0243	1	0.0134	1	0.5037
Total (895)	6 295	3	0.2075	1	0.0464	2	0.0300	6	1.0123

Radiation has been shown to be a risk factor, even in the low doses previously given for benign diseases (for review see 17). Some of the available information on malignancies following medical irradiation pertains to orthovoltage radiotherapy, whereas megavoltage is presently in use. But although the incidence is possibly lower, new malignancies are also reported after megavoltage treatment (18). The carcinogenic effects seem partly to depend on the proliferative state of the target tissue, and age-dependent factors may influence the timing for the appearance of the new malignancy (19, 20). Solid tumors, especially bone and soft tissue sarcomas, thyroid cancers, brain tumors and skin cancers are described with a median latency interval between 10 and 15 years (13, 15). No decrease in risk has so far been seen thereafter. Non-lymphoblastic leukemias may also appear after irradiation, usually after a shorter latency period with a peak incidence at 6–8 years (13, 19). More than half of our patients had received cranial radiation early in the treatment course. With median observation time more than 7 years after completed chemotherapy, and thus about 10 years after radiation, radiation-induced solid tumors as well as leukemias could be expected. Six of our SMN cases developed tumors in tissues known to be within the radiation field. The patient with thyroid cancer may have received scatter radiation doses to the gland. With the exception of Hodgkin's lymphoma, all tumors that appeared within areas exposed to radiotherapy had latency periods consistent with our knowledge of radiation carcinogenesis.

As in adults, new malignancies in children after chemotherapy seem mainly to be associated with previous exposure to alkylating agents (AA) (13, 15, 21). Leukemia, especially acute non-lymphoblastic leukemia (ANLL) is the most frequent new malignancy (22). The latency periods are generally shorter than after radiation, median 4–6 years. Although not among the drugs of choice, cyclophosphamide during maintenance therapy was used in some Nordic protocols (2, 4, 6). However, with new leukemias and lymphomas omitted from the definition of SMN, only one of our SMN patients had received AA.

SMN after leukemia. Long-term disease-free survival after cessation of antileukemic therapy, i.e. 4–5 years, may possibly indicate cure of the original disease (23). But later recurrences are seen and may represent either a true relapse or a new leukemia (24). Diagnostic methods have improved and comparison of diagnoses many years apart is therefore difficult. In addition, the phenotype of a leukemic clone may evolve during the course of the disease (25, 26). Late relapses, new leukemias and lymphomas were therefore not classified as SMN in our study, which yields a conservative risk estimate since these diagnoses are sometimes included by other authors (13, 27). Thus, an early review stated that "lymphoreticular malignancies", often with brief latencies, were the most common second neoplasms following leukemia (28). These authors also reported Hodgkin's disease in patients

All sites		SIR (CI)	
O	E	CNS	All sites
5	0.5086	26.7 (5.5, 78.1)	9.8 (3.2, 22.9)
1	0.5037	0 (0, 38.7)	2.0 (0.1, 11.1)
6	1.0123	14.5 (3.0, 42.3)	5.9 (2.2, 12.9)

still on antileukemic treatment and indicated the possibility of a common underlying cause or immunosuppression rather than direct oncogenic effect of therapy. One of our patients (case 7) had a similar clinical course. Cerebral reticulum cell sarcoma or "microglioma", a histologic diagnosis earlier often associated with brain tumors of short latency (28), has since been classified as cerebral lymphoma, two of which were registered in our study group.

Of clearly different malignancies, various other intracerebral tumors have been reported after ALL; sarcomas, meningiomas and an increasing number of gliomas (29–33). In one study, nine anaplastic gliomas were registered among patients treated according to a protocol which included intrathecal methotrexate and cranial radiation with 24 Gy (16). Unbiopsied tumors have also been classified as SMN when the clinical findings were suggestive of a new disease (13, 15). On the basis of 3 cases and a mean follow-up time of 3.4 years after 3-year survival, the UK population-based study reported the incidence of brain tumors as 20-fold expected (15), and thus of the same order as our study indicates.

It has been suggested that genetically determined susceptibility is involved in the association observed between brain tumors and leukemia/lymphoma. Supporting this hypothesis were reports of increased incidence of CNS tumors and neoplasms of the hematopoietic-lymphatic system in relatives of brain tumor children (34). Leukemia was also seen as SMN subsequent to brain tumor (35). However, attention has later mainly focused on treatment-related carcinogenesis as the most likely cause of CNS tumors occurring after leukemia. Whether specific treatment modalities are directly involved remains to be proved. However, with two distinguishable treatment groups, it is noteworthy that the brain tumors in our study were only observed after cranial irradiation.

The pattern of other solid tumors found in this study is in accordance with previous reports (13, 28, 35). Rhabdomyosarcoma has earlier been registered in an ALL survivor who had only received chemotherapy (36). The rhabdomyosarcoma in our study appeared within the mantle radiation field in a patient who had been treated for Hodgkin's disease following leukemia (case 7). Treatment may have contributed to this development, but there may also have been an underlying cause for all three malignancies.

Conclusion. Although the numbers are still small, our study shows an increased risk of subsequent new malignancies among children who have completed treatment for ALL. The excess of SMN, where brain tumors were particularly notable, was observed only among patients who had received radiation. Cranial radiation, even in the relatively low doses given as prophylaxis against CNS leukemia, may thus represent a special risk factor. The cumulative risk of a SMN of nearly 3 % by 20 years after diagnosis comes in addition to the risk of the same magnitude for a very late reappearance of leukemia, which also could represent a new disease. In view of the long latency periods and long life-expectancy of individuals treated in childhood, as well as the fact that most survivors have not yet reached the age for adult neoplasms, knowledge of carcinogenic consequences of prior treatment remains incomplete. Although the final risk evaluation may have to wait several decades, the importance of monitoring survivors and considering alternative treatment forms is already evident.

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