Second Malignant Neoplasms After Childhood Cancer in Germany – Results from the Long-term Follow-up of the German Childhood Cancer Registry

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Introduction

The German Childhood Cancer Registry (GCCR) at the University Medical Centre of the Johannes Gutenberg University Mainz has been systematically recording all malignant diseases and all brain tumors in children under 15 years of age since 1980. Currently this amounts to data on 43,000 patients. This covers at least 95% of all cases in Germany [8]. The progress in therapies, currently ¾ of all cases survive, is steadily increasing the number of survivors. The most serious late sequelae are second malignant neoplasms (SMN) [2, 5, 12]. Here we describe the current frequency of SMN at the GCCR. This is supplemented by the radiation related results from a case control study on the therapy induced risk of SMN.

Material and Methods

The long-term survivor cohort at the GCCR currently amounts to 22,000 former patients. We are conducting active follow-up by contacting the former patients by letter about every 5 years and asking a small set of follow-up questions: relapse, SMN, vital status, current address. This allows calculating (event free) survival probabilities and incidences of SMN. By requesting address changes from the respective communities the addresses are thus always fairly up to date. As a first step, while patients are still in the aftercare by the hospitals, follow-up information is obtained from the clinical studies (TOS), who receive their information from the hospitals. Experience shows former patients to be willing to consent to continued data storage at the GCCR following the original consent by the parents. Up to the age of 16 and until the patient gives her or his own consent to being contacted directly, the former patients are being contacted via the parents. At 16, the GCCR contacts the patients and informs about data storage and asks for consent to regular personal contact. The most recent contact brought about 2.2% death reports, 3.7% explicit refusals, 79.6% explicit consents and 14.5% did not answer. Municipal address requests are 95% successful [4].

Upon receiving information on an SMN it is validated in tight cooperation with the TOS. The final decision (SMN or relapse, exact diagnosis) is made by these clinical experts.

Using data from the 328 SMN reported between 1980 and 2002 for former childhood cancer cases the GCCR conducted a nested case control study [9]. Each case was matched with two controls of the same sex from the registry diagnosed at the same age in the same period and surviving without SMN at least until the SMN event of the case occurred (639 controls).

The therapy of the primary was recorded in detail (all chemotherapy doses as well as radiotherapy). Wherever possible the actually given individual doses were obtained, which were supplemented by protocol information where necessary. This included relapse therapies up until the SMN event and conditioning for stem cell transplants. The data was analyzed by conditional logistic regression. Chemotherapy effects were adjusted for radiation effects and vice versa.

Results

Frequency of SMN after childhood cancer in Germany: Referring to all patients recorded from 1980 to 2008, 659 SMN (as defined by ICCC-3 [13]) have been reported as of March 2009, occurring after a childhood malignancy or a brain tumor. There is no age restriction for the SMN. Table 1 shows the grouped frequencies of all observed combinations of primary and second neoplasms.

The most frequent primary is lymphatic leukemia (LL) (211 cases, 32.0% of all SMN, followed by cerebral PNET (62 cases, 9.4%), Hodgkin's disease (59 cases, 9.0%), neuroblastomas, and non-Hodgkin lymphomas (42 cases each, 6.4%) (data not shown). The most frequent SMN are the myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (159 cases, 24.1%), brain tumors (141 cases, 21.4%) and various carcinomas (120 cases, 18.2%) most of these are thyroid carcinomas (53 cases, 8.0%). The most frequent combinations are MDS/AML after LL (61

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cases, 9.3%), astrocytoma after LL (34 cases, 5.2%), other brain tumors after LL (26 cases, 3.9%), and thyroid carcinoma after Hodgkin's disease (21 cases, 3.2%). The delay between the primary and the second neoplasm is clearly longer for second solid tumors as compared to second leukemias or lymphomas (current median delay for solid tumors: 7 years, for leukemias/lymphomas: about 2.5 to 3 years). Figure 1 shows the cumulative incidence of SMN after childhood cancer in Germany. It is visible that even after 25 years there is no slowdown of the rate, SMN keep occurring at a steady rate. We estimate the cumulative risk within 10 years of the primary diagnosis at 1.4%, which varies considerably by diagnosis. The 10 year cumulative incidence after nephroblastoma amounts to 0.9%, while more than 3% of the patients with a cerebral PNET develop an SMN.

Results of the case control study: Radiotherapy adjusted for chemotherapy has an effect of Odds Ratio (OR)=2.1 (95%-Confidence Interval (CI) 1.8–3.3), and OR=1.8 (95%-CI 1.0–3.1) for chemotherapy adjusted for radiotherapy, both are statistically significant (data not shown). We observe an increasing effect with dose: Adjusted for chemotherapy, the OR for cumulative radiotherapy doses <24Gy, 24–<40Gy, and 40–<55.2Gy increase from 1.6 to 2.4 to 2.8 (95%-CI 1.7–4.7, 54 cases, 59 controls) compared to patients with no radiotherapy, all effects are significant (data not shown).

The risk of SMN through radiotherapy is higher for primary LL (OR=3.6, 95%-CI 1.9–6.8, 100 cases, 143 controls) compared to primary solid tumors (OR=2.1, 95%-CI 1.1–4.1, 92 cases, 137 controls).

Based on all primaries, the risk for solid SMN through radiotherapy is higher than average, namely 4.5-fold (95%-CI 2.5–8.0, 133 cases, 176 controls), it is especially high for carcinoma (OR=69.0, 95%-CI 3.7–1275, 41 cases, 47 controls).

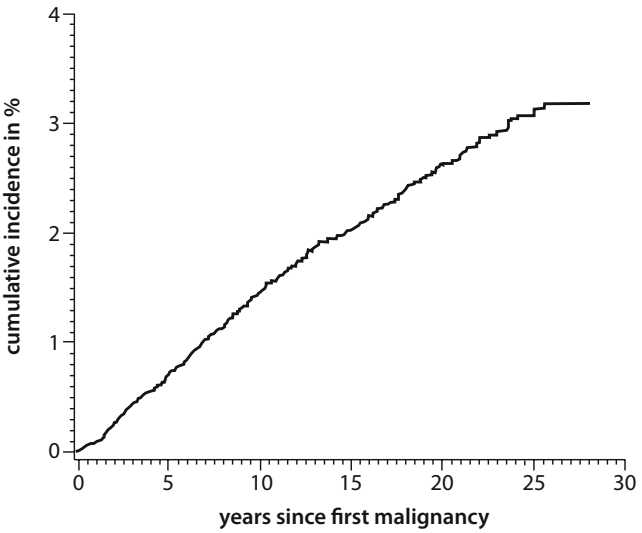

Figure 1. Cumulative incidence of second malignant neoplasms in Germany since 1980.

Discussion

The active long-term follow-up can potentially ascertain the majority of all SMN occurring in the population. The current process misses all SMN among non-consenting and non-participating survivors as well as SMN in a subset of deceased patients. Generally the cumulative incidence is somewhat underestimated. The network of validation between hospitals, TOS, and GCCR leads to

Table 1. Observed cases of second malignant neoplasms in Germany 1980–2008. Grouped combinations of diagnoses.

	Second malignant neoplasms (SMN)							
Primary malignancies	**Leukemias**	**Lymphomas**	**Brain tumors**	**Bone tumors**	**Soft tissue sarcomas**	**Carcinomas, epithelial tumors**	**Other**	**All primary malignancies**
Leukemias	79	37	64	10	6	41	9	246 37,3%
Lymphomas	27	21	8	1	5	48	2	112 17,0%
Brain tumors	19	3	43	6	12	17	8	108 16,4%
Tumors of sympath. nervous system	24	2	3	1	3	5	4	42 6,4%
Bone tumors	20	2	3	5	4	4	1	39 5,9%
Soft tissue sarcomas	13	1	9	12	3	6	4	48 7,3%
Other	13	2	11	10	10	11	7	64 9,7%
All SMN	195 29,6%	68 10,3%	141 21,4%	45 6,8%	43 6,5%	132 20,0%	35 5,3%	659 100%

igh quality information on each case and helps to miss as few cases as possible.

We expect the cumulative incidence to increase further as prognosis improves, observation times lengthen and case ascertainment improves. We are currently establishing a matching procedure with the general cancer registries in Germany. The 659 known SMN cases are one of the largest patient groups world wide, representative for Germany.

The case control study shows that both radiotherapy and chemotherapy lead to a two-fold increase in the risk of SMN. Risk after radiotherapy shows clear dose dependence [9].

An as yet unpublished systematic review (in a doctoral thesis) identified 34 large epidemiological studies investigating the risk for SMN after childhood cancer through radiotherapy (e.g. [6, 7, 11]). The epidemiological studies generally show an increase of risk with radiotherapy dose, depending also on the field of radiation, age at exposure, and primary diagnosis. The risk estimates obtained from the German case control study are generally smaller than what is seen internationally. Our data included therapies since 1980 only, where doses were already lower than in previous years, which are included in most of the international studies. We expect that studies such as our case control study and other national and international research will contribute to adapting therapy protocols towards a generally lower risk of SMN in long-term childhood cancer survivors [1, 3, 5, 10, 14].

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