

SHORT REPORT

Second malignant neoplasms in children treated for primary solid tumors

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Summary

Purpose: To present the incidence of second malignant neoplasms (SMNs) among children treated for primary solid tumors.

Patients and methods: The records of 226 children treated for primary solid tumors during the period 1986-1996 were retrospectively analyzed in order to find those children who developed later SMNs. Registered were the kind of primary tumor, age on primary and SMN, sex, first-line anticancer treatment and family history.

Results: Nine (3.4%) children treated for different primary malignant solid tumors developed SMNs after a median of 10 years (range 1.5-17 years) after primary anticancer treatment. Their median age on SMN manifestation was 14.3 years (range 9-20 years). Histological distribution of the primary tumor was: neuroblastoma 4 patients, Ewing's sar-

coma 2 patients, Wilm's tumor 1 patient, bilateral retinoblastoma 1 patient and glioma of the optic nerve 1 patient. These children developed the following SMNs: rhabdomyosarcoma 4 patients, leukemias 3 patients, ganglioneuroblastoma 1 patient and ovarian cancer 1 patient. In 5 patients neoplastic family history was evident. All 9 children were surgically treated for their primary tumor, and 8 of them also received radiotherapy and chemotherapy. One girl received radiotherapy alone and one boy chemotherapy alone. Two out of 9 patients (22.2%) live without evidence of disease and 7 have died.

Conclusion: The risk factors for the development of SMNs seem to be genetic predisposition, radiation and certain chemotherapeutic agents.

Key words: chemotherapy, childhood tumor, radiotherapy, risk factors, second malignant neoplasm

Introduction

The risk of SMNs in children, who are long-term survivors after anticancer treatment for a primary malignancy, is 10-20-fold compared with the general population of age-matched controls [1-4]. It was estimated that 1 in every 1000 young adults, survivors of childhood cancer, would have the potential risk for developing a second malignancy. Incidence rates for SMNs have

ranged from 3%-12%, proportionally to the length of the follow-up period. Twenty-five years after the initial diagnosis the rate increases to 17% ± 6% [3-5].

Published data show that the kind of SMN depends on the kind of the primary malignancy, patient's age, presence of genetic predisposition and kind of treatment used. Particularly high risk for SMN exists in children with Hodgkin's disease, retinoblastoma and genetic form of Wilm's tumor. The risk is also high in children treated with radiotherapy, alkylating agents or among those with von Recklinghausen's neurofibromatosis or immunodeficiency syndromes [6-12].

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Patients and methods

During the period 1986-1996 the records of 226 children treated for different primary solid tumors were reviewed with an intent to register those children who later developed SMNs. Registered were the kind of the

primary tumor, age on primary and SMN manifestation, sex, first-line anticancer treatment (surgery, chemotherapy or radiation therapy) and family history.

Results

Nine (3.4%) children with primary malignant solid tumors developed SMN after a median of 10 years (range 1.5 - 17 years) after anticancer treatment for their primary malignancy. The age of the patients by the time of SMNs development ranged from 9 to 20 years (median 14.3 years), with a female: male ratio 5:4. The histological distribution of the primary tumor was: neuroblastoma 4 patients (44.5%); Ewing's sarcoma 2 patients (22.2%); 1 child (11.1%) with bilateral retinoblastoma; 1 child (11.1%) with glioma of the optic nerve; and 1 child (11.1%) with Wilm's tumor (Table 1).

These 9 children developed later the following SMNs: rhabdomyosarcoma 4 (44.5%) children; leukemia 3 (33.3%), ganglioneuroblastoma 1 (11.1%); and ovarian carcinoma 1 (11.1%). The group of patients with rhabdomyosarcoma predominated, all of these children having a family history for cancer (2 patients with grandmothers with breast cancer, 1 patient with a father with rectal carcinoma and 1 patient with a grandfather with hepatocellular carcinoma). A family history for cancer of the girl with glioma of the optic nerve (one brother



Figure 1. Case No 6: Primary solid tumor (bilateral retinoblastoma). After 13 years second malignant neoplasm (rhabdomyosarcoma).

with acute lymphocytic leukemia (ALL) and another one with non-Hodgkin's lymphoma) was also registered. Her mother worked in an asbestos factory. Three (33.3%) patients had neurofibromatosis, which was also present

Table 1. Patient demographics and risk factors for development of secondary malignant tumors

No of patient	Sex	Age (years)	Primary tumor	Latency for SMN ¹ (years)	Second tumor	Family history for cancer	RT ² (Gy)	Chemo-therapy	Surgery	Survival after SMN	Outcome
1	F	2	Nbl ³	14	Rhabdomyosarcoma	Grandmother with breast cancer	30	Yes	Radical	4.5 years	Dead
2	F	2	Nbl-neck	17	Rhabdomyosarcoma	Father with rectal cancer	25	Yes	Radical	2 years	Dead
3	F	4	Nbl-supra renal	4	ALL ⁴	-	30	Yes	Radical	1 month	Dead
4	M	8	Ewing's sarcoma	1.5	ANLL ⁵	-	53	Yes	Yes	3 months	Dead
5	M	13	Ewing's sarcoma	1.5	ALL	-	64	Yes	Yes	4 years	Alive
6	M	1	Retinoblastoma bilateral	13	Rhabdomyosarcoma	Mother with breast cancer	30	Yes	Unilateral enucleation	10 months	Dead
7	F	2	Wilm's tumor	13	Rhabdomyosarcoma	Grandfather with liver cancer	25	Yes	Nephrectomy	1.5 years	Dead
8	F	7	Glioma of the optic nerve	13	Ovarian cancer	Brother with ALL; Brother with NHL ⁶	46	No	Radical	1 year	Dead
9	M	1	Nbl	11	Ganglio Nbl mediastinal	-	-	Yes	Radical	3 years	Alive

M: male, F: female

¹second primary malignancy, ²radiotherapy, ³neuroblastoma, ⁴acute lymphocytic leukemia, ⁵acute non lymphocytic leukemia, ⁶non-Hodgkin's lymphoma

in first-degree relatives (patients and brothers / sisters).

All 9 children were surgically treated and 7 of them also had radiotherapy and chemotherapy. The girl with glioma of the optic nerve had radiotherapy alone and 1 boy with neuroblastoma received chemotherapy without radiotherapy. Two (22.2%) children out of 9 survive free of disease for 3 and 4 years and 7 (77.8%) have died (Table 1).

Discussion

Criteria to characterize a malignant tumor as a second separate neoplasm are: 1. Every tumor must be represented by its own specific and histologically distinguished malignant characteristics; and 2. Total exclusion of the possibility for relapse or metastasis of the primary tumor [4].

Important risk factors for SMN development usually include genetic factors and familial predisposition, like retinoblastoma, and carcinogenic effects of anticancer treatments [5,6,8,9].

Radiotherapy is a risk factor for developing a SMN. The most frequently registered SMNs after radiotherapy are sarcomas (osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma), other soft tissue sarcomas and thyroid carcinoma [1,2,4,12-14]. Meadows et al. presenting the results of a study carried out by a consortium of 12 international pediatric oncology centers from the USA and Canada identified 292 cases of children with SMN, 68% of which were radiation-induced [4]. Barancelli et al. had followed up a rare second tumor - myocardial rhabdomyosarcoma-in a patient treated with radiotherapy in the chest for Hodgkin's disease 12 years ago [7]. Radiation-induced carcinomas of the skin and breast are not rare [15]. The development of a SMN after radiotherapy depends on the patient's age, the irradiated tissues, the radiation dose and the radioactive source. In the past, when X-ray kilovoltage machines were routinely used, radiation-induced secondary sarcomas were a frequent pathology compared with the frequency of the cases treated with the modern megavoltage linear accelerators.

Chemotherapy is also considered as a risk factor for inducing SMNs, and cases with ALL are the most frequently encountered. Not all of the cytotoxic drugs have late carcinogenic effects. Such side effects have been registered mainly with alkylating agents (nitrogen mustard, cyclophosphamide, procarbazine), etoposide, but not with actinomycin-D [1-3,16]. Second solid tumors like rhabdomyosarcoma and fibrosarcoma, neoplasms like osteosarcoma and Ewing's sarcoma, skin carcinoma and melanoma, and cancer of the thyroid appear

with a frequency of 5.8% after the 12th year. Usually, the latent period varies from 9.5-12 years [3,5,9,11,17].

In our clinical material the most common SMN was rhabdomyosarcoma (4 children, 44.5%). These 4 children were under 3 years of age when they were treated with radiotherapy for their primary malignancy. All cases had embryonal tumors - 2 neuroblastoma, 1 Wilm's tumor and 1 bilateral retinoblastoma. The latent period before the manifestation of the SMN ranged between 1.5-17 years. One of our cases with primary neuroblastoma was a 4-year-old girl who developed ALL as a SMN within 4 years of the primary treatment. Cases with primary neuroblastoma later developing lymphomas, renal-cell carcinoma and pheochromocytoma as SMN are described in the literature [18-20]. Our case of neuroblastoma had no family history for cancer and she underwent radical surgery for her primary tumor with splenectomy because of spleen infiltration. The child was treated with radiotherapy (total dose 30Gy) and chemotherapy including cyclophosphamide and etoposide. In 2 boys with primary Ewing's sarcoma we registered the development of ALL and acute nonlymphocytic leukemia (ANLL), shortly (1.5 year) after the anticancer treatment was completed. It is uncommon for radiation-induced malignancies to develop in such a short period, but the high radiation doses (54-64 Gy) delivered locally, in combination with chemotherapy may have been the SMN-inducing cause. Both children had neurofibromatosis and the risk for malignancy in such patients is 4-fold compared with the general population.

The carcinogenic potential of chemotherapy for a child is smaller compared with ionizing radiation, but both methods are used more often in combination and the risk of SMN increases as these modalities, when combined, have additional effects. Cases with primary neuroblastoma, ovarian, germ-cell, gastrointestinal malignancies and other solid tumors treated with combination of radio- and chemotherapy (cyclophosphamide, etoposide) can develop secondary ANLL in 5%-20% [1-3,21-24]. There is no increased risk for SMN in children with Wilm's tumor treated with radiotherapy and actinomycin-D, but the risk increases in cases with genetic forms of nephroblastoma [10,16,21,23].

The role of surgery for SMN development is limited, although there are some reports of cases with secondary ANLL after splenectomy and chemotherapy with MOPP for Hodgkin's disease and secondary soft tissue neoplasms after ureterostomia for locally advanced Wilm's tumor [25].

In one boy from our series with primary abdominal neuroblastoma, a mediastinal ganglioneuroblastoma was diagnosed 11 years later. He was operated on and received postoperative chemotherapy. In this case it could

be assumed that both tumors with similar histology probably arose as multiple primary tumors, but an unexplained mechanism had postponed the development of the second tumor (ganglioneuroblastoma).

The mechanisms of carcinogenesis of SMN are complex and difficult to interpret. Genetic predisposition is an important risk factor for SMN development. Five (56%) of 9 patients in our series had a family history for cancer and 4 (44%) had neurofibromatosis. Radiotherapy also plays a significant role in SMN development. Children under 3 years of age treated with radiotherapy, even with small local doses (<30 Gy), have an increased risk for developing SMN. In our series 4 (50%) out of 8 irradiated children were under 3 years of age when they received 25-30 Gy. The risk of SMN was increased when radiotherapy was combined with chemotherapy, especially when the latter included cyclophosphamide or etoposide. Seven (77%) children treated with chemoradiotherapy including cyclophosphamide later developed SMN.

The last 2 decades have seen a dramatic progress in the treatment of childhood malignancies. Long-term disease-free survival for all histological types of primary malignancies in children is about 65%. The prognosis of patients with SMN is worse compared to cases with primary tumors. The possibility to choose the most effective therapeutic regime with minimal long-term side effects is a problem which is still difficult to solve despite the major advances made in the field of pediatric oncology.

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