Second malignant neoplasms in patients treated on SIOP Wilms tumour studies and trials 1, 2, 5, and 6

Carli, M.; Frascella, E.; Tournade, M-F.; de Kraker, J.; Rey, A.; Guzzinati, S.; Burgers, J.M.V.; Delemarre, J.F.M.; Masiero, L.; Simonato, L.

Published in:
Medical and Pediatric Oncology

DOI:
10.1002/(SICI)1096-911X(199710)29:4<239::AID-MPO1>3.0.CO;2-N

Link to publication

Citation for published version (APA):
Carli, M., Frascella, E., Tournade, M-F., de Kraker, J., Rey, A., Guzzinati, S., ... Simonato, L. (1997). Second malignant neoplasms in patients treated on SIOP Wilms tumour studies and trials 1, 2, 5, and 6. Medical and Pediatric Oncology, 29, 239-244. DOI: 10.1002/(SICI)1096-911X(199710)29:4<239::AID-MPO1>3.0.CO;2-N
Second Malignant Neoplasms in Patients Treated on SIOP Wilms Tumour Studies and Trials 1, 2, 5, and 6

Modesto Carli, MD, 1* Emanuela Frascella, MD, 1 Marie F. Tournade, MD, 2
Jan de Kraker, MD, 3 Annie Rey, PhD, 2 Stefano Guzzinati, PhD, 4
J. Marion V. Burgers, MD, 3 Jan F.M. Delemarre, MD, 3 Lucia Masiero PhD, 1 and
Lorenzo Simonato, MD 4

The incidence of second malignant neoplasms (SMNs) was investigated among 1,988 patients with complete data, enrolled in the SIOP Wilms tumor trials and studies 1, 2, 5, and 6, treated between September 1971 and October 1987. By the end of 1992, eight SMNs were documented, whereas only 1.3 were expected (standardized incidence ratio [SIR] = 4.15; 95% CI = 1.79, 8.17). The risk increases in the first 10 years from diagnosis, while no apparent excess of risk is observed in the subsequent periods. This finding however is difficult to interpret due to the low statistical power. The cumulative incidence of a second cancer observed at 15 years after Wilms tumor diagnosis was 0.65%. Six SMNs were registered in the cohort of patients treated in the SIOP studies 1, 2, and 5 (999 cases) compared to the two cases observed in the SIOP6 cohort (989 cases). If the suggested reduced incidence of second cancers between SIOP1-5 and SIOP6 patient cohorts is confirmed by longer follow-up, it might reflect changes in the treatment protocols. Med. Pediatr. Oncol. 29:239–244, 1997. © 1997 Wiley-Liss, Inc.

Key words: Wilms tumor; second malignancy

INTRODUCTION

Wilms tumor provides one of the most impressive examples of success in the treatment of childhood cancers. This success has been made possible through a step-wise process of refinements of a multidisciplinary approach including surgery, radiotherapy, and chemotherapy.

In Europe, the improvement achieved in the cure rate of children with Wilms tumor is well documented by the results reported by the International Society of Pediatric Oncology (SIOP) Wilms tumor studies in the last few decades. Before 1970 the 5-year survival rate of a large series of patients treated in a single institution from 1952 to 1967 [1] was 55%. The 5-year overall survival rate of children enrolled since 1971 in five consecutive SIOP studies increased from 64% for children treated in the early seventies (1971–1974; SIOP1) [2]; to 76% for those treated between 1974–1976 (SIOP2) [3]; 83% for those treated between 1976–1980 (SIOP5) [4]; and 84% for those treated during 1980–1987 (SIOP6) [5]. The 5-year overall survival for patients registered during 1987–1991 in the SIOP9 is 87% [6].

However, successfully treated patients are at risk of developing a second cancer later in life [7–11]. This report examines the risk of second malignant neoplasms (SMNs) among 1,988 children enrolled in the SIOP Wilms tumor trials and studies 1, 2, 5, and 6, treated between 1971–1987.

© 1997 Wiley-Liss, Inc.

PATIENTS AND METHODS

Between September 1971 and October 1987, 2,067 patients with Wilms tumors were entered in one of four SIOP trials and studies (SIOP 1, 2, 5, and 6). Of those, 1,988 were eligible for this report: 79 were excluded because of incomplete data. Of the 1,988, 995 were classified as “study” patients and 993 as “trial” patients. The clinical characteristics of this population of Wilms tumor patients are summarized in Table I. The treatments adopted in the different SIOP studies have already been reported [2–6]. “Study” patients were not included in the “trial” category because of one of the following reasons: age less than 6 months, or more than 15 years, stage IV, bilateral disease, inability to apply preoperative therapy, registration after surgery, parents refusal of the trial, or other reasons. Treatment recommendations for “study” patients were to follow the protocol regimens. Children less than 6 months were operated first and if

1Department of Pediatrics, Hematology Oncology Division, University of Padova, Italy; 2Institut Gustave Roussy, Villejuif, France; 3Emma Kinderziekenhuis/Accademish Medical Center, Amsterdam, The Netherlands; 4Tumor Registry of Regione Veneto, Department of Oncology, University of Padova, Italy.

*Correspondence to: Modesto Carli, Dipartimento di Pediatrìa, Divisione di Emato-Oncologia, Università di Padova, 35128 Padova, Italy.

Received 3 May 1996; Accepted 31 January 1997
they were stage I, no postoperative treatment was given. Detailed treatment information were recorded only for trial patients.

Follow-up status was ascertained by the treating institutions using specific forms reporting any events which occurred during follow-up. No major difference between institutions was detectable in term of efficiency of follow-up. The statistical analysis used all data obtained through December 31, 1992. For every second tumor, relevant clinical data and the histopathological report were obtained, but only the slides of the primary lesions were centrally reviewed by the pathology panel of the SIOP Wilms tumour study.

Data processing and quality control analyses were performed at the Venetian Cancer Registry using common statistical packages [12]. The cohort analysis was performed using the date of diagnosis as the date of entry in the observation period. The date of death (for those who died), or the date of the last contact for those lost to follow-up or the date of the end of the study for those still on follow-up, have been used as the date of exit from the observation period. We report in Table II the distribution of subjects alive, dead, or lost to follow-up by time since Wilms tumour diagnosis.

An effort was made to use national incidence rates for each of the countries included in the study. Only a few European countries, however, had a nationwide cancer registry, and most of the collaborating centres were located in areas not covered by cancer registries. It was therefore decided to use the age, sex, and calendar specific cancer incidence rates of the Danish Cancer Registry because of their known high quality and long standing. Other similar studies carried out in Europe have used the Danish Cancer Registry as the reference [20].

Expected number of cancers (excluding skin cancers) [12] were obtained by multiplying the accumulated per-

### RESULTS

Table III reports results by time since diagnosis. Among all 1,988 patients, eight new cancers were observed during 13979.85 PY of follow-up, whereas only 1.93 were expected (SIR = 4.15; 95% CI = 1.79, 8.17). The average contribution per patient was 7.03 person-years. The risk increases in the first 10 years from diagnosis (eight SMNs observed vs. 1.61 expected; SIR = 4.97 95% CI = 2.15, 9.79) reaching statistical significance ($P < 0.05$) while no apparent excess of risk is observed in the subsequent periods.

The eight SMNs registered occurred in three females and five males during the surveillance period that ranged from 6 to 21 years.

Table IV lists the main clinical data of SIOP patients with SMNs. They include two acute myeloid leukemias, three bone tumors (two osteosarcomas and one chondrosarcoma), two CNS primitive neuroectodermal tumors (PNET), and one histiocytic lymphoma. All patients had received vincristine and dactinomycin associated with doxorubicin (three patients) and ifosfamide (one patient). Radiotherapy in the range of 2000–4000 cGy, was given to six out of eight children. The three bone tumors observed occurred within the field of prior radiation therapy. The two patients who did not receive radiotherapy developed a lymphoma and a CNS tumor respectively. The time interval between first malignancy and SMN ranged between 15 and 101 months (median 53 months); it was shorter for CNS tumors (15 and 29 months) and longer for bone tumors (74, 100, and 101 months respectively).

The cumulative probability of developing an SMN after 5 and 10 years from diagnosis of Wilms tumor was
We examined the risk of SMNs among 1,988 Wilms tumor patients treated between September 1971 and October 1987 on one of four consecutive SIOP trials and studies.

The cumulative incidence of second cancers observed at 15 years after diagnosis in our study population was 0.65%. Eight new cancers developed as compared with 1.93 expected on the basis of cancer incidence rates in the general population of the Danish Cancer Registry (SIR = 4.15). In our series the risk increased in the first 10 years, from diagnosis, (SIR = 4.97) reaching practically the same proportion of patients with second cancer (1%) observed in other similar studies [8,9,16]. No SMNs have been observed in patients followed for more than 10 years from diagnosis.

Other similar hospital-based cohort studies have demonstrated that the incidence of SMN continues to rise even after the first decade from diagnosis with cumulative risk of SMNs of 1.6% [10], 2.95% [17], 5.6% [18], 6% [8], 8.5% [19], and 9.6% [20] between 15–30 years.
after treatment for the first cancer. Comparison with these studies is difficult because of incomplete ascertainment of our patients population after 10 years from diagnosis.

Should the suggested reduced incidence of second tumors between SIOP1–5 and SIOP6 patient cohorts be confirmed by longer follow-up, it might well reflect changes in the treatment protocols. The indications for radiation therapy and the doses delivered both have in fact been reduced. Breslow et al., in their recent update of SMNs in Wilms tumor survivors, found irradiation to be a factor, and a clear correlation between the dose of radiation given and the risk of SMN [10]. We cannot perform this type of analysis because we have detailed treatment information only for trial patients. However according to the guidelines of the protocols, 80% of the patients in the SIOP1–5 studies were irradiated as compared to 40% in the SIOP6 study.

Furthermore, chemotherapy has been reduced in the SIOP series. The number of stage I Wilms’ tumor patients who did not receive radiation therapy and who were treated with minimal chemotherapy increased through the studies. However, it should be emphasized that the two groups have different follow-up time and this might influence the results.

Among the eight cases of SMN, a clear relationship with radiotherapy is evident for the three cases of bone sarcomas occurred in the field of radiation. The two cases of leukemias were also associated with radiotherapy, but the interaction of chemotherapy cannot be excluded. Both cases in fact, were treated with intercalating topoisomerasases II inhibitors such as doxorubicin and/or dactinomycin, which in combination with radiotherapy appeared to be leukemogenic [10,20,21].

Two children developed a CNS PNET. The association of Wilms tumor and cerebral neoplasms does not fit with any known cancer predisposing syndromes or con-

---

**Fig. 1.** Cumulative incidence of SMN after diagnosis of Wilms tumor.

**TABLE V.** Incidence Rates and Standardized Incidence Ratio of Second Malignant Neoplasm Within 10 Years From Wilms Tumor Diagnosis SIOP 1-2-5 vs. SIOP6

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Person-yr</th>
<th>Rates per 10^5</th>
<th>Observed</th>
<th>SIR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIOP 1-2-5</td>
<td>999</td>
<td>6891.84</td>
<td>87.1</td>
<td>6 7.32 (2.69–15.93)</td>
</tr>
<tr>
<td>SIOP 6</td>
<td>989</td>
<td>5154.08</td>
<td>38.8</td>
<td>2 2.56 (0.31–9.26)</td>
</tr>
<tr>
<td>Total</td>
<td>1,988</td>
<td>12045.92</td>
<td>66.4</td>
<td>8 4.97 (2.15–9.79)</td>
</tr>
</tbody>
</table>
ditions. However it is quite interesting to point out that a cerebral PNET has been documented in the cohort of 43 SMNs occurring in long term survivors of Wilms tumor reported by Breslow et al. [10] and that three cases of brain tumors in the absence of brain radiotherapy and use of alkylating agents were reported by Meadows et al. [23] among 36 SMNs observed in Wilms tumor patients. Similarly neither one of our two cases were treated with CNS radiotherapy. It is worthwhile noticing that both children were very young at diagnosis (i.e., 1 and 1.6 years) and the latency period for SMN was the shortest observed in our series. This could suggest that an unknown genetic predisposition could be at the base of this rare tumor combination [24]. It is worthwhile mentioning that the diagnosis of both cases of cerebral PNET have been reviewed by members of the pathology panel of the SIOP Wilms tumor study.

Genetic predisposition has been associated with increased risk of SMNs [25]. Only the 999 patients enrolled in the SIOP1–5 studies have been the object of accurate epidemiologic investigation. Among these, about 20% had a multicentric or bilateral disease or a family member affected by Wilms tumor or characteristic congenital anomalies [26]. Out of the six cases of SMNs documented in this cohort (patients 1–6), two occurred in children having congenital anomalies (patients 2 and 4) which may be interpreted as signs of an underlying genetic defect predisposing to tumor development. Because of small numbers, however, an excess of SMNs among those patients with putative “hereditary conditions,” similarly to Breslow et al. [9,10], cannot be either confirmed or excluded.

In accordance with De Vathaire et al. [20] and with Breslow et al. [10], our results indicate no statistically different risk of SMN for children aged 5 years or more at diagnosis.

Our study cannot contribute to the evaluation of the possible protective or carcinogenic effect of daunomycin as reported in other studies [27,28] because all our irradiated patients also received daunomycin.

In conclusion, compared to the general population, SIOP Wilms tumor patients have a five-fold increased risk of developing a second cancer within 10 years from diagnosis. However, our study tends to confirm the limited risk excess of SMNs in Wilms tumor children as compared to other childhood cancer patients [18,20]. In order to verify whether the risk of SMN in our European cohort of Wilms tumor patients have decreased, a longer follow-up is warranted.

ACKNOWLEDGMENTS

The authors thank Dr. Giulio J. D’Angio for the critical review of the manuscript and the editorial assistance, and Dr. Anna T. Meadows for her valuable suggestions.

Supported in part by Italian Grant “MURST 60%” and CNR PF ACRO.

REFERENCES