

Subsequent malignant neoplasms (SMNs) among non-irradiated survivors of childhood cancer treated with chemotherapy in the Childhood Cancer Survivor Study

Background: In recent treatment eras radiotherapy (RT) use decreased while chemotherapy (CT) increased. RT is an established risk factor for SMNs. Limited data exist on how CT increases risk for SMNs >5 years after childhood cancer.

Methods: SMNs were evaluated in 5-year survivors diagnosed <21 years of age between 1970-99, treated with CT and not RT (N=7447, 138,008 person-years follow-up). 30-year cumulative incidence and 95% confidence intervals (CI) and standardized incidence ratios (SIRs) for SMNs were estimated. SIRs were estimated for chemotherapy exposures (alkylator: 0, 1-3999, 4000-7999, ≥8000 mg/m²; platinum: 0, 1-400, 401-750, >750 mg/m²; anthracycline: 0, 1-100, 101-300, >300 mg/m²; epipodophyllotoxin: 0, 1-1000, 1001-4000, >4000 mg/m²).

Results: There were 154 SMNs among 139 survivors. Cumulative incidence for SMNs at 30 years was 4.5% (95% CI 3.4-5.6) and risk for SMN was 3-fold greater than the general population. Survivors of leukemia, lymphoma, and sarcomas had increased risk for SMNs (Table), whereas, survivors of Wilms tumor, neuroblastoma and CNS cancer did not. Exposure to moderate- to high-dose alkylator (≥4000 mg/m²) or platinum (>400 mg/m²) or high-dose anthracycline (>300 mg/m²) or epipodophyllotoxin (>4000 mg/m²) therapy had SIRs of ≥4.0. A combination of alkylators and platinum, one of the two being high-dose and the other being moderate or high-dose, had a SIR of 13.0 (95% CI 6.5-23.2).

Conclusions: Non-RT exposed survivors are at increased risk for SMN and should be counselled regarding the potential for genetic predisposition and the need for increased surveillance for early detection of subsequent cancers.

Primary Cancer	SMN					
	All SMNs (n=154)	Leukemia/Lymphoma (n=21)	Breast (n=34)	Soft tissue sarcoma (n=14)	Thyroid (n=20)	Melanoma (n=15)
All diagnoses	3.1 (2.6-3.6)	2.9 (2.4-3.4)	6.3 (4.4-8.9)	4.1 (2.2-6.8)	3.5 (2.2-5.5)	3.4 (2.1-5.3)
Leukemia/lymphoma (n=4309)	2.7 (2.2-3.4)	2.1 (1.2-3.4)	6.3 (3.7-10.1)	1.5 (0.3-4.3)	2.6 (1.2-5.0)	4.1 (2.3-6.9)
Sarcoma (n=1484)	3.8 (3.0-4.9)	2.5 (1.0-5.1)	7.1 (4.1-11.3)	10.0 (4.8-18.4)	5.6 (2.6-10.7)	3.2 (1.2-7.0)