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Surveillance of Childhood Cancer Survivors: A Lifelong Affair

Mark A. Applebaum, **Susan L. Cohn**

University of Chicago, Chicago, IL

Treatment advances in the past several decades have greatly improved the prognosis for children diagnosed with cancer, and 5-year overall survival is now greater than 80% across all cancers.[1] For many children with cancer, the improvement in survival has been achieved through the use of increasingly intensive, multimodal therapeutic approaches that include combinations of high-dose chemotherapeutic agents with or without radiation therapy. Survivors are known to be at risk for developing a spectrum of adverse outcomes, including early death, impaired growth and development, decreased fertility, and impaired cognitive function.[2,3] However, one of the most serious treatment-related adverse events is the development of subsequent malignant neoplasms (SMNs). These subsequent cancers are a major cause of premature death, and recent studies indicate that patients surviving their first SMN remain at risk for additional neoplasms.[4]

The Childhood Cancer Survivor Study (CCSS) has led to significant advances in our understanding of the health outcomes of childhood cancer survivors.[3] This ongoing multi-institutional research initiative has established a large and extensively characterized cohort of 5-year survivors of childhood and adolescent cancer. Importantly, follow-up of the aging CCSS cohort has provided new information about the long-term effects of treatment. Previous analysis of the CCSS cohort has demonstrated that the cumulative incidence of SMNs in patients 20 and 30 years from diagnosis was 3.2% and 7.9%, respectively, with standardized incidences higher than population controls.[5] Additional studies have demonstrated that specific treatment exposures influence the risk of particular histologic

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Mark A. Applebaum

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Susan L. Cohn

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types of subsequent malignancies. Notably, there is a 43-fold (95% CI, 27.2- to 70.3-fold) increased risk of breast cancer in women after whole-lung radiation[6] and increased odds of 3.5 (95% CI, 1.6 to 7.7) for developing a secondary sarcoma after exposure to anthracycline.[7]

The Children's Oncology Group and others have developed risk-based guidelines for long-term follow-up of childhood and adolescent cancer survivors for SMNs and other adverse health outcomes based on the primary disease, treatment exposure, and established therapy-related morbidities and mortality observed in the survivorship population.[8] However, little is known about the health outcomes and/or risk of developing an SMN in the aging survivor population. Although small studies using the Surveillance, Epidemiology, and End Results (SEER) database have described the continuously increased incidence of SMNs decades after the diagnosis in osteosarcoma and neuroblastoma,[9,10] the small numbers of patients and lack of detail regarding treatment exposures limit the ability to determine specific SMN risk.

In the accompanying article, Turcotte et al[11] have analyzed subsequent neoplasms (SNs) in patients included in the CCSS cohort who have reached their fifth or sixth decade of life. Of the 14,364 patients in the CCSS cohort diagnosed between 1970 and 1986, 3,171 met inclusion criteria of being at least 40 years old at the time of last survey, totaling 15,985 person-years after age 40. A total of 679 SNs were reported, and SMNs (n = 196) were diagnosed in 180 unique individuals. The cumulative incidence of SNs and SMNs between the ages of 40 and 55 years was 34.6% (95% CI, 28.7% to 40.6%) and 16.3% (95% CI, 11.7% to 20.9%), respectively. There was no difference in the cumulative incidence of SMNs between those who did or did not develop an SN before age 40 years (20.8% [95% CI, 12.5% to 29.1%] and 15.4% [95% CI, 10.2% to 20.5%]; $P = .35$). However, exposure to radiation and a history of SNs put patients at higher risk of developing an SN than those without either risk factor with cumulative incidences of 62.3% (95% CI, 51.2% to 73.5%) and 13.3% (95% CI, 4.8% to 21.8%), respectively.

The correlation between therapeutic exposures and development of SMNs is well established in survivors observed for two to three decades. In the CCSS cohort of survivors older than age 40 years, all classes of chemotherapeutics were associated with a higher incidence of SMNs, although only platinum-based agents remained significant in a multivariable analysis. Therapeutic radiation exposure also increased the risk for SMNs in this cohort well into their fifth and sixth decades. Interestingly, male survivors age 40 years or older who were not exposed to therapeutic radiation were not at increased risk for SMNs, regardless of their SN history before age 40 years.

Childhood cancers that generally occur at older ages such as Hodgkin lymphoma (HL) were overrepresented in the aging CCSS cohort that was analyzed, whereas malignancies that are commonly diagnosed in younger children, such as neuroblastoma and Wilms tumor, were relatively underrepresented. The makeup of the aging CCSS cohort clearly influenced the histologic types of SMNs observed. For example, 30% of the patients were HL survivors, and this group experienced a high number of new SNs (57%) after age 40 compared with other primary diagnoses, largely as a result of the high incidence of breast cancer. Females

and HL survivors had increased risk of breast cancer compared with the general population regardless of prior SN status. Furthermore, female sex (relative risk, 1.9; 95% CI, 1.3 to 2.6) and radiation exposure (relative risk, 2.2; 95% CI, 1.4 to 3.3) were determined to be significant risk factors in a multivariable Poisson regression model for SMNs. Thus, it seems clear that female survivors of HL remain at significant risk of developing breast cancer into their 40s and 50s warranting vigilant surveillance well beyond this age. Because of the relatively small numbers of patients with other primary childhood malignancies in this cohort, specific risks for SMNs cannot be determined. As the CCSS cohort continues to age, more patients will reach the fifth and sixth decades of life and beyond, and their health outcomes will provide an improved understanding of the risk of SNs and SMNs in survivors of multiple different tumor types.

Although the authors highlight the increased risk of SMNs that occur in survivors of pediatric cancer, it is also important to recognize the potential SMNs that were not significantly increased in this cohort. These survivors were at no statistically increased risk compared with the general population of developing subsequent head and neck, lung, or colon cancers, as had previously been described.[5] Whether this is because the excess risk caused by some treatments diminishes over time or that other risk factors more common to the general population increase remains unclear. Despite this, it seems that for certain types of SMNs, screening recommendations for survivors may return to those of the general population.

Because of the strong association between the intensity of treatment received and SMNs, attempts to decrease the intensity of therapy while retaining excellent outcomes whenever possible have been made during the past three decades. Changes in therapy have included reduced rates of cranial radiotherapy for patients with acute lymphoblastic leukemia and decreases in radiotherapy for children and adolescents with HL and Wilms tumors. Recently, Armstrong et al[12] evaluated late mortality in an expanded CCSS cohort of more than 34,000 patients younger than age 21 years diagnosed between 1970 and 1999. Significant reductions in late mortality were observed across treatment eras for acute lymphoblastic leukemia ($P < .001$), HL ($P = .005$), and Wilms tumor ($P = .005$). Importantly, significant reductions in the cumulative incidence of death at 15 years from SN diagnosis were reported.

More recently, host factors have been identified that influence treatment-related SMNs. Best et al[13] have demonstrated that *PRDM1* genomic variants play a key role in the etiology of breast cancers in childhood cancer survivors of HL who were treated with radiation therapy. Additional genomic variables that modify genes that regulate drug metabolism and/or disposition or those responsible for DNA repair may also influence SMN susceptibility.[14] Learning more about how the interactions between genomic and treatment-related factors modify the risk for SMNs and other adverse health outcomes in individual survivors as they age will be critical for the development of more personalized strategies for screening, intervention, and prevention.

REFERENCES

1. Howlander N, Noone AM, Krapcho M, et al.: (eds): SEER Cancer Statistics Review, 1975–2009 (Vintage 2009 Populations). Bethesda, MD, National Cancer Institute, 2012
2. Oeffinger KC, Hudson MM: Long-term complications following childhood and adolescent cancer: Foundations for providing risk-based health care for survivors. CA Cancer J Clin 54:208–236, 2004 [PubMed: 15253918]
3. Robison LL, Armstrong GT, Boice JD, et al.: The Childhood Cancer Survivor Study: A National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol 27:2308–2318, 2009 [PubMed: 19364948]
4. Armstrong GT, Liu W, Leisenring W, et al.: Occurrence of multiple subsequent neoplasms in long-term survivors of childhood cancer: A report from the childhood cancer survivor study. J Clin Oncol 29:3056–3064, 2011 [PubMed: 21709189]
5. Friedman DL, Whitton J, Leisenring W, et al.: Subsequent neoplasms in 5-year survivors of childhood cancer: The Childhood Cancer Survivor Study. J Natl Cancer Inst 102:1083–1095, 2010 [PubMed: 20634481]
6. Moskowitz CS, Chou JF, Wolden SL, et al.: Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncol 32:2217–2223, 2014 [PubMed: 24752044]
7. Henderson TO, Rajaraman P, Stovall M, et al.: Risk factors associated with secondary sarcomas in childhood cancer survivors: A report from the childhood cancer survivor study. Int J Radiat Oncol Biol Phys 84:224–230, 2012 [PubMed: 22795729]
8. Landier W, Bhatia S, Eshelman DA, et al.: Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol 22:4979–4990, 2004 [PubMed: 15576413]
9. Applebaum MA, Henderson TO, Lee SM, et al.: Second malignancies in patients with neuroblastoma: The effects of risk-based therapy. Pediatr Blood Cancer 62:128–133, 2015 [PubMed: 25251613]
10. Lee JS, DuBois SG, Boscardin WJ, et al.: Secondary malignant neoplasms among children, adolescents, and young adults with osteosarcoma. Cancer 120:3987–3993, 2014 [PubMed: 25116228]
11. Turcotte LM, Whitton JA, Friedman DL, et al.: Risk of subsequent neoplasms during the fifth and sixth decades of life in the Childhood Cancer Survivor Study cohort. J Clin Oncol doi: 10.1200/JCO.2015.60.9487
12. Armstrong GT, Yasui Y, Chen Y, et al.: Reduction in late mortality among 5-year survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). J Clin Oncol 33, 2015 (suppl 15s; abstr LBA2)
13. Best T, Li D, Skol AD, et al.: Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma. Nat Med 17:941–943, 2011 [PubMed: 21785431]
14. Bhatia S: Genetic variation as a modifier of association between therapeutic exposure and subsequent malignant neoplasms in cancer survivors. Cancer 121:648–663, 2015 [PubMed: 25355167]