Long-term Complications of Therapeutic Exposures in Childhood: Lessons Learned From Childhood Cancer Survivors

AUTHOR: Smita Bhatia, MD, MPH

Department of Population Sciences, City of Hope, Duarte, California

KEY WORDS

childhood, cancer survivors, treatment-related complications, chronic health conditions

ABBREVIATION

SMN—second malignant neoplasms

Opinions expressed in these commentaries are those of the author and not necessarily those of the American Academy of Pediatrics or its Committees.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-2884

doi:10.1542/peds.2012-2884

Accepted for publication Sep 20, 2012

Address correspondence to Smita Bhatia, MD, MPH, Department of Population Sciences, City of Hope National Medical Center, 1500 East Duarte Rd, Duarte CA 91010. E-mail: sbhatia@coh.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: *The author has indicated she has no financial relationships relevant to this article to disclose.*

FUNDING: Dr S was supported by The Leukemia & Lymphoma Society grant 6093 and the National Institutes of Health grant NCI: R01 CA 139633. Funded by the National Institutes of Health (NIH).

COMPANION PAPER: A companion to this article can be found on page 1003, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2012-0727.

More than 12 000 children and adolescents are diagnosed with cancer each year in the United States.¹ Advancements in therapeutic and supportive care strategies have resulted in significant improvements in survival; the overall 5-year survival rate is approaching 80%.¹ However, two-thirds of these survivors experience at least one chronic health condition,² resulting in considerable morbidity and premature mortality among childhood cancer survivors.³ A clear and unambiguous relation exists between therapeutic exposures and specific adverse events experienced by the survivors. A brief overview illustrates the therapeutic exposure–adverse event relation observed in childhood cancer survivors. This overview reinforces the need to develop risk-reduction strategies in childhood cancer survivors, as exemplified by the study conducted by Lipshultz et al⁴ in this issue of *Pediatrics* that focuses on use of continuous infusion anthracyclines to reduce the risk of cardiomyopathy.

Cardiomyopathy is a dose-limiting complication of anthracyclines⁵; exposure to cumulative anthracycline doses exceeding 250 mg/m² increases the risk significantly,⁶ and younger age, female gender, and exposure to chest irradiation modify this dose-response relation.⁴ Lungs are particularly susceptible to radiation-induced injury, resulting in pneumonitis and pulmonary fibrosis.⁷ The incidence and severity of lung damage is related to the total dose of radiation, fractionation of that dose, total volume of lung irradiated, and age at exposure.⁷

Osteonecrosis is a well-recognized complication of prolonged corticosteroids, characterized by collapse of bone architecture, pain, and loss of function of weight-bearing joints,^{8,9} often requiring total joint replacement.^{8,9} Older children and whites are particularly susceptible to steroid-induced osteonecrosis.

All therapeutic modalities (radiation, surgery, and chemotherapy) can cause both germ (Sertoli) cell depletion and abnormalities of gonadal endocrine function (Leydig cells) among male cancer survivors. Radiation-related effects on sperm production are dose-dependent; doses exceeding 6 Gy cause irreversible injury.¹⁰ Chemotherapeutic agents, such as classic alkylators, heavy metals, and nonclassic alkylators, decrease spermatogenesis in a dose-dependent manner. Cumulative cyclophosphamide doses exceeding 7.5 gm/m² result in prolonged, and in some cases, permanent azoospermia.¹¹ Radiation-related Leydig cell damage is dose-dependent (needing higher doses of radiation), and inversely related to age at treatment. Female germ cell failure and loss of ovarian endocrine function are synchronous. Survivors can lose ovarian function during cancer treatment or shortly thereafter (premature ovarian failure).¹² Some survivors are able to

retain ovarian function after completion of therapy, yet will experience premature menopause before 40 years of age.¹³ Older age at treatment, exposure to abdominal or pelvic radiation, and exposure to alkylating agents have been associated with increased risk of ovarian failure.^{12,13}

Patients treated with radiation involving the thyroid gland are at risk for developing hypothyroidism.¹⁴ Risk factors include female gender, young age at treatment, and radiation dose.

Severe growth retardation has been observed in as many as 30% to 35% of survivors of childhood brain tumors¹⁵ and in 10% to 15% of patients treated with some antileukemia regimens.¹⁶ Whole-brain irradiation is the single most important risk factor; children younger than 5 years at radiation are particularly susceptible.

Platinum-containing chemotherapy causes serious, permanent, bilateral hearing loss in more than 60% of children receiving the drug.¹⁷ Risk of dose-dependent platinum-related hearing loss is modified by exposure to other ototoxic agents and young age at exposure.

In addition to the specific treatment-related long-term nonmalignant complications described previously, exposure to radiation and chemotherapy increase the risk of developing histologically distinct new malignancies or

second malignant neoplasms (SMNs). The cumulative incidence of SMNs exceeds 20% at 30 years after diagnosis of childhood cancer, representing a four- to sixfold increased risk for cancer survivors, compared with the general population.¹⁸ SMNs are classified into 2 distinct groups: chemotherapy-related myelodysplasia and acute myeloid leukemia, and radiation-related solid SMNs. Chemotherapy-related myelodysplasia and acute myeloid leukemia is classically associated with exposure to alkylating agents and topoisomerase II inhibitors. Radiation induces solid SMNs within the radiation field. The risk is highest when radiation exposure occurs at a younger age, and increases with increasing doses of radiation and with increasing time since radiation. Some of the well-established radiation-related solid SMNs include breast cancer,¹⁹ thyroid cancer,²⁰ brain tumors,²¹ and sarcomas.²²

As shown here, the health and well-being of childhood cancer survivors have been studied quite thoroughly for the first 2 to 3 decades after diagnosis of the primary cancer. Specifically, the burden of morbidity has been described in terms of the magnitude of risk, the relationship with specific therapeutic exposures, and subgroups at particularly high risk have been identified. This research has informed the development of the Children's Oncology Group Long-Term Follow-Up

Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers²³ (guidelines can be downloaded from www.survivorshipguidelines.org). This research has also informed primary prevention strategies that have resulted in a reduction in dose or elimination of use of certain therapeutic agents. Research is currently focused on understanding the pathogenesis of these adverse outcomes, and on developing intervention strategies.

It is important to note that more than ~19% of all children in the United States live with a chronic health condition resulting in a special health care need.²⁴ Examples of chronic health conditions include asthma, diabetes, cerebral palsy, sickle cell anemia, cystic fibrosis, AIDS, epilepsy, spina bifida, congenital heart problems, and, of course, cancer. Management of these conditions involves exposure to a variety of therapeutic agents on a chronic basis, with a potential for long-term organ toxicities, with significant impact on the morbidity and mortality in these populations. Using the childhood cancer outcomes research paradigm in patients with other chronic health conditions would help describe the landscape of long-term treatment-related toxicity and identify vulnerable subpopulations with the ultimate goal to reduce long-term morbidity and mortality.

REFERENCES

1. Ries LAG, Melbert D, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2005*. Bethesda, MD: National Cancer Institute; 2007
2. Oeffinger KC, Mertens AC, Sklar CA, et al; Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572–1582
3. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100(19):1368–1379
4. Lipshultz SE, Miller TL, Lipsitz SR, et al. Continuous versus bolus infusion of doxorubicin in children with ALL: Long-term cardiac outcomes. *Pediatrics*. 2012; 130(6):1003–1011
5. Kremer LC, van Dalen EC, Offringa M, Voûte PA. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. *Ann Oncol*. 2002;13(4):503–512
6. Blanco JG, Sun CL, Landier W, et al. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes—a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30(13):1415–1421

7. Abid SH, Malhotra V, Perry MC. Radiation-induced and chemotherapy-induced pulmonary injury. *Curr Opin Oncol*. 2001;13(4):242–248
8. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). *N Engl J Med*. 1992;326(22):1473–1479
9. Mattano LA, Jr, Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol*. 2000;18(18):3262–3272
10. Clifton DK, Bremner WJ. The effect of testicular x-irradiation on spermatogenesis in man. A comparison with the mouse. *J Androl*. 1983;4(6):387–392
11. Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. *JAMA*. 1988;259(14):2123–2125
12. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the childhood cancer survivor study. *J Clin Endocrinol Metab*. 2006;91(5):1723–1728
13. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Natl Cancer Inst*. 2006;98(13):890–896
14. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. 2000;85(9):3227–3232
15. Gurney JG, Ness KK, Stovall M, et al. Final height and body mass index among adult survivors of childhood brain cancer: childhood cancer survivor study. *J Clin Endocrinol Metab*. 2003;88(10):4731–4739
16. Chow EJ, Friedman DL, Yasui Y, et al. Decreased adult height in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Pediatr*. 2007;150(4):370–375, 375, e1
17. Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. *J Clin Oncol*. 2005;23(34):8588–8596
18. 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*. 2010;102(14):1083–1095
19. Bhatia S, Yasui Y, Robison LL, et al; Late Effects Study Group. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol*. 2003;21(23):4386–4394
20. Sigurdson AJ, Ronckers CM, Mertens AC, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet*. 2005;365(9476):2014–2023
21. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2006;98(21):1528–1537
22. Wong FL, Boice JD, Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA*. 1997;278(15):1262–1267
23. 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*. 2004;22(24):4979–4990
24. Bethell CD, Kogan MD, Strickland BB, Schor EL, Robertson J, Newacheck PW. A national and state profile of leading health problems and health care quality for US children: key insurance disparities and across-state variations. *Acad Pediatr*. 2011;11(suppl 3):S22–S33