REVIEW

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Late Effects in Adult Survivors of Pediatric Cancer: A Guide for the Primary Care Physician

Lisa M. Kopp, DO, Puja Gupta, MD, Luz Pelayo-Katsanis, CPNP, Brenda Wittman, MD, MPH, Emmanuel Katsanis, MD

Department of Pediatrics, University of Arizona, Tucson.

ABSTRACT

Because of significant medical advances in the past 50 years, the number of adult survivors of childhood/adolescent cancer has increased dramatically. Unfortunately, more than 60% of these survivors will have at least 1 long-term side effect from treatment. This growing population requires dedicated care by their primary physicians because they have specific risk factors depending on their initial cancer diagnosis and the treatment modalities they received. Internists and family physicians play an integral role in providing appropriate screening, treatment, and counseling to prevent morbidity and mortality in these patients.
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KEYWORDS: Cancer treatment late effects; Childhood cancer survivors

Improvements in the treatment of pediatric cancers have led to a large increase in childhood cancer survivors, which now make up approximately 300,000 adults in the United States.[1] Awareness of the short- and long-term health risks of these patients is critical as they transition from the care of a pediatric oncology center to an adult primary care setting.[2] The Children's Oncology Group (COG) assembled a task force in 2002 to develop evidence-based guidelines for screening and management of late effects resulting from treatment of childhood malignancies (http://www.survivorshipguidelines.org).[3] Because these follow-up guidelines are based on therapy received, the primary care provider should request a concise summary that includes the patient's cancer diagnosis and therapy. Close monitoring of these cancer survivors is vital because they are at risk for organ system complications and secondary malignancies. This article reviews late effects by system and provides recommendations for primary care physicians on the care of survivors.

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Requests for reprints should be addressed to Lisa M. Kopp, DO, University of Arizona, Department of Pediatrics, 1501 N. Campbell Ave, PO Box 245073, Tucson, AZ 85724-5073.

E-mail address: lkopp@email.arizona.edu

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ENDOCRINE

Endocrinopathies of 1 or multiple organs may be present or develop in up to half of childhood cancer survivors. These may include alterations in the hypothalamic-pituitary axis affecting growth, thyroid or gonadal dysfunction, and complications of glucose homeostasis.[4]

Hypothyroidism is the most common late effect of the thyroid gland. Patients exposed to radiation, such as in Hodgkin's lymphoma, brain and head/neck tumors, or total body irradiation used in hematopoietic stem cell transplant conditioning, are at highest risk of hypothyroidism with an incidence of up to 50%.[5,6] Thyroid-stimulating hormone and T4 screening may be done yearly as part of the lifelong evaluation for this subset of cancer survivors.[7]

Deficiency of luteinizing hormone and follicle-stimulating hormone may result from damage to the hypothalamic-pituitary axis from radiation, surgery, or alkylating chemotherapy agents leading to secondary hypogonadism.

In men, germ cells are more sensitive, especially to alkylating agents, manifested by high follicle-stimulating hormone levels and azoospermia. Exposure at a young age increases the risk of infertility because the prepubertal testis is more sensitive to chemotherapy. Leydig cell dysfunction is less common; injury to Leydig cells may lead to elevated luteinizing hormone levels and low testosterone, resulting in low libido and erectile dysfunction. Semen analysis along with measurements of follicle-stimulating hormone, luteinizing hormone, and testosterone may be done for the assessment of male fertility.[8]

In women, in addition to infertility, damage to the ovarian follicle also leads to decreased estrogen causing a higher incidence of sexual dysfunction and dyspareunia.[4] Irregular menses can be a predictor of ovarian failure along with elevated follicle-stimulating hormone and low estradiol. Risk factors include exposure to alkylating agents; central nervous system, pelvic, or scatter from abdominal radiation; and exposure to chemotherapy after puberty. There is an 8% cumulative incidence of premature menopause, according to the Childhood Cancer Survivor Study (CCSS).[9,10] Along with infertility, premature menopause leads to an increase risk of osteoporosis and coronary heart disease. Female survivors who are able to become pregnant had no adverse pregnancy outcomes according to the CCSS.[11]

Obesity is a multifactorial disease associated with glucose metabolism abnormalities and insulin resistance. Survivors of acute lymphoblastic leukemia and brain tumors in particular are at risk of obesity because of chronic steroid therapy and cranial radiation therapy. Cancer survivors are 1.8 times more likely to have symptoms of diabetes mellitus compared with siblings, mainly because of insulin resistance.[12] The development of the metabolic syndrome (obesity, hypertension, dyslipidemia, or impaired glucose tolerance) is known to cause cardiovascular complications. Survivors may develop metabolic syndrome without developing obesity.[13] The COG Long-Term Follow-Up (LTFU) Guidelines recommend that patients with a history of total body irradiation, cranial radiation, or acute lymphoblastic leukemia receive a routine fasting glucose and lipid prolife every 2 years, or annually if clinically indicated, because of their increased risk for metabolic syndrome.

CLINICAL SIGNIFICANCE

- The number of adult survivors of pediatric cancer has increased dramatically over the years; this growing population comprises approximately 300,000 adults in the United States.
- Primary care physicians will initially evaluate the majority of these survivors. It is imperative they are aware of screening and management of late effects.
- The Children's Oncology Group Long-Term Follow-Up Guidelines are an invaluable tool for physicians to care for survivors.

CARDIOVASCULAR

Mortality due to cardiovascular disease is 7-fold higher in adult survivors of pediatric cancers.[14] According to the CCSS, survivors of leukemia, brain tumors, lymphoma, and rhabdomyosarcoma are the most susceptible to cardiac morbidity.[14] Risk factors include mediastinal radiation, scatter from abdominal radiation, cumulative doses of anthracycline treatment (>300 mg/m^2), and younger age at time of treatment.[15] Lower cumulative doses of anthracyclines combined with radiation involving the cardiac field also predispose survivors to increased cardiac risk. Cardiac changes include hypertension and dilated or restrictive cardiomyopathy that leads to left ventricular dysfunction, congestive heart failure, or myocardial infarction. These alterations in the muscle of the heart also can result in valvular defects and arrhythmias.[15-18] The mechanism of anthracycline-induced cardiac toxicity seems to be related to free radical formation and direct myocyte damage, whereas radiation injury to endothelial cells within the capillary lumen leads to fibrosis and ischemia, mimicking atherosclerosis.[17,19] These pathologic changes occur over time, and deterioration can first present as late as 20 years after treatments.[17]

Recommendations based on treatment received include yearly physical examination (including blood pressure measurements) and an electrocardiogram and echocardiogram at specific intervals. The COG LTFU guidelines provide more specific monitoring recommendations based on additional therapeutic exposures. All survivors with risk factors, even those asymptomatic, may be screened, because symptoms do not always correlate with ventricular dysfunction.[20] Female survivors need close monitoring during pregnancy because increased cardiac output can precipitate failure.[21]

PULMONARY

Patients who were exposed to radiation to the lungs or scatter from the abdomen or spine, or who were a younger age at exposure are at risk for long-term pulmonary morbidities.[22] Chemotherapy-induced lung injury from bleomycin, cyclophosphamide, and carmustine are not uncommon.[22] Chest wall surgery, lobectomy, or wedge resection also can increase morbidity. Populations at risk for long-term pulmonary morbidities include survivors of hematopoietic stem cell transplant, Wilms tumor, and Hodgkin's lymphoma. Pulmonary fibrosis, bronchiolitis obliterans with organizing pneumonia, restrictive and obstructive lung disease, and interstitial pneumonitis are rare, yet potentially serious sequelae.[22]

Survivors with exposure risks should be discouraged from smoking and should report exercise intolerance changes, history of cough, or any other pulmonary symptoms during their annual examination, which includes a yearly influenza vaccine. Screening for pulmonary diseases includes a chest x-ray and pulmonary function test with diffusion lung capacity for carbon monoxide at baseline and then repeated as clinically indicated.[9] The COG LTFU guidelines also advise medical clearance by a pulmonologist for survivors with an abnormal chest x-ray or pulmonary function test result who plan to scuba dive or undergo general anesthesia.

CENTRAL NERVOUS SYSTEM

Survivors of central nervous system tumors are at highest risk of neurologic sequelae related to diagnosis, surgery, chemotherapy, and radiation.[9] Survivors of acute lymphoblastic leukemia also are at risk for neurocognitive deficits