Late Effects of Childhood Cancer and Its Treatment

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KEYWORDS

• Childhood • Cancer • Late effects • Treatment

KEY POINTS

- As survival rates for pediatric cancers continue to improve, the number of childhood cancer survivors continues to increase.
- The burden of long-term therapy-related morbidity experienced by childhood cancer survivors is substantial.
- Childhood cancer survivors require lifelong follow-up care to monitor for late treatment-related sequelae.

INTRODUCTION

With advances in therapeutic strategies for common childhood malignancies such as leukemia, lymphoma, and central nervous system (CNS) tumors, the number of childhood cancer survivors in the United States continues to increase, and is estimated to exceed 500,000 by 2020.[1] About 1 of every 530 young adults between 20 and 39 years of age in the United States is a childhood cancer survivor.[2] Treatment of childhood cancer with chemotherapy, radiation, or hematopoietic cell transplant (HCT) can result in adverse sequelae, which may not become evident for many years. In this article, commonly occurring late effects associated with childhood cancer treatment are reviewed.

BURDEN OF MORBIDITY

The burden of morbidity experienced by childhood cancer survivors is substantial, as shown by the fact that approximately 40% of childhood cancer survivors experience a late effect that is severe, life threatening, disabling, or fatal at 30 years from diagnosis.[3] A primary diagnosis of Hodgkin lymphoma (HL) or brain tumors and exposure to chest radiation or anthracyclines increases the risk of these chronic health conditions. Furthermore, the burden of morbidity increases as the cohort ages.[4] HCT recipients experience a higher burden of morbidity when compared with childhood cancer

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survivors treated with conventional therapy.[5] The potential for serious therapy-related sequelae provide the rationale for ongoing follow-up of childhood cancer survivors into adult life.

STANDARDIZED RECOMMENDATIONS FOR FOLLOW-UP OF CHILDHOOD CANCER

In response to a call from the Institute of Medicine for a systematic plan for lifelong surveillance of cancer survivors,[6] the Children's Oncology Group (COG) developed exposure-related, risk-based guidelines (*Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*)[7] for follow-up of patients treated for pediatric malignancies. Specially tailored patient education materials, known as Health Links, accompany the Guidelines to enhance health promotion in this population. The Guidelines and the Health Links can be downloaded from http://www.survivorshipguidelines.org.[8] Recommendations for screening of specific treatment-related late effects are summarized in **Table 1**. The COG Guideline group, along with several other guideline groups addressing survivorship care,[9–11] have initiated the international harmonization of long-term follow-up guidelines for childhood cancer survivors.[12] To use these guidelines, the first step entails the development of a treatment summary (**Box 1**). This treatment summary allows the survivor and their health care provider to determine recommended follow-up care according to the guidelines. In this article, the more commonly occurring late effects in survivors of childhood cancer, and the relationship between these late effects and specific therapeutic exposures, are reviewed, to suggest reasonable starting points for evaluation of specific long-term problems using the screening recommendations from the *COG Long-Term Follow-Up Guidelines*.

AUDITORY IMPAIRMENT

Children with cancer often require therapy with potentially ototoxic agents, including platinum-based chemotherapy, aminoglycoside antibiotics, loop diuretics, and radiation therapy. These agents are all capable of causing sensorineural hearing loss.[13,14] Risk for hearing loss is increased with higher doses of platinum-based chemotherapy, particularly cisplatin in cumulative doses exceeding 360 mg/m^2 and myeloablative doses of carboplatin,[15–18] combining platinum chemotherapy with cranial irradiation,[13] treatment with multiple ototoxic agents,[19] age younger than 5 years at treatment,[20] and surgery that involves cranial nerve VIII.[21] Radiation-related hearing loss may be multifactorial. Although sensorineural loss increases in association with high doses of radiation involving the ear, treatment with higher doses of radiation has also been associated with conductive hearing loss.[22,23]

COGNITIVE SEQUELAE

Childhood cancer survivors are at risk for impaired cognition. Cranial radiation is a well-established risk factor for cognitive impairment,[24–26] although corticosteroids and antimetabolite chemotherapy have been implicated as contributors.[27] Cognitive impairment usually become evident within 1 to 2 years after cranial radiation and is progressive, likely because of the child's failure to acquire new abilities at a rate similar to peers. Affected children experience academic difficulties, resulting in problems with receptive and expressive language and attention span. Fatigue and sleep disruption also serve as contributors to the cognitive impairment observed in childhood cancer survivors.[28]