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EDITORIAL

Late effects of the treatment of childhood cancer

Jelena Roganovic

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Abstract

Excellent progress has been made in the last few decades in the cure rates of pediatric malignancies, with more than 80% of children with cancer who have access to contemporary treatment being cured. However, the therapies responsible for this survival can also produce adverse physical and psychological long-term outcomes, referred to as late effects, which appear months to years after the completion of cancer treatment. Research has shown that 60% to 90% of childhood cancer survivors (CCSs) develop one or more chronic health conditions, and 20% to 80% of survivors experience severe or life-threatening complications during adulthood. Therefore, understanding the late side effects of such treatments is important to improve the health and quality of life of the growing population of CCSs.

Key Words: Survivorship; Cancer; Children; Treatment; Late effects

Core Tip: Childhood cancer and contemporary anticancer therapies responsible for excellent cure rates can produce adverse, long-term, health-related outcomes, referred to as late effects. Therapy-related long-term complications may affect multiple organs and organ systems, including cardiovascular, endocrine/metabolic, reproductive, neurologic, immune, pulmonary, gastrointestinal, urinary, musculoskeletal, auditory, ocular, dermatologic and oral/dental organs, as well as contribute to the risk of neurocognitive and psychosocial difficulties, and subsequent malignant neoplasms. Many of these late effects are life-altering or potentially life-threatening. Long-term multidisciplinary follow-up of childhood cancer survivors is recommended for the prevention, early detection, and treatment of late effects.

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INTRODUCTION

The results of the treatment of children with cancer have improved significantly over the past decades, with more than 80% of patients in high-income countries becoming five-year survivors[1]. However, the therapies used to successfully treat childhood cancer may lead to chronic health problems, generally referred to as "late effects". Late effects are defined as physical, psychological, and psychosocial adverse outcomes that develop or persist five years from the diagnosis of primary cancer[2].

Late effects are common in childhood cancer survivors (CCSs), and the prevalence increases over time from the cancer treatment. Sixty percent to more than 90% of CCSs develop at least one adverse health-related outcome, and 20% to 80% experience serious or life-threatening complications during adulthood[3]. The St. Jude Lifetime Cohort Study (SJLIFE) showed that by the age of 50 years, CCSs experienced 17.1 chronic health conditions of any grade (grade 1-5), of which 4.7% were severe, life-threatening or fatal (grade 3-5). The cumulative burden of chronic health conditions in age- and sex-frequency-matched community controls was 9.2 of grade 1-5, and 2.3 of grade 3-5[4]. CCSs are also at increased risk of premature mortality[5]. Cancer recurrence remains the most frequent cause of death, followed by subsequent malignant neoplasms, and cardiac and pulmonary toxicity[6,7]. The childhood cancer survivor study (CCSS) found that, with a median follow-up of 29 years after diagnosis, the cumulative all-cause mortality rate over 40 years was 23.3%, with 51.2% of deaths from health-related causes. CCSs ≥ 40 years from diagnosis experienced 138 excess deaths per 10000 persons per year, of which 131 were attributable to health-related causes including deaths from the late effects of cancer therapy[8].

The range of the late effects of pediatric cancer is very wide, affecting any organ, system, or function, with variable etiology, timing of onset, complexity, and severity[9]. The risk of adverse health outcomes among CCSs differs by primary cancer diagnosis, treatment exposure, and patient-specific factors. Cancer-related factors include the type of cancer, localization, the extent of disease, direct tissue effects, mechanical effects, and cancer-induced organ dysfunction. Treatment-related factors comprise chemotherapy (drug type, dose-intensity, schedule, cumulative dose), radiation therapy (type, total dose, fractionation, site, organ or tissue volume exposed), surgery (technique, site, effects on the functional status), hematopoietic stem cell transplant (HSCT), targeted therapy, immunotherapy, combined modality therapies, time from treatment, chronic graft-versus-host-disease, and blood product transfusion. Patient-related factors encompass sex, race/ethnicity, age at diagnosis (developmental status), genetic predisposition, premorbid and comorbid conditions, the ability of healthy tissue affected by the cancer treatment to self-repair, hormonal status, socioeconomic factors, and health and lifestyle habits[10,11]. Research evaluating the influence of these multifactorial modifiers on cancer treatment-related health risk is the key to comprehensively addressing the complications affecting CCSs and improving the survivor-specific, risk-based approach to screening and follow-up. It is also important to address survivors' distinct needs regarding communication, information provision, decision-making, and care coordination[12]. Several models of long-term follow-up care have been developed to address these needs, including pediatric oncologist-led follow-up, multi-disciplinary survivorship clinic, the adult oncology specialist aftercare model, primary care-led follow-up, oncology nurse-led care, shared care (the joint pediatric/adult aftercare model, the primary care provider/the pediatric oncologist model, the primary care provider/adult oncology specialist), and multidisciplinary telehealth-delivered survivorship intervention[13-15]. Although the evidence to date fails to adequately demonstrate an optimal model of care for all CCSs, all improved models have shifted from a predominant focus on the detection of the recurrence of cancer, and seek to implement preventive strategies, reduce the consequences of late effects and improve the quality of life of survivors.

In this editorial, we will briefly discuss the more frequent late effects of childhood cancer and the main preventive strategies.

MORE FREQUENT LATE EFFECTS OF CHILDHOOD CANCER AND THE MAIN PREVENTIVE STRATEGIES

Subsequent neoplasms

Subsequent neoplasms (SNs) refer to histologically distinct (benign or malignant) tumors that develop at least two months after the completion of therapy of primary cancer[3]. SNs are the leading cause of non-relapse related mortality in CCSs[16]. The CCSS reported a sixfold increased risk of SNs among five-year CCSs at a median age of 30 years, compared to the general population. A 30-year cumulative incidence rate was 20.5% for all SNs, 9.1% for nonmelanoma skin cancer, 7.9% for SNs with malignant histology excluding nonmelanoma skin cancer, and 3.1% for meningioma. Excess risk was evident for all primary cancers, with the highest being for Hodgkin lymphoma and Ewing sarcoma[17].

The occurrence of SNs depends on the type of primary cancer, treatment received, the age at the time of diagnosis/treatment, genetic susceptibility, and a follow-up duration[3,18]. The most common SNs related to radiation are the breast, thyroid, central nervous system (CNS), bone, soft tissue, and skin tumors[3]. Alkylating agents and topoisomerase

II inhibitors are associated with the development of myelodysplastic syndrome and acute myeloid leukemia[19]. CCSs who have recently completed treatment experience a decreased risk of SNs compared to those treated on older protocols. This lower risk is mainly attributed to decreased exposure to radiation therapy[18]. Studies suggest that CCSs with SNs have poorer overall survival than their age-matched, sex-matched, and race-matched peers without a history of cancer [20].

It is important to provide sufficient information and appropriate education on the individual risks, promoting self-observation and highlighting the need to avoid additional risk factors (tobacco and other drugs of abuse, alcohol, direct sun exposure). Symptoms and warning signs ("red flags") that may be related to the tumor should also be monitored.

Cardiac late effects

Cardiac late effects are the second leading cause of non-relapse premature mortality among CCSs, after SNs. Specific cardiac late effects include cardiomyopathy/heart failure, ischemic heart disease, pericardial disease, valve disease, and conduction disorders[21]. The cumulative incidence of cardiac disease 30 years from diagnosis is 4.8%[22]. Chemotherapy, in particular anthracyclines (daunorubicin, doxorubicin, idarubicin, and epirubicin) and anthraquinones (mitoxantrone), and thoracic radiotherapy are the most important risk factors for cardiovascular morbidity in CCSs[23,24]. While anthracyclines damage cardiomyocytes directly, radiation therapy primarily affects the fine vasculature[25]. Risk factors for anthracycline-related late effects include cumulative doses (> 250-300 mg/m^2), a younger age at exposure, increased time from exposure, concurrent chest/heart radiotherapy, and the presence of other cardiometabolic traits (hypertension, diabetes mellitus, dyslipidemia, and obesity)[3,22]. Radiation-associated late effects are related to the total radiation dose, individual fraction size, and the volume of the heart that was exposed to radiation[21].

Surveillance in high-risk survivors should begin no later than two years after the end of cardiotoxic therapy and should be repeated every five years (or more frequently if necessary). Echocardiography with specific attention to the left ventricular function is the main imaging technique, with electrocardiogram as a tool for the diagnosis of arrythmias. An N-terminal pro B-type natriuretic peptide test is not recommended as the sole follow-up strategy, but could be a predictor of subsequent dysfunction if it is elevated during treatment. Screening should be conducted for modifiable cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking and low levels of physical activity). Female CCSs should be closely followed during pregnancy, particularly during the first trimester.

Late effects of the CNS

Neurocognitive deficits are commonly observed after CNS-directed therapies, including cranial radiation, intrathecal chemotherapy, the systemic administration of high-dose methotrexate and cytarabine, and neurosurgical interventions [26]. Other risk factors include the female sex, the younger age at exposure, the tumor site, a higher cranial radiation dose, radiation to specific brain regions, including the temporal lobes and hippocampi, and the time since treatment. Survivors of pediatric CNS tumors and acute lymphoblastic leukemia (ALL) are at the highest risk of being affected[3]. CCSs may be at risk of cognitive decline throughout their lives[27].

Late neurological sequelae include late-onset seizures, peripheral neuropathy, stroke and other cerebrovascular toxicities (transient ischemic attack, moyamoya, and arteriopathy), hypersomnia or narcolepsy, coordination problems, motor problems, and headaches[3,28]. CNS neuroimaging studies show a variety of abnormalities, including leukoencephalopathy, cerebral atrophy, cerebral lacunes, and mineralizing microangiopathy[29].

CCSs are at risk of developing adverse psychosocial outcomes including psychological distress, anxiety, depression, post-traumatic stress disorder and suicidality, a reduced quality of life, and deficits in achievements of expected social outcomes during adulthood[30-32].

A comprehensive neurological and psychological follow-up is recommended (at least every two years in survivors ≤ 18 years of age and at least every five years in survivors > 18 years of age), with specific attention to educational and/or vocational progress or decline. It is also relevant to monitor the emotional and social situation.

Endocrinologic late effects

Approximately 50% of CCSs will experience at least one hormonal disorder over the course of their lives. Endocrinologic complications are common in CCSs treated with surgery or radiation that involved hormone-producing organs and those who received alkylating agents. The more frequent sequelae include hypothalamic-pituitary (HP) dysfunction, thyroid dysfunction, obesity, diabetes mellitus, metabolic syndrome, and decreased bone mineral density (BMD)[3,33]. HP injury is most common after treatment for CNS tumors. It can result from growth hormone (GH) deficiency, central precocious puberty, luteinizing hormone/follicle-stimulating hormone deficiency (hypogonadotropic hypogonadism), thyroid-stimulating hormone deficiency (central hypothyroidism), and adrenocorticotropic hormone deficiency (central adrenal insufficiency)[33]. The occurrence of late HP dysfunction is primarily a result of radiotherapy, and is affected by patient-related factors (sex, age at treatment), tumor location (suprasellar and non-suprasellar), therapy-related factors (radiation volume and dose, and time from exposure)[34]. The most common pituitary hormone deficit in CCSs is GH deficiency, with a reported prevalence of 12.5% overall and 46.5% after HP radiotherapy[35,36]. Thyroid disorders include hypothyroidism, hyperthyroidism, and thyroid neoplasia. Primary hypothyroidism is one of the most frequently observed late effects, with a reported prevalence of 13.8% to 20.8% in the overall population of CCSs[33]. The highest incidence was reported in survivors of Hodgkin lymphoma who received neck irradiation > 45 Gy, with up to 50% diagnosed after 20 years[37]. CCSs are at risk of experiencing abnormal body composition, including underweight, overweight, and obesity [3]. Overweight is primarily seen in survivors of childhood ALL and CNS tumors who were treated with cranial radiation [38]. The etiology is multifactorial, and includes GH deficiency, leptin sensitivity, and reduced levels of physical activity [3]. There is also a higher rate of metabolic syndrome in CCSs (31.8%) than in the general population of adults < 40 years of age (18.3%)[39].

Regular surveillance with the patient and family clinical history, anthropomorphic measures including the growth pattern in prepubertal and peripubertal CCSs, a physical examination with the pubertal status, and laboratory measurements are recommended for at-risk survivors. When endocrinologic disorders are suspected, it is prudent to make a timely referral to specialized services for a complete evaluation. In CCSs who are overweight, the body mass index, blood pressure, fasting lipid profile, blood glucose and glycosylated hemoglobin should be closely monitored.

Late gonadotoxicity

Reproductive outcomes in CCSs may be affected by surgery (oophorectomy and orchiectomy), chemotherapy, radiation therapy (exposing the HP axis or gonads), and HSCT. Alkylating agents and similar DNA interstrand cross-linking agents are the primary cytotoxic agents associated with a high risk of gonadal injury. Prepubertal ovaries are typically more resistant to chemotherapy damage when compared to post-pubertal ovaries. The radiation-associated risk is related to dose, fractionation, and age at exposure[40]. In addition, genetic factors influence the risk of permanent infertility[3].

Female CCSs are at increased risk of delayed/arrested puberty, a reduced ovarian follicular pool, premature ovarian failure/premature menopause, pregnancy complications (hypertension, fetal malposition, fetal loss/spontaneous abortion, premature delivery, and low birth weight), and infertility[41]. In SJLIFE study, sexual dysfunction was present in 19.9% of female CCSs and was associated with psychosexual health[42].

At long-term follow-up, male CCSs may experience delayed/arrested puberty, impaired spermatogenesis, testosterone deficiency, erectile dysfunction, reduced fertility, and infertility[3,43]. Germinal testicular epithelium exhibits greater sensitivity to radiation damage compared to androgen-producing Leydig cells. Although there is concern about their offspring, the children of CCSs are not at a significantly increased risk of congenital anomalies, single-gene disorders, or cancer[3].

Surveillance recommendations for CCSs treated with potentially gonadotoxic agents vary considerably. As a minimum, the pubertal stage should be checked every 12 months until the completion of sexual development and until the final height is reached. In cases of failure to thrive, premature/delayed pubertal development, and hypogonadism, referral should be made to endocrine and male/female reproductive medicine services.

Other late effects

Cancer treatment in childhood may affect any other organ, organ system, or tissue in the body. We shall now review some of the other more common late effects.

Respiratory late effects are radiation-related (restrictive or obstructive chronic lung disease, pulmonary fibrosis, and spontaneous pneumothorax), and chemotherapy-related (subclinical pulmonary dysfunction, interstitial pneumonitis, pulmonary fibrosis, restrictive or obstructive lung disease)[44]. Combined-modality therapy, including thoracic surgery, increases the risk of lung injury[45]. Lung auscultation with oxygen saturation should be performed during follow-up. If symptoms are present, chest X-ray and pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide, should be performed. The avoidance of tobacco use and passive smoking is recommended.

Late oral and dental complications include dental maldevelopment, salivary gland dysfunction, abnormalities in craniofacial development, osteoradionecrosis of the jaw, and subsequent tumors in the oral cavity[3,46]. Gastrointestinal (GI) tract–related late effects include esophageal dysmotility and stricture, gastroesophageal reflux, chronic enterocolitis, bowel obstruction/fistula/strictures, GI motility dysfunction (constipation, encopresis, diarrhea), and SNs[3,47].

Late skeletal morbidity includes abnormal bone growth, low BMD/osteopenia/osteoporosis (especially in survivors of ALL and lymphoma), fractures, and osteonecrosis. Therapy-related factors that affect bone mineral loss include chemotherapy (corticosteroids, methotrexate), radiation-induced endocrinopathies (GH deficiency, hypogonadism), suboptimal nutrition, and physical inactivity[48]. Besides discomfort, bone toxicity may cause permanent disability and require major surgical interventions[49]. Surveillance should be planned after careful consideration of the potential harm, benefits, and the additional risk factors. In CCSs at risk, dual-energy X-ray absorptiometry should be performed at entry into long-term follow-up, and, if normal (Z score > -1), should be repeated at the age of 25 years. Regular physical activity (especially weight-bearing exercises) and adequate dietary calcium intake should be recommended. Vitamin D supplements may be required.

Late ototoxicity can occur after exposure to platinum-based chemotherapy, cranial radiation exposing the ear, or both. The prevalence of hearing loss in CSSs is 10% compared with 3% in siblings[50]. In survivors of pediatric CNS and head-and-neck tumors, the cumulative incidence of high-frequency hearing loss was 50% or greater at five years after radiotherapy (if the mean cochlea dose was > 30 Gy), while the incidence of hearing loss across all frequencies continued to increase beyond five years after radiotherapy[51]. Risk factors include the younger age at treatment, a higher cumulative dose of platinum compounds, CNS tumors, cranial radiation therapy, and neurosurgery[3].

Ocular late effects can be radiotherapy-related (orbital hypoplasia, xerophthalmia, keratitis, retinopathy, optic chiasm neuropathy, enophthalmos, glaucoma, maculopathy, chronic painful eye), chemotherapy-related (cataract), and surgery (enucleation)-related (orbital hypoplasia, cosmetic defects)[52]. Cataract was noted in 35% of CCSs and dry eye syndrome in 31% of survivors after HSCT[53].

CONCLUSION

CCSs represent a unique and growing population that is facing complex medical and psychosocial challenges. A wide spectrum of adverse late effects results from the complex interplay of factors related to cancer and its treatment, influenced by numerous factors that are not directly linked to cancer history. Structured life-long follow-up care,

including prevention, detection, and timely interventions, is fundamental to optimize health outcomes and improve the quality of life of CCSs.

FOOTNOTES

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