—Review—

Late Effects of Childhood Cancer: Life-threatening Issues

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Abstract

Improvements in therapies for childhood cancers have increased the number of survivors. However, with this prolonged survival, the late effects of disease and anti-cancer therapy are becoming increasingly important. Approximately two-thirds of survivors of childhood cancer will have at least one late effect, and about one-third will have a late effect that is severe or life-threatening. A second neoplasm is one of the most severe late effects in survivors of childhood cancer. Compared with normal populations, persons with a history of childhood cancer have a 10- to 20-fold greater risk of a second malignant neoplasm. Patients who have undergone radiation therapy or been given specific chemotherapeutic agents and patients with a known genetic predisposition to malignancy have been shown to be at higher risk for a second malignant neoplasm. Cardiac problems are another serious late effect for survivors of childhood cancer. Anthracycline-induced cardiotoxicities are common in these patients. A cumulative dose of anthracycline greater than 300 mg/m^2 is associated with an 11-fold higher risk of clinical heart failure compared with a cumulative dose of less than 300 mg/m^2. Serial monitoring of cardiac functioning in children receiving anthracycline allows early identification of cardiac damage. One cardioprotectant (dexrazoxane) has proven effective in adult patients, but larger trials are needed to determine its efficacy in children. It is important to recognize that it may not be best to categorize surviving patients by primary diagnosis. Instead, strategies for surveillance of survivors should be based on the treatment each patient received.

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Key words: late effects, childhood cancer, survivors of childhood cancer, second neoplasm, cardiotoxicity

Introduction

Dramatic advances have been made in the treatment of childhood cancer in the last three decades. The survival rate for children with cancer is now about 80%[1], and more than 0.1% of young adults are survivors of childhood cancer. As the survival rates for childhood cancer have been improving, the late effects of cancer therapy have become a significant problem. To varying degrees, adverse outcomes, including second neoplasms, cardiac dysfunction, pulmonary dysfunction, neurocognitive dysfunction, impaired intellectual function, various endocrine problems, gonadal dysfunction, decreased fertility, and reduced growth (**Table 1**), have been shown to be more likely in long-term survivors. Late mortality in 5-year

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Table 1 Major physical late effects of childhood cancer

Category	Late effects
Second malignant neoplasm (SMN)	Second leukemia
	SMN in radiation field (brain, skin, bone, soft tissure, breast, thyroid)
Cardiac	Cardiomyopathy
	Valvular disease
	Pericardial complications
Pulmonary	Pulmonary fibrosis
Neuropathy	Neurocognitive deficit
	Leukoencephalopathy
Endocrine	Hypothyroidism
	Hyperthyroidism
	Growth hormone deficiency
	Adrenal insufficiency
Gonadal function	Gonadal failure
	Premature menopause
	Infertility
Growth	Short stature (Growth hormone deficiency. bone atrophy, etc)
Bone	Scoliosis
	Osteoporosis
	Avascular necrosis
Liver	Heepatitis B
	Heepatitis C
Ear	Hearing loss
Teeth	Deantal abnormalities

survivors of childhood cancer is 10.8 times higher than that in the general population[2]. Although the most common cause of death is relapse, late sequelae of treatment of the original disease also contribute to later mortality in survivors of childhood cancer.

Two life-threatening late effects of childhood cancer treatment are reviewed in this article: secondary neoplasm and cardiotoxicity.

Second Neoplasm

Second malignant neoplasm (SMN) is a severe late effect in survivors of childhood cancer. The Childhood Cancer Survivors Study (CCSS), a large cohort study of survivors of childhood cancer, has reported that the cumulative incidence of SMN 20 years after the original cancer diagnosis is 3.2% overall and varies by diagnostic subgroup: 7.6% in Hodgkin disease, 4.0% in soft-tissue sarcoma, 3.3% in bone sarcoma, 2.1% in leukemia, 2.1% in central nervous system cancer, 1.9% in neuroblastoma, and 1.6% in kidney tumor[3]. Compared with persons in the general population, persons with a history of childhood cancer have a 10- to 20-fold greater risk of a SMN[4]. Independent risk factors for SMN (adjusted for radiation exposure) include female sex, original cancer diagnosed at a younger age, original diagnosis of Hodgkin's lymphoma or soft tissue sarcoma, and exposure to alkylating agents[3]. The second adult-type carcinoma occurred at a median of 27 years (range, 10–44 years), and the median elapsed time between the development of the second carcinoma and primary therapy was 15 years (range, 6–28 years)[5].

Radiation therapy is a major cause of SMN[6]. Eighty to ninety percent of SMNs following radiation therapy occur within the radiation field. Breast cancer is the most frequent SMN in female survivors of Hodgkin's lymphoma. This represents a 57-fold risk compared with that in the general population. An increased risk of breast cancer is present in patients who have received more than 40 Gy to the chest, with a notable dose-response relationship. The risk of skin cancer also increases following radiation exposure. Basal cell carcinoma is the most commonly observed subsequent cancer. Forty-six percent of patients with secondary skin cancer have multiple occurrences: 90% have received radiation, and 90% of the cancers are within the radiation field[7]. Radiation therapy is associated with a 6.3-fold higher risk of skin cancer. Thyroid cancer may develop after irradiation of the head, neck, or chest. Papillary carcinoma accounts for 75% to 90% of all radiation-induced thyroid cancers. The incidence of thyroid cancer increases linearly with the dose of radiation but reaches a plateau with doses greater than 30 Gy[8]. This finding may be due to high-dose radiation inhibiting cellular proliferation and preventing the development of an expanded malignant clone. Bone and soft tissue sarcoma may occur after radiation therapy, and the risk is proportional to the dose and the concurrent use of alkylating agents. The British Childhood Survivor of Cancer Study has reported that the overall cumulative risk in a cohort of patients

treated from 1940 through 1983 was approximately 1% within a 20-year period following the original diagnosis[9].

Treatment-related leukemia and myelodysplastic syndrome may be caused by topoisomerase II inhibitors[10] and alkylating agents[11]. The cumulative risk for second leukemia after treatment with a topoisomerase II inhibitor is 0.5% to 18.4%, and the median latency period is 1 to 3 years (range, 0.5–4.5 years)[10]. There is usually rearrangement involving the *MLL* gene on chromosome band 11q23. Recently, Relling et al have reported that short-term use of granulocyte colony-stimulating factor after etoposide therapy might increase the risk of acute myeloid leukemia or myelodysplastic syndrome[12]. Secondary leukemias are also associated with alkylating agents. The cumulative risk for secondary leukemia after treatment with alkylating agents is 0.8% to 2.8%, and the median latency period is 4 to 6 years (range, 1–20 years)[11]. Alkylating-agent-related secondary leukemia is generally associated with abnormalities, usually deletions of chromosome 5 or 7[6].

Secondary brain tumors have been reported to occur with increased frequency in patients who have undergone cranial irradiation for brain tumors or acute lymphoblastic leukemia. A 10-fold or greater risk for brain tumors has been observed for survivors of cancers of the central nervous system (CNS) than for persons who have not had cancer. The CCSS has found that 116 subsequent CNS neoplasms in 14,361 5-year survivors of childhood cancer and glioma occurred at a median of 9 years after the original diagnosis and that meningioma occurred at a median of 17 years after the original diagnosis[13]. The cumulative risk of secondary CNS neoplasms is 0.5% to 2.0% at 20 years. Younger age at initial therapy is a risk factor for secondary CNS malignancies. Other potential risk factors for secondary CNS malignancies are an inherited genetic predisposition to cancer and genetic polymorphisms of metabolic enzymes. An example of a polymorphism that has been found to be predictive of the risk of second CNS tumors in childhood acute lymphoblastic leukemia is thiopurine S-methyl-transferase[14].

Stem cell transplantation (SCT) is another cause of second malignancies. The overall cumulative incidence of developing posttransplant malignancies is 6.9% at 20 years and increases by 2% with each successive 5-year follow-up period[15]. The CCSS has reported that patients who have undergone SCT had a 3-fold increased risk of posttransplant malignancies during 7-year periods[13]. Children younger than 10 years at the time of SCT have a greater risk than do older children[16].

Cardiotoxicity

Cardiologic problems are serious late effects in survivors of childhood cancer. Chief among these late adverse effects is the cardiotoxicity associated with anthracycline therapy. Valvular disease, pericardial disease, and arrhythmias have been reported as late cardiologic effects in cancer survivors. After anthracycline therapy, the risk of congestive heart failure is 0% to 16%, and that of subclinical cardiomyopathy is 0% to 57%. There are two kinds of anthracycline-induced cardiotoxicity: acute and chronic. In some cases, chronic cardiotoxicity is subdivided into two addition types: early and late (i.e., more than 1 year after completion of therapy). Most cases of acute cardiotoxicity are not severe. The incidence of anthracycline-induced chronic cardiomyopathy depends on the cumulative dose of anthracycline. A cumulative dose of anthracycline greater than 300 mg/m^2 is associated with an 11-fold higher risk of clinical heart failure than is a cumulative dose of less than 300 mg/m^2[17]. Steinherz et al have reported that 23% of 201 patients who have received a median cumulative dose of doxorubicin of 450 mg/m^2 have echocardiographic abnormalities at a median interval of 7 years after the completion of therapy[18]. An increased risk of cardiac abnormalities is associated with the cumulative dose of anthracycline, the length of follow-up, and mediastinal irradiation. Moreover, girls appear to be more likely than are boys to have cardiotoxic effects of anthracycline therapy[19]. Although the reason for this difference is not known, differences in sex-specific body fat percentages may be involved. In addition, patients younger than 4 years at the time of anthracycline

exposure are at a significantly greater risk for abnormal cardiac function than are older patients[20]. Recent studies have examined whether genetic factors affect anthracycline processing[21], but no conclusive findings have been obtained.

The precise mechanism underlying anthracycline-induced cardiotoxicity is not understood. Most evidence shows that anthracycline therapy generates free radicals through an enzymatic mechanism using the mitochondrial respiratory chain and through a nonenzymatic pathway incorporating iron. Both free radicals and iron can damage cells. Cardiac cells are more vulnerable to free radical damage. Furthermore, anthracycline has a high affinity for cardiolipin and a phospholipid in the inner mitochondrial membrane of cardiomyocytes, resulting in the accumulation of anthracycline inside cardiac cells[22]. The free radicals may continue to be generated after anthracycline treatment has been completed and could account for late cardiotoxic effects of this therapy. Once cardiomyocytes are damaged by anthracycline, the cells might not recover their function. Loss of cardiomyocytes leads to progressive left ventricular dilatation, left ventricular wall thinning, and decreased contractility.

Serial monitoring of cardiac function in children receiving anthracycline allows early identification of cardiac damage. There are many methods to monitor anthracycline-induced cardiotoxicity, including echocardiography, electrocardiography, and radionuclide ventriculography. Fractional shortening and ejection fraction are reliable echocardiographic measures of left ventricular systolic function. Some reports suggest that exercise testing is useful for detecting cardiac function abnormalities that were not significant at rest[23,24]. Signal-averaged echocardiography is another useful tool for early detection of anthracycline-induced cardiotoxicity[25]. Cardiac markers are an accurate and convenient means of monitoring the cardiac health of patients during and after cancer therapy. For example, brain natriuretic peptide and troponin T are markers of cardiomuscular function.

The best treatment for cardiotoxicity is prevention. Although early reports in adults have suggested a lower prevalence of cardiotoxicity with continuous infusion of anthracycline than with bolus administration, more recent reports in children show that the method of administration does not provide cardioprotection[26]. One recent approach to preventing or minimizing chemotherapy-induced cardiotoxicity is to add a cardioprotectant to the treatment regimen. Dexrazoxane (Ziecard; Phamacia & Upjohn, Peapack, NJ) is a cardioprotectant that has been proven to be effective in adult patients. Dexrazoxane was approved in 2002 by the United States Food and Drug for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who had received a cumulative doxorubicin dose of at 300 mg/m^2 and continued to receive anthracycline treatment to maintain tumor control[21]. Clinical trials with dexrazoxane in children have been encouraging. For example, children who received dexrazoxane before doxorubicin were significantly less likely to have cardiac injury during treatment as measured by elevated serum levels of cardiac troponin T[27]. An association between the use of dexrazoxane and the risk of SMN in children with Hodgkin's disease has also been reported[28]. However, a recent report found the absence of an association of secondary malignant neoplasm in children with acute lymphoblastic leukemia who had received dexrazoxane[29].

Conclusions

The number of long-term survivors of childhood cancer will continue to increase, and almost 75% will have a chronic health problem resulting from cancer therapy. More than 40% will have a severe, disabling, or life-threatening condition or will die of because of a chronic condition resulting from cancer therapy[30]. The most important method for preventing these problems is a follow-up survey of cancer survivors. It is important to recognize that patients are not necessarily best categorized by primary diagnosis in such a follow-up survey and that strategies for surveillance of survivors must be based on the treatment each patient received. Therefore, we are establishing a follow-up system

for survivors of childhood cancer that includes an individual treatment summary and follow-up notebook for patients.

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