Childhood Cancer : Late Effects of Cancer Treatment

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As a result of advances in treatment of childhood cancer about 75% of the affected children and adolescents become long-term survivors. It has been estimated that in the United States by the year 2010, one of 250 adults will be a long-term survivor of childhood cancer.
The successful treatment of childhood cancer using combinations of chemotherapy, surgery and radiotherapy may be associated with significant morbidity and mortality in later life.
Unlike the adult, the growing child tolerates the acute side effects of therapy relatively well. However, the use of cancer therapy at an early age can produce complications that may not become apparent until years later as the child matures or has become an adult. The treatment varies from one type of cancer to another. Late effects will also vary and depend largely on the type of therapy received and the doses of that therapy. The very young child may be at greatest risk.

Subsequent Mortality

Recent large epidemiological studies have analysed the subsequent mortality and its causes in children and adolescents, who survived 5 years from the diagnosis of cancer. Two landmark studies by Mertens et al. and Möller et al. published in the Journal of Clinical Oncology in 2001 found that 5-year survivors of childhood and adolescent cancer have a standardized mortality ratio (SMR) of 10.8 or in other words, a 10.8-fold increased risk of death in the subsequent years when compared with age and sex-specific expected rates for the general population. The American study described a cohort of 20 227 five-year survivors of cancer diagnosed between 1970 and 1986 before the age of 21. The risk of death in this cohort was statistically higher in females (SMR 18.2) and individuals diagnosed with cancer before the age of 5 years (SMR 14.0). The leading cause of death was recurrence of the original cancer accounting for 67% of all deaths and more common between five and nine years after diagnosis, while treatment-related causes accounted for 21% of all deaths, of which 12.7% due to a second cancer, 4.5% due to cardiac and 1.8% due to pulmonary toxicity.

Long-term Morbidity

Some small and one large study have assessed the long-term morbidity that follows the treatment of childhood cancer. The incidence and severity of chronic health conditions in 10,397 adults who received a diagnosis of childhood cancer between 1970 and 1986 were studied by Oeffinger et al. and published in the New England Journal of Medicine in 2006.
Among the adult survivors, 62.3% had at least one chronic condition; 27.5% had a severe or life-threatening condition. 30 years after the cancer diagnosis, the cumulative incidence of a chronic health condition reached 73.4%; 42.4% for severe, disabling, or life-threatening conditions or death due to a chronic condition. The risk of chronic health conditions is high, particularly for second cancers, cardiovascular disease, renal dysfunction, severe musculo-skeletal problems and endocrinopathies. The incidence increases over time and does not appear to plateau. Three groups were at highest risk: survivors of bone tumors, CNS tumors and Hodgkin's disease. Survivors of these tumors were also more likely to have multiple conditions. In the 1970s, effective treatment for osteosarcoma of the limbs generally included amputation. Even with modern limb-sparing procedures, the life-altering musculoskeletal morbidity faced by bone-tumor survivors is clinically significant and will increase as weight-bearing joints age more rapidly. Survivors of CNS tumors, who often have significant cognitive, visual, and auditory impairment and endocrinopathies, are the group most likely to

be functionally impaired. Hodgkin's disease survivors have the highest risk of second cancers and heart disease.
Five treatment combinations were associated with an at least 10-fold increased risk of severe or life-threatening conditions : chest radiation plus bleomycin, chest radiation plus an anthracycline, chest radiation plus abdominal or pelvic irradiation, an anthracycline plus an alkylating agent and abdominal or pelvic irradiation plus an alkylating agent. An increase in cumulative dose of an alkylating agent was associated with an increased risk of any condition. In contrast, an increase in the cumulative dose of an anthracycline was not associated with an increased risk of any condition that was listed.
As compared with men, women who survive childhood cancer have been reported to have a greater risk of diminished health status, second cancers, anthracycline-related cardiomyopathy and congestive heart failure, and cranial radiation-related cognitive dysfunction, growth hormone deficiency and obesity.
When interpreting the findings of this study, it is important to keep in mind that the conditions were self-reported without external verification, with exception of second cancers and death. Several key chronic conditions such as late-onset cardiomyopathy associated with anthracycline exposure, may remain clinically silent for long periods before becoming clinically apparent. Other conditions that may be underreported are osteoporosis, hypertension and insuline resistance.

Complications by organ system

The degree of abnormalities relating to each system depends on the specific modality used and the total dose administered. Although most organ systems are affected by radiotherapy and chemotherapy, the musculoskeletal and endocrine systems are most affected by the use of radiotherapy. Only the most frequent complications are discussed below.

Musculoskeletal System

Bone and Soft Tissue

The higher the radiation dose (total and fractional) and the younger the patient, the more pronounced are the late effects. When radiotherapy impairs bone growth it can cause leg-length discrepancy, scoliosis and short stature. The patients most affected are those treated before puberty with high-dose, large-volume radiotherapy, followed by patients treated with the same modality during puberty.

Teeth and Salivary Glands

Patients treated with high-dose radiation to the head and neck area are predisposed to poor enamel and root formation (especially of the premolars). Radiotherapy can also produce a dry mouth secondary to salivary gland dysfunction.

Cardiopulmonary System

Cardiac

The potential cardiac complications are multiple and related to the use of chemotherapy, radiotherapy or both. In particular, patients treated with anthracyclines are at risk for the development of a cardiomyopathy associated with congestive heart failure. The risk increases dramatically with cumulative doses of over 550 mg/m2, but in children most frequently occurs with doses between 400 and 550 mg/m2. The risk is also related to the patient's age and is approximately 1.5% in patients under 15 years of age when cumulative doses are below 400 mg/m2. There has been increasing concern that even treatment with lower doses places children once adults at increased risk. The extent of cardiac complications associated with the use of anthracyclines in pediatric patients, the clinical significance and the risk factors for cardiotoxicity are not yet completely understood. Radiotherapy to the mediastinum can also

injure the myocardium, and when combined with anthracylines, it can potentiate cardiotoxicity even at relatively low cumulative doses.
Other cardiac complications seen with radiotherapy include valvular heart disease and premature atherosclerosis, with an increased risk of coronary artery disease and acute myocardial infarction, the risk directly related to the use of high-dose radiotherapy (> 30 Gy) at an early age.

Pulmonary

Bleomycin can cause pulmonary toxicity and the carbon monoxide diffusing capacity is an accurate predictor of subclinical toxicity. In addition, radiotherapy can cause pulmonary complications including paramediastinal fibrosis, pulmonary function abnormalities and radiation pneumonitis. Radiotherapy also potentiates the pulmonary toxicity of bleomycin.

Genitourinary Complications

Renal

The occurrence and severity of genitourinary complications are related to the cumulative dose of drugs administered and to the concomitant use of radiotherapy. Ifosfamide, carboplatin and cisplatin can produce renal complications. These include acute tubular dysfunction manifested by increased excretion of potassium, phosphorus and magnesium. The tubular defect is not always reversible. Chronic administration of cisplatin and ifosfamide can lead to glomerular dysfunction including renal failure.

Bladder

Patients treated with radiotherapy to the pelvis can develop bladder fibrosis with a small bladder capacity and a predisposition to urinary tract infections.

Endocrine Complications

Pituitary

Radiation can produce deficiency of growth hormone or other hypothalamic or pituitary hormones. The most common appears to be growth hormone deficiency which occurs in up to 80% of patients treated with cranial radiotherapy for brain tumors or leukemia. The degree of injury is related to the total dose and fractionation schedule. Patients with leukaemia treated with prophylactic cranial irradiation to 2400 cGy have varying degrees of damage, depending on the fractional doses, the injury can also be partial.
Females with ALL treated with prophylactic cranial irradiation tend to develop puberty earlier. The risk of precocious puberty is increased in girls and boys with brain tumors treated with high-dose radiotherapy. Most patients with precocious puberty have concomitant growth hormone deficiency. Another more common consequence of high-dose cranial radiotherapy is gonadotropin deficiency with either primary or secondary amenorrhea occurring in up to one third of patients receiving doses between 3000 en 6000 cGy.

Thyroid

The most common abnormality reported after radiotherapy to the neck area is hypothyroidism which can be clinical or subclinical and only detected by the presence of elevated TSH with normal FT4. Subclinical hypothyroidism is detected in up to two thirds of patients treated with mantle radiotherapy for Hodgkin’s disease. The risk is related to the total dose with an increased risk in children receiving more than 2600 cGy. Other complications associated with the use of radiotherapy include thyroid nodules, hyperthyroidism or thyroid cancer.
Patients treated with cranial irradiation for brain tumors are also at risk for hypothyroidism.

Gonads

The possible late effects on the gonads are discussed in a separate topic.

Neurologic System

Central Nervous System

Neurocognitive defects are an accepted consequence of the use of cranial radiotherapy and are related to the dose and the patient's age at the time of treatment. These defects are more severe in patients receiving higher doses and in younger children. One third to one half of children treated with surgery and irradiation for brain tumours will have a subnormal IQ and 35% of children with leukemia under 5 years of age treated with prophylactic cranial irradiation will develop learning disabilities. Also at increased risk are those children who develop a meningeal leukemic relapse and require more than one course of cranial or craniospinal irradiation. Other potential neurologic complications of radiotherapy include radiation necrosis, cerebrovascular accidents and microangiopathy. Radiation necrosis is rare (especially with doses under 6000 cGy). Cerebrovascular accidents most commonly manifest as hemiparesis, aphasia and other stroke-related symptoms and are also rare complications.

Neurocognitive sequelae from the use of chemotherapy have become more evident with the routine use of increasing doses and combined modality regimens. Originally neurocognitive deficits were reported to spare patients treated with systemic and intrathecal methotrexate and no cranial irradiation. More recently, however, various studies have described neurocognitive impairment in children treated with higher doses of systemic and intrathecal methotrexate. Although IQ scores remained stable, arithmetic achievement declined significantly as well as patient's verbal fluency and visual motor skills.

Sensory Nervous System

Chronic administration of cisplatin can result in a dose-related hearing loss occurring most frequently with doses in excess of 400 mg/m2 and mostly irreversible. Radiotherapy in combination with cisplatin will potentiate the hearing loss.

The lens is the most radiosensitive structure within the eye and posterior subcapsular cataract is the characteristic late complication of radiotherapy. Cataracts with visual impairment occur in about 90% of patients treated with local radiotherapy for orbital rhabdomyosarcoma.

Second Malignancies

Survivors of childhood cancer are at a 10-fold increased risk of developing a second primary cancer compared to the general population with an estimated cumulative incidence of 3.2% at 20-year follow-up. However the absolute excess risk is not high with 1.88 excess second cancers occurring per 1000 years of patient follow-up.

Younger age at diagnosis, female gender and certain primary diagnoses, such as hereditary retinoblastoma, Hodgkin's disease and soft tissue sarcomas are associated with an increased risk of second cancers. 50 years after diagnosis of hereditary retinoblastoma 51 % of the patients have a second cancer. In female Hodgkin's disease survivors diagnosed and treated before 16 years of age between 1955 and 1986, the estimated cumulative probability of developing respectively breast and thyroid cancer approached 28% and 6.7% at 30 years from diagnosis.

Radiation-associated risk is highest when the exposure occurs at young age and increases with the dose of radiation and increasing follow-up from radiation. Radiation-associated second primary cancers include bone tumors, breast cancer, thyroid cancer, brain tumors and basal cell carcinoma.

Exposure to certain chemotherapeutic agents, such as alkylating agents and topoisomerase II inhibitors, have been shown to increase the risk of secondary myelodysplasia and acute myeloid leukemia, characterized by a short latency period and a finite period of increased risk.

Summary

The late effects of cancer therapy are a significant problem and the risk can be predicted based on each individual's prior therapy. Continued education of cancer survivors regarding their risks of late effects is essential and gives them the ability to maintain healthy lifestyles, avoiding cancer-promoting behaviors such as smoking. It also gives them the opportunity to participate in screening programs to help in early recognition of the late effects. It is hoped that the use of early intervention will lead to an improved long-term outcome. Continued surveillance of this population is essential. Because the number of childhood cancer survivors will continue to increase, it is imperative that pediatricians and internists in the community who care for these survivors are aware of their risks for late effects so that they have access to and can benefit from early intervention.

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