Long-term Complications of Therapeutic Exposures in Childhood: Lessons Learned From Childhood Cancer Survivors

More than 12,000 children and adolescents are diagnosed with cancer each year in the United States.\(^1\) Advancements in therapeutic and supportive care strategies have resulted in significant improvements in survival; the overall 5-year survival rate is approaching 80%.\(^1\) However, two-thirds of these survivors experience at least one chronic health condition,\(^2\) resulting in considerable morbidity and premature mortality among childhood cancer survivors.\(^3\) A clear and unambiguous relation exists between therapeutic exposures and specific adverse events experienced by the survivors. A brief overview illustrates the therapeutic exposure–adverse event relation observed in childhood cancer survivors. This overview reinforces the need to develop risk-reduction strategies in childhood cancer survivors, as exemplified by the study conducted by Lipshultz et al\(^4\) in this issue of Pediatrics that focuses on use of continuous infusion anthracyclines to reduce the risk of cardiomyopathy.

Cardiomyopathy is a dose-limiting complication of anthracyclines\(^5\); exposure to cumulative anthracycline doses exceeding 250 mg/m\(^2\) increases the risk significantly,\(^6\) and younger age, female gender, and exposure to chest irradiation modify this dose-response relation.\(^4\) Lungs are particularly susceptible to radiation-induced injury, resulting in pneumonitis and pulmonary fibrosis.\(^7\) The incidence and severity of lung damage is related to the total dose of radiation, fractionation of that dose, total volume of lung irradiated, and age at exposure.\(^7\)

Osteonecrosis is a well-recognized complication of prolonged corticosteroids, characterized by collapse of bone architecture, pain, and loss of function of weight-bearing joints,\(^8,9\) often requiring total joint replacement.\(^8,9\) Older children and whites are particularly susceptible to steroid-induced osteonecrosis.

All therapeutic modalities (radiation, surgery, and chemotherapy) can cause both germ (Sertoli) cell depletion and abnormalities of gonadal endocrine function (Leydig cells) among male cancer survivors. Radiation-related effects on sperm production are dose-dependent; doses exceeding 6 Gy cause irreversible injury.\(^10\) Chemotherapeutic agents, such as classic alkylators, heavy metals, and nonclassic alkylators, decrease spermatogenesis in a dose-dependent manner. Cumulative cyclophosphamide doses exceeding 7.5 gm/m\(^2\) result in prolonged, and in some cases, permanent azoospermia.\(^11\) Radiation-related Leydig cell damage is dose-dependent (needing higher doses of radiation), and inversely related to age at treatment. Female germ cell failure and loss of ovarian endocrine function are synchronous. Survivors can lose ovarian function during cancer treatment or shortly thereafter (premature ovarian failure).\(^12\) Some survivors are able to

AUTHOR: Smita Bhatia, MD, MPH

Department of Population Sciences, City of Hope, Duarte, California

KEY WORDS cancer survivors, treatment-related complications, chronic health conditions

ABBREVIATION SMN—second malignant neoplasms

Finances: The author has indicated she has no financial relationships relevant to this article to disclose.
retain ovarian function after completion of therapy, yet will experience premature menopause before 40 years of age. Older age at treatment, exposure to abdominal or pelvic radiation, and exposure to alkylating agents have been associated with increased risk of ovarian failure.

Patients treated with radiation involving the thyroid gland are at risk for developing hypothyroidism. Risk factors include female gender, young age at treatment, and radiation dose.

Severe growth retardation has been observed in as many as 30% to 35% of survivors of childhood brain tumors and in 10% to 15% of patients treated with some antileukemia regimens.

Whole-brain irradiation is the single most important risk factor; children younger than 5 years at radiation are particularly susceptible.

Platinum-containing chemotherapy causes serious, permanent, bilateral hearing loss in more than 60% of children receiving the drug. Risk of dose-dependent platinum-related hearing loss is modified by exposure to other ototoxic agents and young age at exposure.

In addition to the specific treatment-related long-term nonmalignant complications described previously, exposure to radiation and chemotherapy increase the risk of developing histologically distinct new malignancies or second malignant neoplasms (SMNs). The cumulative incidence of SMNs exceeds 20% at 50 years after diagnosis of childhood cancer, representing a four- to sixfold increased risk for cancer survivors, compared with the general population. SMNs are classified into 2 distinct groups: chemotherapy-related myelodysplasia and acute myeloid leukemia, and radiation-related solid SMNs. Chemotherapy-related myelodysplasia and acute myeloid leukemia is classically associated with exposure to alkylating agents and topoisomerase II inhibitors. Radiation induces solid SMNs within the radiation field. The risk is highest when radiation exposure occurs at a younger age, and increases with increasing doses of radiation and with increasing time since radiation. Some of the well-established radiation-related solid SMNs include breast cancer, thyroid cancer, brain tumors, and sarcomas.

As shown here, the health and well-being of childhood cancer survivors have been studied quite thoroughly for the first 2 to 3 decades after diagnosis of the primary cancer. Specifically, the burden of morbidity has been described in terms of the magnitude of risk, the relationship with specific therapeutic exposures, and subgroups at particularly high risk have been identified. This research has informed the development of the Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (guidelines can be downloaded from www.survivorshipguidelines.org). This research has also informed primary prevention strategies that have resulted in a reduction in dose or elimination of use of certain therapeutic agents. Research is currently focused on understanding the pathogenesis of these adverse outcomes, and on developing intervention strategies.

It is important to note that more than ~19% of all children in the United States live with a chronic health condition resulting in a special health care need. Examples of chronic health conditions include asthma, diabetes, cerebral palsy, sickle cell anemia, cystic fibrosis, AIDS, spina bifida, congenital heart problems, and, of course, cancer. Management of these conditions involves exposure to a variety of therapeutic agents on a chronic basis, with a potential for long-term organ toxicities, with significant impact on the morbidity and mortality in these populations. Using the childhood cancer outcomes research paradigm in patients with other chronic health conditions would help describe the landscape of long-term treatment-related toxicity and identify vulnerable subpopulations with the ultimate goal to reduce long-term morbidity and mortality.

REFERENCES


# Long-term Complications of Therapeutic Exposures in Childhood: Lessons Learned From Childhood Cancer Survivors

Smita Bhatia

*Pediatrics* 2012;130;1141; originally published online November 19, 2012; DOI: 10.1542/peds.2012-2884

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: /content/130/6/1141.full.html</th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 23 articles, 11 of which can be accessed free at: /content/130/6/1141.full.html#ref-list-1</td>
</tr>
<tr>
<td>Citations</td>
<td>This article has been cited by 3 HighWire-hosted articles: /content/130/6/1141.full.html#related-urls</td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): Pharmacology /cgi/collection/pharmacology_sub Therapeutics /cgi/collection/therapeutics_sub</td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml</td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: /site/misc/reprints.xhtml</td>
</tr>
</tbody>
</table>

---

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2012 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.
Learned From Childhood Cancer Survivors

Smita Bhatia

Pediatrics 2012;130;1141; originally published online November 19, 2012;
DOI: 10.1542/peds.2012-2884

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/130/6/1141.full.html