Long-term risk for subsequent leukemia after treatment for childhood cancer: a report from the Childhood Cancer Survivor Study


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Previous investigations of cancer survivors report that the cumulative incidence of subsequent leukemia plateaus between 10 and 15 years after primary therapy. Risk beyond 15 years has not been comprehensively assessed, primarily because of lack of long-term follow-up. Among 5-year survivors from the Childhood Cancer Survivor Study cohort, 13 pathologically confirmed cases of subsequent leukemia occurred ≥ 15 years after primary malignancy, with a mean latency of 21.6 years (range, 15-32 years). Seven were acute myeloid leukemia (2 acute promyelocytic leukemia with t(15;17), 2 with confirmed preceding myelodysplastic syndrome), 4 acute lymphoblastic leukemia (2 pre-B lineage, 1 T cell, 1 unknown), and 2 other. Two acute myeloid leukemia cases had the 7q- deletion. The standardized incidence ratio was 3.5 (95% confidence interval, 1.9-6.0). Median survival from diagnosis of subsequent leukemia was 2 years. This is the first description of a statistically significant increased risk of subsequent leukemia ≥ 15 years from primary diagnosis of childhood cancer. (Blood. 2011;117(23):6315-6318)

Introduction

Almost 80% of children diagnosed with cancer will achieve 5-year survival, with the majority becoming long-term survivors. These survivors have an increased risk of subsequent malignant neoplasms. Reports evaluating cancer survivors have found that the cumulative incidence of subsequent leukemia, predominantly acute myeloid leukemia (AML), plateaus at approximately 2% 10 to 15 years after primary cancer therapy. Treatment-related AML is associated with exposure to alkylating agents, typically preceded by myelodysplastic syndrome and a loss or partial deletion of tumor suppressor genes on chromosomes 5 or 7 and epipodophyllotoxins, which are associated with translocations of the MLL gene at chromosome band 11q23. Anthracyclines have also been linked to leukemia with 11q23 abnormalities when used in conjunction with alkylator therapy. Time to development of alkylating agent-induced leukemia is 5 to 7 years from primary cancer, whereas epipodophyllotoxin-associated leukemia has a latency of 2 to 3 years.

Risk of subsequent leukemia ≥ 15 years beyond initial cancer diagnosis has not been comprehensively assessed, in part because of the lack of sufficient sample size and extended surveillance. The Childhood Cancer Survivor Study (CCSS) cohort offers a unique opportunity to evaluate a large population of 5-year survivors with a variety of primary malignancies and follow-up into adulthood. We report the first description of a statistically significantly increased risk of subsequent leukemia occurring ≥ 15 years from treatment of a primary malignancy.

Methods

The CCSS is a retrospective cohort study, with longitudinal follow-up of 14 358 5-year survivors of childhood cancer treated at 26 institutions in the United States and Canada between 1970 and 1986. CCSS methodology was previously described. The CCSS was approved by the institutional review boards of all participating institutions. Subsequent leukemia includes leukemias occurring ≥ 5 years from diagnosis, initially ascertained through self- or proxy-report questionnaires, and confirmed by pathology report, death certificate, or other medical records. Relapses of primary leukemia, based on comparison of pathologic reports, were considered recurrences, not subsequent leukemia. Bone marrow samples and cytogenetic reports were acquired for 10 of the 13 cases of leukemia occurring ≥ 15 years from diagnosis of primary malignancy. Bone marrow samples were centrally reviewed by the CCSS pathologist (S.H.) to further validate the diagnoses. Consent for release of initial cancer treatment records was obtained from 10 of the 13 cases. Cumulative incidence estimates, based on patients at risk at a given time point, were calculated from 5 years after childhood cancer diagnosis to first occurrence of leukemia, treating death as a competing risk. The standardized incidence ratio (SIR) and absolute excess risk were derived using age, sex, and calendar year specific rates from the Surveillance Epidemiology and End Results database.

Results and discussion

Of the 14 358 survivors in the CCSS, 43 developed subsequent leukemia ≥ 5 years from primary diagnosis; 25 occurred to 10 years, 5 at 10 to 15 years, and 13 at ≥ 15 years. The 30-year cumulative incidence for development of subsequent leukemia was
than the background incidence (SIR > 6-fold increased risk (SIR of acute lymphoblastic leukemia, one had a complex karyotype that included t(9;22) and another had a p53 mutation. Six patients with subsequent leukemia received radiation therapy, which was the sole therapy in 2 patients. Six patients received both an alkylating agent and anthracycline, and none received epipodophyllotoxins. Median survival time after subsequent leukemia diagnosis was 2 years (range, 0.4-5.8 years, Figure 1B).

In this study of aging adult survivors of childhood cancer, we identified a statistically significant increased risk of subsequent leukemia \( \geq 15 \) years from primary cancer therapy. This is contrary to numerous reports in the literature on treatment-related leukemia, which suggest that the cumulative incidence plateaus after 10 years. Similar to patients with subsequent leukemia occurring in the first 10 years after diagnosis, those \( \geq 15 \) years have a poor prognosis with median survival of 2 years. Median survival of therapy-related AML is 5 to 11 months.

It is unclear why this long latency exists. Studies in atomic bomb exposed children show a peak incidence of leukemia at 5 to 7 years after exposure, and the incidence decreases thereafter, returning to the population risk at 15 years. As radiation therapy was the most common exposure for these late-occurring subsequent leukemias, one hypothesis is that these cases undergo a series of alterations in oncogenes or tumor suppressor genes, which may require an extended time period and additional environmental exposures to create a prolific clone. In addition, it is possible that this group of patients may have an underlying genetic predisposition that was either not tested for or is not yet known. Polymorphisms in the \( NQO1 \) gene are associated with treatment-related AML (t-AML) but are not routinely tested for in clinical practice. Only one patient in our series had an established genetic cancer syndrome involving p53. Telomere shortening is associated with treatment-related myelodysplastic syndrome/AML in lymphoma patients after autologous stem cell transplant; however, this has not been studied in the nontransplantation, long-term survivor population.

The main limitation of this analysis is the small number of late subsequent leukemias, which precludes identification of definitive associations with therapeutic exposures. However, the continued follow-up of the large and aging CCSS cohort and the extensive confirmatory process using central review to validate these cases allows identification of this novel finding. Therapy received in this historic cohort may differ slightly from modern therapies; however, alkylating agents, anthracyclines, and radiation therapy remain the backbone of treatment for a considerable proportion of pediatric cancers. Another limitation includes the absence of confirmed treatment information for the subsequent leukemias, making interpretation of the survival probability in these cases more difficult.

This is the first description of increased risk of subsequent leukemia \( \geq 15 \) years from primary malignancy, demonstrating a 3.5-fold increased risk above that of the general population. This challenges current screening practices put forth by the Children’s Oncology Group long-term follow-up guidelines, which recommend a screening complete blood count up to 10 years after diagnosis. A high level of suspicion should be maintained for long-term survivors presenting with pancytopenia, particularly those exposed to radiation and/or anthracycline and alkylating agent therapy.

Acknowledgments

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<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Subsequent leukemia subtype</th>
<th>Time to subsequent leukemia, y</th>
<th>Cytogenetics</th>
<th>Radiation site and dose</th>
<th>Chemotherapy and cumulative dose (if known)</th>
<th>Vital status</th>
<th>Time from subsequent leukemia to death, y</th>
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<tbody>
<tr>
<td>Hodgkin lymphoma</td>
<td>T-cell large granular leukemia</td>
<td>31</td>
<td>T-cell gene rearrangements; cytogenetics: normal</td>
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<td>No chemotherapy received</td>
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<td>APL</td>
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<td>t(15;17)</td>
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<td>t(15;17)</td>
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<td>Inverted Y 3600 cGy</td>
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<td>Dead</td>
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</tbody>
</table>

NOS indicates not otherwise specified; CPM, cyclophosphamide; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; and APL, acute promyelocytic leukemia.

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**Authorship**

Contribution: K.N., J.L., J.P.N., S.B., S.H., A.M., D.S., Z.L., W.L., and D.S. analyzed and interpreted data; K.N. and G.T.A. wrote the manuscript; and all authors gave final approval of the manuscript.

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