Long-Term Risk for Subsequent Leukemia after Treatment for Childhood Cancer: A Report from the Childhood Cancer Survivor Study

Short title: Long-Term Risk for Subsequent Leukemia

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ABSTRACT

Previous investigations of cancer survivors report that the cumulative incidence of subsequent leukemia plateaus between 10-15 years after primary therapy. Risk beyond 15 years has not been comprehensively assessed, primarily due to lack of long-term follow-up. Among five-year survivors from the Childhood Cancer Survivor Study (CCSS) cohort, 13 pathologically-confirmed cases of subsequent leukemia occurred >15 years after primary malignancy, with mean latency of 21.6 years (range 16-32 years). Seven were AML (2 APL with t(15;17), 2 with confirmed preceding MDS), 4 ALL (2 pre-B lineage, 1 T-cell, 1 unknown) and 2 other. Two AML cases had 7q- deletion. The standardized incidence ratio was 3.5 (95% CI 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.

INTRODUCTION

Almost 80% of children diagnosed with cancer will achieve five year survival, with the majority becoming long term survivors.1 These survivors have an increased risk of subsequent malignant neoplasms.2,3 Reports evaluating cancer survivors have found that the cumulative incidence of subsequent leukemia, predominantly acute myeloid leukemia (AML), plateaus at approximately 2% 10-15 years after primary cancer therapy.4 Treatment-related AML is associated with exposure to alkylating agents, typically preceded by myelodysplastic syndrome (MDS) and a loss or partial deletion of tumor suppressor genes on chromosomes 5 or 7 5,6 and epipodophyllotoxins, which are associated with translocations of the MLL gene at chromosome band 11q23.7-9 Anthracyclines have also been linked to leukemia with 11q23 abnormalities when used in conjunction with
alkylator therapy.\textsuperscript{10} Time to development of alkylating agent induced leukemia is 5-7 years from primary cancer while epipodophyllotoxin associated leukemia has a latency of 2-3 years.\textsuperscript{11,12}

Risk of subsequent leukemia $\geq 15$ 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.

\textbf{METHODS}

The CCSS is a retrospective cohort study, with longitudinal follow-up of 14,358 five-year survivors of childhood cancer treated at 26 institutions in the United States and Canada between 1970 and 1986. CCSS methodology was previously described.\textsuperscript{13,14} The CCSS was approved by the institutional review board 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 (AER) were derived using age, gender, and calendar year specific rates from the Surveillance Epidemiology and End Results (SEER) database.  

RESULTS/DISCUSSION

Of the 14,358 survivors in the CCSS, 43 developed subsequent leukemia >5 years from primary diagnosis; 25 occurred 5 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 0.31% (95% confidence intervals (CI) of 0.21 to 0.41%) (Figure 1a). Compared to the general population, CCSS survivors had a greater than six-fold increased risk (SIR = 6.3, 95% CI 4.6 - 8.5) for developing leukemia. Risk was highest between 5-10 years (SIR = 15.4, 95% CI 10.0 - 22.8) and remained significantly higher than the background incidence >15 years from primary diagnosis, (SIR = 3.5, 95% CI 1.9 - 6.0). The AER of leukemia as a SMN ≥ 15 years in CCSS survivors was 0.02 cases per 1000 person-years. Risk of AML > 15 years was increased (SIR = 5.3, 95% CI 2.1 - 10.9).

Among the 13 subsequent leukemia cases occurring >15 years (Table), mean age at diagnosis was 31.2 years (range 18-51 years) with mean latency of 21.6 years (range 16-32 years). Subsequent leukemias included seven cases of AML (two with documented preceding MDS and two acute promyelocytic leukemia, both with documented t(15;17) translocation), and four acute lymphoblastic leukemia (two pre-B lineage, one T-cell, and one unknown). For the remaining two cases, one was T-cell large granular leukemia, and one was only verified as “leukemia” via death certificate, without supporting documentation or pathology slides. Two patients with subsequent AML had 7q- deletion. Among cases of subsequent acute lymphoblastic leukemia,
one had a complex karyotype that included t(9;22) and another had a p53 mutation. Sarcomas (n=5) and Hodgkin lymphoma (n=4) were the most common primary diagnoses, with only one patient having had an initial diagnosis of leukemia. Six patients with subsequent leukemia received radiation therapy, which was the sole therapy in two. 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, Figure 1b).

In this study of aging adult survivors of childhood cancer, we identified a statistically significant increased risk of subsequent leukemia >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 ten years. Similar to patients with subsequent leukemia occurring in the first 10 years after diagnosis, those >15 years have a poor prognosis with median survival of two years. Median survival of therapy related AML is 5-11 months.12

It is unclear why this long latency exists. Studies in atomic bomb exposed children show a peak incidence of leukemia at 5-7 years post 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. Additionally, 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 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 MDS/AML in lymphoma patients after autologous stem cell transplant; however, this has not been studied in the non-transplant, long-term survivor population.\textsuperscript{25}

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 utilizing 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 >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 CBC up to ten years post 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.
FUNDING

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AUTHOR CONTRIBUTIONS

Conception and Design: Nottage, Lanctot, Neglia, Bhatia, Hammond, Leisenring, Meadows, Srivistava, Robison, Armstrong

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Manuscript Writing: Nottage, Armstrong

Final Approval of Manuscript: Nottage, Lanctot, Li, Neglia, Bhatia, Hammond, Leisenring, Meadows, Srivistava, Robison, Armstrong

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.
REFERENCES


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<tr>
<th>Primary Diagnosis</th>
<th>Subsequent Leukemia Subtype</th>
<th>Time to Subsequent Leukemia (years)</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 (years)</th>
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<td>46,xx.der(4)(1;4)(q11;p16), t(9;16), t(9;22)(q34;q11.2)</td>
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<td>CPM 9,200 mg/m² Cisplatin 635 mg/m² Doxorubicin 459 mg/m² Actinomycin–D 0.28 mg/kg Bleomycin 123 mg/m² Methotrexate 36,875 mg/m²</td>
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</table>

¹acute myeloid leukemia, ²myelodysplastic syndrome, ³not otherwise specified, ⁴acute lymphoblastic leukemia, ⁵acute promyelocytic leukemia; CPM=Cyclophosphamide
FIGURE LEGENDS

Table – Characteristics of long-term survivors of childhood cancer with subsequent leukemia >15 years from diagnosis

Figure 1a – Cumulative incidence with 95% confidence intervals of subsequent leukemia among five year childhood cancer survivors in the CCSS cohort

Figure 1b – Overall survival after diagnosis of subsequent leukemia >15 years from diagnosis of childhood cancer
Long-term risk for subsequent leukemia after treatment for childhood cancer: a report from the Childhood Cancer Survivor Study