Decreased Adult Height in Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study

Eric J. Chow, MD, MPH, Debra L. Friedman, MD, MS, Yutaka Yasui, PhD, John A. Whitton, MS, Marilyn Stovall, PhD, Leslie L. Robison, PhD, and Charles A. Sklar, MD

Objective To determine risk factors associated with reduced adult height in survivors of childhood acute lymphoblastic leukemia (ALL).

Study design This was a cross-sectional study. Attained adult height was determined among 2434 ALL survivors participating in the Childhood Cancer Survivor Study, a cohort of 5-year survivors of common pediatric cancers diagnosed from 1970 to 1986, and compared with 3009 siblings.

Results All survivor treatment exposure groups (chemotherapy alone, chemotherapy with cranial or craniospinal radiotherapy) had decreased adult height and an increased risk of adult short stature (height standard deviation score <-2) compared with siblings ($P < .001$). Compared with siblings, the risk of short stature for survivors treated with chemotherapy alone was elevated (OR, 3.4; 95% CI, 1.9, 6.0). Among survivors, significant risk factors for short stature included diagnosis of ALL before puberty, higher-dose cranial radiotherapy (≥20 Gy versus <20 Gy), any radiotherapy to the spine, and female sex.

Conclusions Survivors of childhood ALL are at increased risk of adult short stature, including those treated with chemotherapy alone. Risk is highest for those treated with cranial and craniospinal radiotherapy at a young age. *(J Pediatr 2007;150:370-5)*

See editorial, p 332

Cranial and craniospinal radiotherapy were commonly used in the 1970s and early 1980s to treat as well as to prevent the spread of acute lymphoblastic leukemia (ALL) to the central nervous system (CNS) in children. Although radiotherapy was effective, it was associated with adverse endocrine and neurocognitive outcomes.[1] As a result, over the past three decades, radiotherapy doses have been reduced or eliminated in an attempt to decrease these adverse long-term outcomes and have been replaced by more intensive chemotherapy.

Several studies have examined growth in ALL survivors. Growth deficits have been reported consistently after doses of ≥24 Gy cranial radiotherapy, but the data are less consistent for doses <20 Gy.[2-17] The effect on loss of stature was greater in children who also received radiotherapy to the spine, secondary to direct inhibition of vertebral growth.[13] For most studies in which the impact of chemotherapy without radiotherapy was examined, growth suppression during treatment was followed by catch-up growth.[2,3,10,11,15,18] However, catch-up growth has not been observed consistently across studies.[6,14]

We hypothesized that adult survivors of childhood ALL would have shorter adult heights than their siblings and that cranial or craniospinal radiotherapy would be a significant risk factor, in a dose-dependent manner. We also hypothesized that the risk for decreased adult height among ALL survivors treated with chemotherapy alone would be smaller than that conferred by cranial or craniospinal radiotherapy. Therefore, we compared the attained adult height of a large population of pediatric ALL survivors enrolled in the Childhood Cancer Survivor Study (CCSS) with a sibling cohort to determine more precisely the risk factors associated with adult short stature.

ALL	Acute lymphoblastic leukemia	CNS	Central nervous system
CCSS	Childhood Cancer Survivor Study	SDS	Standard deviation score

From the Department of Pediatrics, University of Washington, Seattle, Washington; Fred Hutchinson Cancer Research Center, Seattle, Washington; the Department of Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada; the Department of Radiation Physics, University of Texas, M.D. Anderson Cancer Center, Houston, Texas; the Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee; and the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, New York.

The list of Childhood Cancer Survivor Study institutions and investigators is available at www.jpeds.com.

Supported by grant U24-CA55727 (L.L. Robison, Principal Investigator), from the National Institutes of Health and funding provided to the University of Minnesota by the Children's Center Research Fund.

Submitted for publication May 25, 2006; last revision received Aug 19, 2006; accepted Nov 9, 2006.

Reprint requests: Dr Eric J. Chow, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N (M4-C308), PO Box 19024, Seattle, WA 98109-1024. E-mail: ericchow@u.washington.edu.

0022-3476/$ - see front matter

10.1016/j.jpeds.2006.11.036

METHODS

Childhood Cancer Survivor Study Description

The CCSS is a resource cohort study that was established to evaluate hypotheses associated with long-term health-related outcomes in childhood cancer survivors. Specifics concerning the methodology and subject accrual for this cohort have been reported in detail.[19] Briefly, the cohort was constructed from rosters of all children treated for most forms of childhood cancer at each of 26 institutions in the United States and Canada (see Appendix). Inclusion criteria included (1) diagnosis of one of the following forms of childhood cancer before 21 years of age: leukemia, Hodgkin and non-Hodgkin lymphoma, neuroblastoma, soft-tissue sarcoma, bone cancer, malignant CNS tumor, or kidney tumor; (2) initial treatment at one of the collaborating institutions between January 1, 1970, and December 31, 1986; and (3) survival for at least 5 years after diagnosis.

The Human Subjects Committee at each participating institution reviewed and approved the CCSS protocol. Beginning August 1, 1994, all cohort members (or parents of patients under 18 years of age) completed a baseline questionnaire that included information on demographic and socioeconomic characteristics, health conditions and health-related behaviors, family history of cancer, inherited conditions and congenital anomalies, and reproductive history. Two follow-up questionnaires have been sent since, to all participants as well. For those patients who survived for 5 years after the initial cancer diagnosis and subsequently died, a family member completed the baseline questionnaire. Medical records were reviewed and abstracted for cancer diagnosis and treatment data including chemotherapy and radiotherapy exposures, using a standardized protocol.[19]

ALL Survivors and Sibling Control Subjects

Of 5814 ALL survivors eligible for the CCSS, 811 were lost to follow-up despite tracking, 801 declined participation, and 47 were pending contact at the time of analysis. Prior analysis found no significant differences between participants and nonparticipants with respect to sex, cancer diagnosis, age at diagnosis, age at contact, and type of cancer treatment.[19] The rate of nonparticipation was significantly higher among next-of-kin of deceased as opposed to living patients.[19] Survivors were excluded from this analysis if diagnosed after 17 years of age or if they had a recurrence of their primary leukemia, developed a second malignant neoplasm, or underwent hematopoietic stem cell transplant before 18 years of age, leaving 2990 survivors available for analysis. Those who lacked self-reported or proxy-reported adult height data (defined as the tallest height recorded at age ≥18 years) or had incomplete radiotherapy exposure data also were excluded, resulting in a final study cohort of 2434 (2384 alive at time of study enrollment).

A cohort of 5857 siblings was randomly selected from all eligible CCSS cases. At the time of this analysis, 3846 siblings had agreed to participate and were recruited to serve as a comparison group. If a cancer survivor had more than one sibling, the sibling of closest age was selected for participation. Among siblings, 3009 were ≥18 years of age at the time of study enrollment and had self-reported adult height data. Of these siblings, 818 were siblings of ALL survivors, with the remainder being related to other CCSS cases.

Exposure and Outcome Assessment

Cumulative chemotherapy doses were available for selected agents, which included anthracyclines (daunorubicin and doxorubicin summed), cyclophosphamide, cytarabine, epipodophyllotoxins (etoposide and teniposide summed), and methotrexate (intravenous, intramuscular, and intrathecal doses). Systemic and intrathecal doses were classified separately. To examine dose-response, each agent was categorized into none, low, medium, and high doses, based on tertiles or previously published cut-points when available.[20] Although systemic doses were adjusted for the patient's body surface area at the time of administration, intrathecal doses were not. For asparaginase, corticosteroids, oral methotrexate, mercaptopurine, thioguanine, and vincristine, dosage information was not available, only exposure recorded "yes" or "no." Scores for overall chemotherapy intensity were created on the basis of the cumulative number of drugs received as well as their dose (if known), with higher scores assigned to patients exposed to higher levels of individual agents. All agents were analyzed individually and in combination, along with overall treatment duration (<2.5, 2.5 to 3.5, and >3.5 years) and measures of chemotherapy intensity.

CNS radiotherapy doses were abstracted in 5-Gy increments. Ninety-five percent of survivors (1511 of 1584) who received cranial radiotherapy were treated with doses between 15 to 29 Gy to the brain and 88% of survivors (180 of 204) who received spinal radiotherapy received doses between 10 to 24 Gy to the spine. Remaining patients received radiotherapy to the brain and spine outside these ranges, but their numbers were too small to allow meaningful stratification. As a result, CNS radiotherapy doses were categorized into <20 Gy and ≥20 Gy doses. Exclusion of survivors exposed to <15 Gy or ≥30 Gy did not affect reported estimates. Radiotherapy exposures occurring after age 17 were excluded from analysis.

Height was assessed both in absolute terms as well as by standard deviation scores (SDS). Raw heights were converted to SDS by Epi Info (version 3.3.2, Centers for Disease Control and Prevention, Atlanta, GA), based on the Centers for Disease Control Year 2000 growth charts. In general, one SDS change in height was approximately 7 cm for both male and female subjects.

Statistical Analysis

For mean height comparisons between survivor subgroups, *t* tests were used. Multivariable linear regression was applied to simultaneously examine factors that contributed to changes in height SDS among survivors. Multivariable logis-