Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort

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Summary

Background Treatment of patients with paediatric acute lymphoblastic leukaemia has evolved such that the risk of late effects in survivors treated in accordance with contemporary protocols could be different from that noted in those treated decades ago. We aimed to estimate the risk of late effects in children with standard-risk acute lymphoblastic leukaemia treated with contemporary protocols.

Methods We used data from similarly treated members of the Childhood Cancer Survivor Study cohort. The Childhood Cancer Survivor Study is a multicentre, North American study of 5-year survivors of childhood cancer diagnosed between 1970 and 1986. We included cohort members if they were aged 1·0–9·9 years at the time of diagnosis of acute lymphoblastic leukaemia and had received treatment consistent with contemporary standard-risk protocols for acute lymphoblastic leukaemia. We calculated mortality rates and standardised mortality ratios, stratified by sex and survival time, after diagnosis of acute lymphoblastic leukaemia. We calculated standardised incidence ratios and absolute excess risk for subsequent neoplasms with age-specific, sex-specific, and calendar-year-specific rates from the Surveillance, Epidemiology and End Results Program. Outcomes were compared with a sibling cohort and the general US population.

Findings We included 556 (13%) of 4329 cohort members treated for acute lymphoblastic leukaemia. Median follow-up of the survivors from 5 years after diagnosis was 18·4 years (range 0·0–33·0). 28 (5%) of 556 participants had died (standardised mortality ratio 3·5, 95% CI 2·3–5·0). 16 (57%) deaths were due to causes other than recurrence of acute lymphoblastic leukaemia. Six (1%) survivors developed a subsequent malignant neoplasm (standardised incidence ratio 2·6, 95% CI 1·0–5·7). 107 participants (95% CI 81–193) in each group would need to be followed-up for 1 year to observe one extra chronic health disorder in the survivor group compared with the sibling group. 415 participants (376–939) in each group would need to be followed-up for 1 year to observe one extra severe, life-threatening, or fatal disorder in the group of survivors. Survivors did not differ from siblings in their educational attainment, rate of marriage, or independent living.

Interpretation The prevalence of adverse long-term outcomes in children treated for standard risk acute lymphoblastic leukaemia according to contemporary protocols is low, but regular care from a knowledgeable primary-care practitioner is warranted.

Funding National Cancer Institute, American Lebanese-Syrian Associated Charities, Swiss Cancer Research.

Introduction

Acute lymphoblastic leukaemia is the most common childhood malignant disease, accounting for more than a quarter of paediatric cancer diagnoses.[1] Improvements in treatment and supportive care have resulted in 5-year survival exceeding 80%;[2] in children with no high-risk features, survival now exceeds 90%.[3] Consequently, the population of survivors of childhood acute lymphoblastic leukaemia in the USA exceeds 50 000.[4]

Studies of long-term survivors of childhood cancer have shown that many patients have significant late effects due to their treatment, including premature mortality, subsequent neoplasms, congestive heart failure, stroke, obesity, neurocognitive dysfunction, and osteonecrosis.[5,6] Treatment of acute lymphoblastic leukaemia has evolved substantially over time, particularly with the elimination of cranial and craniospinal radiation for the prevention of CNS leukaemia in most patients, and the risk-adjusted use of chemotherapy to minimise the risk of late effects.[7] Nowadays, most children treated with contemporary protocols receive less intensive treatments than did those treated decades ago; consequently, the profile of late effects in newly diagnosed children is expected to differ from those noted in children treated in the past. This possibility restricts the ability of oncologists to extrapolate outcomes from historical cohorts to counsel newly diagnosed patients and their parents about future risks. Furthermore, published surveillance guidelines for survivors of acute lymphoblastic leukaemia might not be appropriately adapted to the true risk for late effects in newly diagnosed patients.[8,9] Although oncologists can attempt to predict late effects on the basis of present

Lancet Oncol 2014; 15: 841–51

Published Online
June 20, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70265-7

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knowledge about the long-term effects of individual chemotherapy drugs,[7] no study has assessed the association between the totality of the treatments in contemporary protocols of acute lymphoblastic leukaemia and long-term outcomes.

To estimate the risk of late effects in children diagnosed with acute lymphoblastic leukaemia in the present day, we examined the long-term outcomes noted in participants of the Childhood Cancer Survivor Study treated in a manner consistent with present standard-risk protocols.

Methods

Study design and participants

For the **original cohort questionnaires from the Childhood Cancer Survivor Study** see https://ccss.stjude.org/documents/original-cohort-questionnaires

The Childhood Cancer Survivor Study is a longitudinal cohort study of 5-year survivors of childhood or adolescent cancer diagnosed between 1970–86 at one of 26 institutions in North America.[10] This analysis included study participants who were diagnosed with acute lymphoblastic leukaemia between the ages of 1·0–9·9 years (consistent with US National Cancer Institute criteria for standard-risk acute lymphoblastic leukaemia[11]), completed the Childhood Cancer Survivor Study baseline questionnaire, and had received treatment for acute lymphoblastic leukaemia that was analogous to the treatments presently used in the protocols for standard-risk acute lymphoblastic leukaemia of the Children's Oncology Group,[12] St Jude Children's Research Hospital,[13] Dana-Farber Cancer Institute,[14] and the Associazione Italiana Ematologia Oncologia Pediatrica—Berlin-Frankfurt-Münster[15] (table 1). Between 40% and 70% of present patients with acute lymphoblastic leukaemia are considered standard risk. Almost all patients with standard-risk disease in North America, Europe, Australia or New Zealand, and Japan are treated on one of these protocols or a similar protocol. Eligible survivors had received treatment that included 0–120 mg/m² of anthracyclines and 0–1000 mg/m² of cyclophosphamide. We applied an isotoxic dose conversion (daunorubicin×0·833) to calculate the cumulative dose of anthracyclines in doxorubicin equivalents.[8] Between 1970 and 1986, most patients with standard-risk acute lymphoblastic leukaemia were given cranial irradiation; we excluded irradiated survivors from the present analysis.

For more on the **study design of the Childhood Cancer Survivor Study** see https://ccss.stjude.org/

The Childhood Cancer Survivor Study has also recruited a random sample of siblings of its survivors. A control group similar in age to the survivors of acute lymphoblastic leukaemia was constructed to include siblings of survivors of any cancer type who were diagnosed between ages 1·0 and 9·9 years. As with the survivor cohort, siblings who had not completed the

	Contemporary protocols for ALL therapy						Eligible dose range
	COG-AALL0932 average risk group A		SJCRH Total Therapy XV study low risk		DFCI protocol (2012)	AIEOP-BFM ALL (2009)	CCSS
	Female	Male	Female	Male			
Dexamethasone (mg/m²)	908	1298	1160	1160	1020	210 (plus tapering)	Any
Prednisone (mg/m²)	0	0	1120	1120	1280	1680 (plus tapering)	Any
Asparaginase (IU/m²)	5000 (iv PEG)	5000 (iv PEG)	240 000 (im *Escherichia coli*)	240 000 (im *Escherichia coli*)	40 000 (iv PEG) or 2500 (iv PEG) then 750 000 (im *Escherichia coli*)	7500 (iv PEG)	Any
Doxorubicin (mg/m²)	75	75	60	60	60	120	Cumulative anthracycline 0–120
Daunorubicin (mg/m²)	0	0	50	50	0	0	Cumulative anthracycline 0–120
Cyclophosphamide (mg/m²)	1000	1000	1000	1000	0	120	0–1000
Cytarabine (mg/m²)	600	600	600	600	0	1800	Any
High-dose methotrexate (mg/m²)	0	0	11 000	11 000	5000	20 000	Any
Methotrexate iv (mg/m²)	2000	2000	3640 (iv or im)	4680 (iv or im)	2970 (iv or im)	0	Any
Methotrexate oral (mg/m²)	1480	2420	0	0	0	0	Any
Mercaptopurine (mg/m²)	42 000	69 300	63 490	77 140	24 500	28 980	Any
Thioguanine (mg/m²)	840	840	0	0	0	840	Any
Vincristine (mg/m²)	57	76·5	61	61	76	12	Any
Intrathecal chemotherapy (number of doses)	17	22	13 (17 for CNS high risk) triple IT after first	13 (17 for CNS high risk) triple IT after first	16	9 (11 for CNS2 or TLP positive; 13 for CNS positive)	Any
Radiation (Gy)	0	0	0	0	0	0 (18 Gy for CNS positive)	0

COG=Children's Oncology Group. ALL=acute lymphoblastic leukaemia. SJCRH=St Jude Children's Research Hospital. DFCI=Dana-Farber Cancer Institute. AIEOP-BFM=Associazione Italiana Ematologia Oncologia Pediatrica-Berlin-Frankfurt-Münster. CCSS=Childhood Cancer Survivor Study. iv=intravenous. im=intramuscular. PEG=polyethylene glycol. IT=intrathecal. CNS2/TLP+=CNS status ≤5 white blood cells per µL cerebrospinal fluid with blasts/traumatic lumbar puncture positive.

Table 1: **Cumulative doses of chemotherapy and radiation in present protocols for treatment of standard-risk ALL and definition of dose ranges for inclusion for CCSS subcohort of ALL survivors**