

Cumulative Incidence of Secondary Neoplasms as a First Event After Childhood Acute Lymphoblastic Leukemia

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ACUTE LYMPHOBLASTIC LEUKEMIA is the most common cancer in children and adolescents, with almost 4000 new cases diagnosed in the United States each year.¹ It is also one of the most curable pediatric cancers: survival rates for patients treated with contemporary risk-based protocols now exceed 80%,¹⁻⁵ and most of these survivors are cured (no evidence of disease for at least 10 years).^{6,7} Accordingly, characterization of long-term outcomes in acute lymphoblastic leukemia patients who remain in first complete remission for at least a decade has assumed increasing importance, especially in view of the long life expectancy of this survivor population.

See also Patient Page.

Context Little is known about the incidence of secondary neoplasms after 15 to 20 years in children and adolescents who were treated for acute lymphoblastic leukemia.

Objectives To investigate the cumulative incidence of secondary neoplasms in pediatric patients treated for acute lymphoblastic leukemia over 30 years and to characterize late-occurring tumors.

Design, Setting, and Patients Retrospective study of 2169 patients with acute lymphoblastic leukemia treated between 1962 and 1998 at St Jude Children's Research Hospital, Memphis, Tenn, who achieved complete remission and had a median follow-up time of 18.7 years (range, 2.4-41.3 years).

Main Outcome Measures Cumulative incidences of secondary neoplasms in first remission and standard incidence ratios of observed rates compared with rates of cancer development in the general US population.

Results Secondary neoplasms developed as the first event in 123 patients and comprised 46 myeloid malignancies, 3 lymphomas, 14 basal cell carcinomas, 16 other carcinomas, 6 sarcomas, 16 meningiomas, and 22 other brain tumors. The cumulative incidence of secondary neoplasm was 4.17% (SE, 0.46%) at 15 years and increased substantially after 20 years, reaching 10.85% (SE, 1.27%) at 30 years. When meningiomas and basal cell carcinomas were excluded, the overall cumulative incidence was 3.99% (SE, 0.44%) at 15 years and 6.27% (SE, 0.83%) at 30 years, representing a 13.5-fold increase in overall risk compared with the general population. The cumulative incidence of each tumor type at 30 years was 2.19% (SE, 0.32%) for myeloid malignancy, 0.17% (SE, 0.10%) for lymphoma, 3.00% (SE, 0.59%) for brain tumor, 4.91% (SE, 1.04%) for carcinoma, and 0.57% (SE, 0.37%) for sarcoma.

Conclusions The cumulative incidence of secondary neoplasms increases steadily over 30 years after treatment of acute lymphoblastic leukemia. Although the majority of the late-occurring secondary neoplasms are low-grade tumors, the increase in incidence of more aggressive malignant neoplasms is significantly higher than expected in the general population. These results suggest that lifelong follow-up of acute lymphoblastic leukemia survivors is needed to ascertain the full impact of treatment and other leukemia-related factors on secondary neoplasm development.

JAMA. 2007;297:1207-1215

www.jama.com

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A secondary neoplasm is one of the most devastating sequelae of cancer treatment. The risk of this complication varies among long-term survivors with different histologic subtypes of cancer at diagnosis.⁸ For pediatric patients with acute lymphoblastic leukemia, the reported cumulative risk of secondary neoplasm ranges from 1.2% to 3.3% after 10 to 15 years of follow-up⁹⁻¹¹; however, it is not clear whether the incidence of secondary neoplasms reaches a plateau at 15 to 20 years or continues to increase. We therefore reviewed the medical records of patients with acute lymphoblastic leukemia treated at St Jude Children's Research Hospital, Memphis, Tenn, over 3 decades to estimate the long-term cumulative incidence of secondary neoplasm occurring in first complete remission, to compare the observed number of secondary neoplasms developing in patients with acute lymphoblastic leukemia with the expected number of cancer cases in the general US population, and to identify risk factors associated with secondary neoplasm development in first complete remission.

METHODS

After approval by the St Jude institutional review board, we undertook a retrospective review of the medical records of 2304 consecutive patients 21 years of age or younger with newly diagnosed acute lymphoblastic leukemia, who were enrolled in 14 consecutive clinical trials (St Jude Total Therapy Studies I-XIIIB) from 1962 to 1998. The details of the treatment regimens have been previously published.^{2,12-16} After completion of therapy, patients were examined at least annually for 10 years after diagnosis or until they reached 18 years of age. Thereafter, the St Jude Cancer Registry monitored discharged adult survivors, using a mailed questionnaire to determine the occurrence of late effects. For all patients who developed a secondary neoplasm, we recorded the date of diagnosis, histologic subtype, and primary/involved site(s). A pathology review confirmed

the histologic findings of secondary neoplasms in all cases.

This analysis excluded 135 patients who failed to achieve complete remission because they received various additional therapies that may have influenced the incidence of secondary neoplasm; hence, the clinical courses of 2169 patients were analyzed. All secondary neoplasms were noted, but the analyses focused on secondary neoplasm development as a first event after acute lymphoblastic leukemia to determine the impact of frontline acute lymphoblastic leukemia therapy more reliably and to facilitate interpretation, given the recognized influence of remission retrieval therapy on the development of secondary neoplasms.

Chemotherapy (including anthracyclines and alkylating agents) and cranial/craniospinal irradiation were coded for each patient on the basis of protocol-specified doses and schedules, using an intention-to-treat rationale. For patients whose treatment was unclear, this approach was combined with a chart review. Patients whose first event (eg, secondary neoplasm or relapse) occurred before the planned initiation of a specific therapy considered in the analysis (eg, cranial/craniospinal radiation) were included in the analysis but coded as not having received that therapy because the exposure would not have affected the risk of a first event. The study results reflect events recorded as of October 26, 2005.

To estimate the probability of secondary neoplasms in first complete remission, the cumulative incidence (with standard error) was calculated for all patients achieving complete remission.¹⁷ Competing events were relapse (including central nervous system [CNS] and testicular disease), secondary acute lymphoblastic leukemia, and death in first complete remission. Survival times were calculated from the complete remission date to the date of first event. Patients who were still alive without experiencing an event were censored on their last follow-up date. Those undergoing hematopoietic stem cell transplantation before experiencing any event were cen-

sored at the time of transplantation (n=16, none of whom developed a secondary neoplasm). This analysis was performed with and without the inclusion of low-grade tumors (basal cell carcinoma and meningioma) and according to specific classes of tumors. When a specific tumor type was analyzed, other types of secondary neoplasms were also treated as competing events.

To compare secondary neoplasm incidence rates with rates of cancer development in the general US population, we used standardized incidence ratios (SIRs) and 95% confidence intervals (CIs). The SIR was calculated as the observed number over the expected number of secondary malignancies. The expected number of cases was determined with the Epilog Plus program, version 3 (Epicenter Software, Pasadena, Calif) by multiplying the number of person-years of follow-up in our sample with the corresponding cancer incidence rates in the general population matched for age and sex using national data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Institutes of Health for 1997-2001,¹⁸ following the approach of Breslow and Day.¹⁹ To be consistent with our analysis of cumulative secondary neoplasm incidence, we calculated the time to an event from the complete remission date to the date of secondary neoplasm detection, relapse, death in complete remission, or last follow-up, whichever came first. When the observed number of malignancies was less than 20, exact CIs for a Poisson-distributed variable were computed by multiplying SIRs with tabulated multipliers, which vary for the number of events (eg, secondary neoplasms); otherwise, the Byar approximation was used by applying a formula to the observed and expected number of secondary neoplasms.¹⁹ Three tumors developing in first complete remission were in fact third neoplasms but were considered as first events in SIR calculations because they arose after low-grade malignancies not included or only recently included in SEER descriptions.

Because of the wide differences in treatment regimens and incidence rates

of late-occurring secondary neoplasms between patients treated before and after 1979, we evaluated risk factors by separate methods. For those treated in the modern era (Total Therapy studies X-XIIIB), we updated results from previously published studies, defining cohorts, events, and risk factors as in the original articles.²⁰⁻²⁴ Analyses were likewise performed as in the published studies except when newer analytical methods (eg, cumulative incidence with competing events) were deemed more appropriate. For patients treated in the earlier era (studies I-IX), we conducted a new analysis. The cumulative incidences of secondary neoplasm for different subgroups were compared using the test of Gray,²⁵ which allows for comparisons of cause-specific failure distributions when competing risks are present.

RESULTS

Patient Characteristics

Among the 2169 patients who achieved complete remission without additional therapy, 879 had relapse as a first event and 1290 patients remained in complete remission. At the time of analysis, 1349 of 2169 were alive, with 1022 (75.8%) having a follow-up contact within the last 2 years. The median time since the date of the last follow-up was 0.9 years (range, 0.1-15.4 years). Patients with follow-up within the last 2 years did not differ from those without recent follow-up in terms of race and sex. There were significant differences according to current age and the study in which patients were enrolled, reflecting the difficulty of obtaining information from patients in continued remission for 20 to 30 years. Among 478 patients who were treated in Total Therapy studies XII through XIIIB (1988-1998), 86.4% had follow-up within 2 years. The median follow-up time for surviving patients was 18.7 years (range, 2.4-41.3 years) after diagnosis of acute lymphoblastic leukemia, and their median age at last follow-up was 24.8 years (range, 6.1-52.5 years). Overall, the cohort had accrued 29 179 person-years of follow-up.

Secondary Neoplasms Observed in First Complete Remission and After Relapse of Acute Lymphoblastic Leukemia

Of the 2169 patients included in this study, 168 (7.7%) developed a secondary neoplasm. Among the 1290 patients who remained in complete remission, 123 (9.5%) developed a secondary neoplasm as their first event, 1099 (85.2%) remained alive without events, and 68 (5.3%) died in complete remission. Among the 879 in complete remission who had relapse as a first event, 45 (5.1%) subsequently developed a secondary neoplasm, 170 (19.3%) remained in second complete remission without a secondary neoplasm, and 664 (75.5%) died without secondary neoplasm.

TABLE 1 summarizes the characteristics of the secondary neoplasm cases observed in this cohort (n=168). Among the

123 patients who developed a secondary neoplasm as their first event, acute myeloid leukemia represented the most common subtype, occurring in 37 patients (30.1%), followed by CNS tumors other than meningioma (22 patients [17.9%]), meningioma (16 patients [13.0%]), carcinoma (excluding basal cell carcinoma) (16 patients [13.0%]), and basal cell carcinoma (14 patients [11.4%]). Basal cell carcinoma (n=10) was the most prevalent tumor among secondary neoplasms developing after relapse. The histologic subtypes of CNS tumors other than meningioma, carcinomas excluding basal cell carcinoma, and soft-tissue sarcomas in first complete remission or after relapse are noted in Table 1.

Eighteen patients had third malignant neoplasms: acute myeloid leukemia (n=3), basal cell carcinoma (n=4), squamous cell carcinoma (n=2), thyroid car-

Table 1. Secondary Neoplasms Observed in the Study Population

Type of Secondary Neoplasm	No. (%)		
	Overall	In First Complete Remission	After Relapse
Myeloid			
Acute myeloid leukemia	45 (26.8)	37 (30.1)	8 (17.8)
Chronic myeloid leukemia	2 (1.2)	2 (1.6)	0
Myelodysplastic syndrome	10 (6.0)	7 (5.7)	3 (6.7)
Lymphoma			
Hodgkin	3 (1.8)	3 (2.4)	0
Non-Hodgkin	3 (1.8)	0	3 (6.7)*
Central nervous system			
Meningioma	24 (14.3)	16 (13.0)	8 (17.8)
Other	24 (14.3)	22 (17.9)†	2 (4.4)‡
Carcinoma			
Basal cell	24 (14.3)	14 (11.4)	10 (22.2)
Other	23 (13.7)	16 (13.0)§	7 (15.6)
Sarcoma			
Ewing sarcoma	1 (0.6)	1 (0.8)	0
Osteosarcoma	2 (1.2)	1 (0.8)	1 (2.2)
Soft tissue sarcoma	6 (3.6)	4 (3.3)¶	2 (4.4)#
Melanoma	1 (0.6)	0	1 (2.2)
Total	168 (100)	123 (73.2)	45 (26.8)

*All 3 cases presented as central nervous system lymphoma. Two patients had large cell lymphoma. Another had a cystic mass in the frontal lobe with a lymphomatous infiltrate appearing 10 years after the diagnosis of acute lymphoblastic leukemia.

†Glioblastoma multiforme (n = 9), astrocytoma (n = 8), oligodendroglioma (n = 2), dysembryoplastic neuroepithelial tumor (n = 1), ependymoma (n = 1), and primitive neuroectodermal tumor (n = 1).

‡Glioblastoma multiforme (n = 1) and astrocytoma (n = 1).

§Thyroid carcinoma (n = 4), carcinoma of the parotid gland (n = 4), breast adenocarcinoma (n = 1), transitional cell carcinoma (n = 1), hepatocellular carcinoma (n = 2), squamous cell carcinoma (n = 2), neuroendocrine carcinoma (n = 1), and ovarian adenocarcinoma (n = 1).

||Transitional cell carcinoma (n = 1), neuroendocrine carcinoma (n = 1), breast adenocarcinoma (n = 1), carcinoma of the parotid gland (n = 1), thyroid carcinoma (n = 1), microcystic adnexal carcinoma (n = 1), and squamous cell carcinoma (n = 1).

¶Fibrosarcoma (n = 1), hemangiopericytoma (n = 1), myxoid chondrosarcoma (n = 1), and spindle cell sarcoma (malignant gastrointestinal stromal tumor) (n = 1). The myxoid chondrosarcoma presented as central nervous system metastatic disease with an unknown primary tumor site.

#Fibrosarcoma (n = 1) and other high-grade sarcoma (n = 1).

cinoma (n=2), meningioma (n=3), other CNS tumors (n=2), hepatocellular carcinoma (n=1), and melanoma (n=1). Five of these third malignancies developed after basal cell carcinoma or squamous cell carcinoma, 4 after other carcinomas, and 4 after meningioma. The remaining 5 developed after Hodgkin disease (n=1), melanoma (n=1), osteosarcoma (n=1), and myelodysplastic syndrome (n=2).

There were 2 patients with acute lymphoblastic leukemia that was considered secondary acute lymphoblastic leukemia because of the shift in cytogenetic findings thought to represent a new clone. One patient had t(9;22) at the time of diagnosis and developed i(9q) 6 years

later. The second patient developed t(4;11)(q21;q23), which differed from the complex translocation involving chromosomes 3, 8, and 18 at the time of initial diagnosis 3.5 years earlier. These cases were treated as a competing event, similar to relapse of acute lymphoblastic leukemia, in this analysis.

Latency From Diagnosis of Acute Lymphoblastic Leukemia to Development of a Secondary Neoplasm in First Complete Remission

FIGURE 1 illustrates the latency from the time of diagnosis of acute lymphoblastic leukemia to the development of a

secondary neoplasm in the 123 patients who had this complication as a first event. When patients who developed a secondary neoplasm after relapse (n=45) were included, the results did not change substantially.

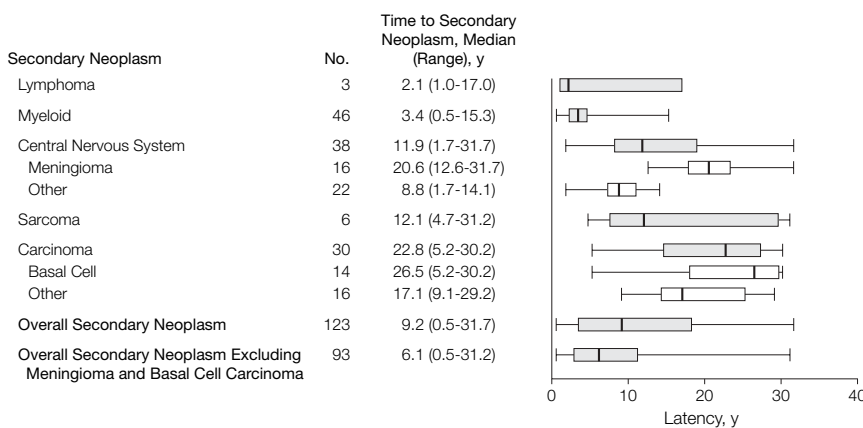
Cumulative Incidence of Secondary Neoplasms in First Complete Remission Over 30 Years

FIGURE 2 depicts the cumulative incidence of secondary neoplasms in all patients with this complication as the first event after complete remission induction: 4.17% (SE, 0.46%) at 15 years, increasing to 5.37% (SE, 0.55%) at 20 years and to 10.85% (SE, 1.27%) at 30 years. The relatively rapid increase in incidence at 20 years after complete remission can be attributed largely to the late development of meningiomas and basal cell carcinomas. Indeed, when these 2 neoplasms are excluded, the incidence of CNS tumors reaches a plateau at 15 years (1.17% [SE, 0.25%]) (FIGURE 3), while the rate of increase of carcinoma development from 15 to 30 years after induction slows considerably (0.39% [SE, 0.16%] to 2.16% [SE, 0.63%] vs 0.51% [SE, 0.18%] to 4.91% [SE, 1.04%] for all carcinomas) (Figure 3). However, even with exclusion of basal cell carcinomas, there remains an impressive increase in carcinoma incidence between 25 and 30 years after induction, reflecting cases of more aggressive malignant neoplasms (Figure 3). Finally, the remaining proportion of the increased long-term risk is for secondary neoplasm development, represented by 2 cases of sarcoma diagnosed in patients who had been followed up for 30 and 31 years. Figure 3 shows the cumulative incidences of each tumor type at 5, 10, 15, 20, and 30 years after complete remission.

Late-Occurring Secondary Neoplasms in Patients in First Complete Remission

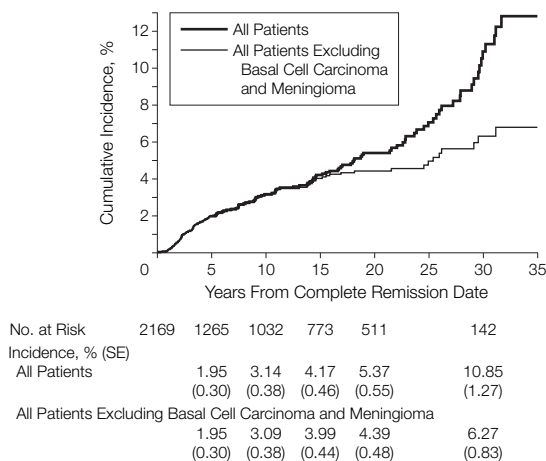
Forty-one patients developed secondary neoplasms after 15 years of follow-up. Among them, there were 14 men and 27 women. The median age of acute lymphoblastic leukemia diagnosis was 4.0 years (range, 2 months to 18 years). The

Figure 1. Time From Diagnosis of Acute Lymphoblastic Leukemia to Development of Secondary Neoplasms in Patients Who Achieved First Complete Remission (n=123)



Median is the line within each box; boxes indicates interquartile ranges and error bars indicate ranges.

Figure 2. Cumulative Incidence of Secondary Neoplasms Occurring in First Complete Remission



initial Total Therapy Study treatment protocols were study V (n=5), study VI (n=10), study VII (n=4), study VIII (n=9), study IX (n=5), study X (n=1), and study XI (n=7). The median duration from diagnosis of acute lymphoblastic leukemia to secondary neoplasm in this population was 23.7 years (range, 15.3-31.7 years). All patients but 1 with Hodgkin disease received cranial/craniospinal irradiation for acute lymphoblastic leukemia. Among 41 patients, 4 (9.8%) died. Three patients (1 each with acute myeloid leukemia, transitional cell carcinoma, and hepatocellular carcinoma) died of secondary neoplasms, and a patient with meningioma died after developing hepatocellular carcinoma as a third neoplasm.

TABLE 2 summarizes the 14 patients with neoplasms excluding meningioma (n=15) and basal cell carcinoma (n=12).

The second patient listed had chronic hepatitis B and C, which could have contributed to the development of hepatocellular carcinoma.

Incidence of Secondary Neoplasms in First Complete Remission vs General US Population

The SIR was calculated by comparing the observed incidence of secondary neoplasm in patients with the expected age- and sex-specific rates of cancers in the general population using data from SEER (TABLE 3). The observed number of events including all patients was significantly higher than the expected number of secondary neoplasms, representing myeloid malignancies, lymphomas, brain tumors, and other solid tumors (SIR, 13.5; 95% CI, 10.9-16.8). When the patients were stratified into 2 groups (those who did vs did not receive cranial/

craniospinal irradiation), the addition of cranial/craniospinal irradiation had a significant impact on the SIR for CNS tumors and other solid tumors (SIRs, 45.8 vs 4.3 and 5.1 vs 2.5, respectively) but not on the SIR for lymphomas or myeloid malignancies (Table 3).

We also estimated the SIR in different periods over 30 years. As expected, this ratio was highest for overall tumors in the first 5 years of follow-up (SIR, 335.1; 95% CI, 232.8-436.7), reflecting the overwhelming impact of myeloid leukemias (SIR, 3951.7; 95% CI, 2782.9-5448.9). The ratio for overall tumors decreased thereafter to 64.1 (95% CI, 39.4-97.3) in years 6 to 10 and to 8.0 (95% CI, 4.6-12.9) in years 11 to 20, as myeloid leukemias decreased (SIRs, 139.5 [95% CI, 28.7-407.3] in years 6-10 and 12.0 [95% CI, 0.3-67.0] in years 11-20). After 20 years, the SIR for overall tu-

Figure 3. Cumulative Incidence of Each Tumor Type in Patients Who Developed Secondary Neoplasm in First Complete Remission

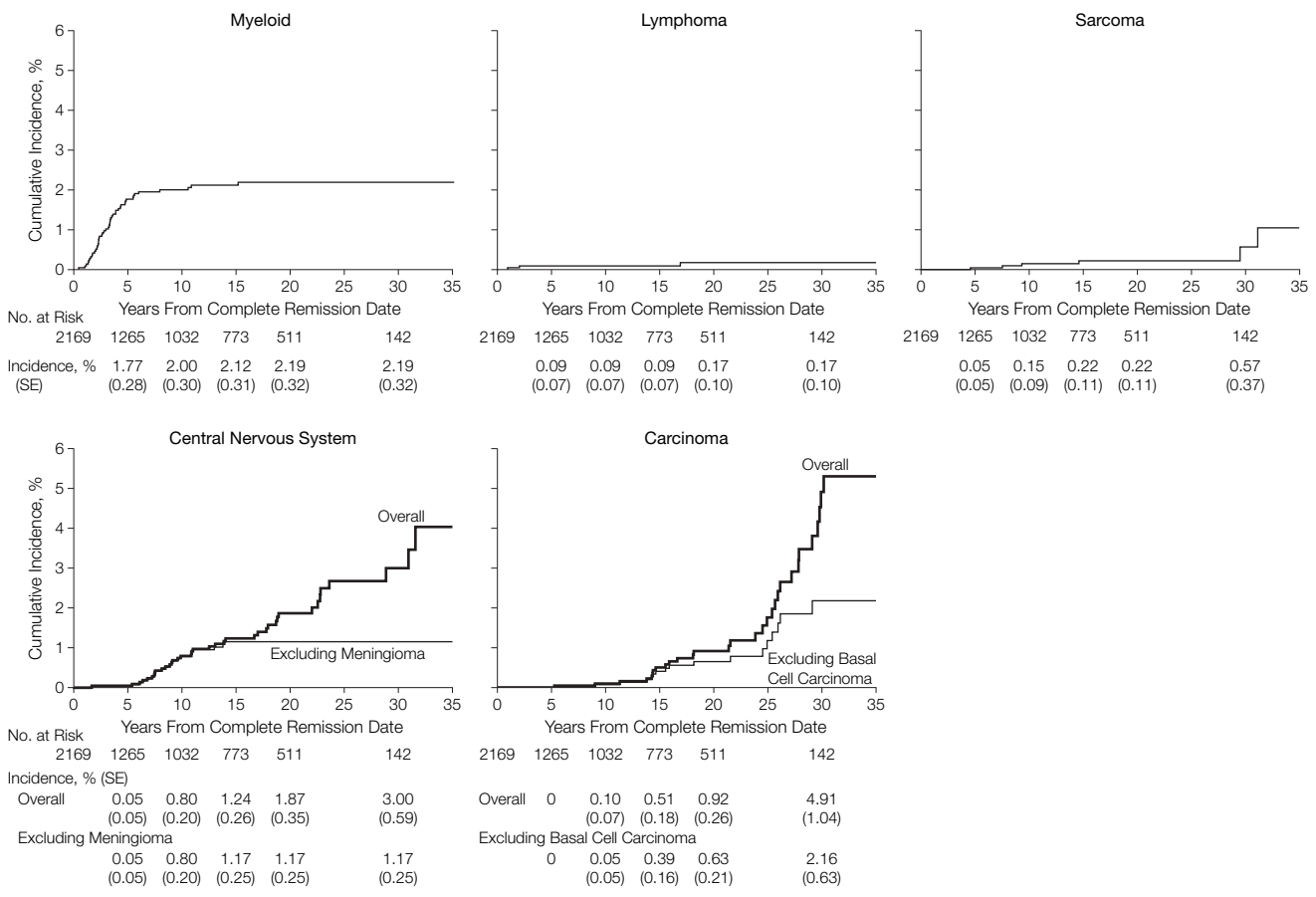


Table 2. Second Neoplasms Excluding Meningioma and Basal Cell Carcinoma That Occurred After 15 Years of Follow-up in Patients in First Complete Remission From Acute Lymphoblastic Leukemia

Patient Sex/Age at Diagnosis	Secondary Neoplasms, Histology, and Sites	Latency, y	St Jude Total Therapy Study ⁷	Outcomes	Notes
M/3 y	Acute myeloid leukemia	15.3	XI	Died of secondary neoplasm	
F/3 y	Hepatocellular carcinoma	25.5	VI	Died of secondary neoplasm	Had chronic hepatitis B and hepatitis C; unresectable tumor; died in 2 mo
F/13 y	Neuroendocrine carcinoma, carcinoid	26.2	VI	Alive >34.6 y postdiagnosis	Metastatic tumors; had third cancer (papillary carcinoma of thyroid) 2 y after secondary neoplasm
F/6 y	Adenocarcinoma, ovary	24.6	VI	Alive >35.1 y	Grade I, well differentiated
M/3 y	Acinic cell carcinoma, parotid gland	15.6	VIII	Alive >29.2 y	
M/15 y	Acinic cell carcinoma, parotid gland	18.3	XI	Alive >18.5 y	
F/8 y	Squamous cell carcinoma, tongue	25.0	V	Alive >37.0 y	Moderately differentiated
F/2 y	Squamous cell carcinoma, hand	21.6	V	Alive >36.6 y	Moderately to well differentiated
M/2 mo	Papillary carcinoma, follicular variant, thyroid	26.0	VII	Alive >34.5 y	
M/5 y	Follicular carcinoma, thyroid	29.2	VI	Alive >34.7 y	Had third cancer (basal cell carcinoma) 1 y after secondary neoplasm
F/14 y	Papillary transitional cell carcinoma, bladder	16.0	VII	Died of secondary neoplasm	Grade III-IV
M/4 y	Hodgkin disease, lymphocyte predominant	17.0	X	Alive >22.3 y	
F/3 y	Malignant gastrointestinal stromal tumor, retroperitoneum	29.6	VI	Alive >34.6 y	
F/5 y	Fibrosarcoma, frontal sinus	31.2	VIII	Alive >31.2 y	Low grade

Table 3. Incidence of Secondary Neoplasm in Patients in First Complete Remission Who Were Treated for Acute Lymphoblastic Leukemia in 1962-1998 vs US General Population

Cancer Type/Site	No. of Events		Standardized Incidence Ratio (95% Confidence Interval)*
	Observed	Expected	
All tumors†			
All patients	87	6.4	13.5 (10.9-16.8)
Cranial/craniospinal irradiation	69	5.1	13.6 (10.5-17.1)
No cranial/craniospinal irradiation	18	1.4	13.3 (7.9-21.0)
Myeloid			
All patients	41	0.3	150.9 (98.1-185.4)
Cranial/craniospinal irradiation	27	0.2	138.6 (88.9-196.4)
No cranial/craniospinal irradiation	14	0.1	182.2 (99.5-306.1)
Central nervous system			
All patients	22	0.7	31.8 (19.7-47.6)
Cranial/craniospinal irradiation	21	0.5	45.8 (26.0-64.2)
No cranial/craniospinal irradiation	1	0.2	4.3 (0.1-24.0)
Lymphoma			
All patients	3	1.0	3.0 (0.6-8.8)
Cranial/craniospinal irradiation	2	0.7	2.7 (0.3-9.7)
No cranial/craniospinal irradiation	1	0.3	4.0 (0.1-22.3)
Other solid tumors†			
All patients	21	4.5	4.7 (2.9-7.1)
Cranial/craniospinal irradiation	19	3.7	5.1 (3.1-8.0)
No cranial/craniospinal irradiation	2	0.8	2.5 (0.3-9.0)

*See "Methods" section of the text for details on the calculation of standardized incidence ratios.

†These types of secondary neoplasms in first complete remission were omitted because they are not included or were only recently included in the Surveillance, Epidemiology, and End Results database: myelodysplastic syndrome (n = 7), meningioma (n = 16), and basal cell/squamous cell carcinoma (n = 16). Three malignancies occurring after meningioma or myelodysplastic syndrome were included (2 myeloid leukemias after myelodysplastic syndrome and 1 thyroid carcinoma after meningioma). See text for details.

mors was 1.8 but did not attain statistical significance (95% CI, 0.8-3.5). The SIR for CNS tumors remained signifi-

cant through the 20-year period (SIRs, 57.5 [95% CI, 7.0-207.5], 197.3 [95% CI, 110.5-325.6], and 13.6 [95% CI, 4.4-

31.7] in years 0-5, 6-10, and 11-20, respectively) and there were no cases after 20 years. Other solid tumors were no more frequent than expected in the general population in the first 5 years (SIR, 14.8; 95% CI, 0.4-82.4) but became significant when the SIR reached 17.3 (95% CI, 3.6-50.4) in years 6 to 10 of follow-up and remained significant for the duration of follow-up (SIRs, 9.8 [95% CI, 4.5-18.6] in years 11-20 and 2.4 [95% CI, 1.1-4.5] after 20 years).

Risk Factors Associated With Development of Secondary Neoplasms

Since the major emphasis of this study was on the development of secondary neoplasms in patients who had at least 15 years of follow-up, we first report the results of a risk factor analysis for the 845 patients who were treated in the early era of therapy (Total Therapy studies I to IX), with survivors accruing 17.1 to 41.3 years of follow-up (median, 30.1 years). There were 51 cases of secondary neoplasms overall. Carcinoma (n=27) and CNS tumor (n=16) were the only subcategories investigated because the incidences of myeloid malig-

nancies (n=4), lymphomas (n=2), and sarcomas (n=2) were too low to warrant separate consideration. Overall, none of the factors analyzed (age ≥ 10 vs < 10 years old; sex; white vs non-white race; white blood cell count at diagnosis ≥ 50 vs $< 50 \times 10^9/L$; anthracyclines; alkylating agents; and cranial/craniospinal irradiation) showed a significant relationship to the cumulative incidence of secondary neoplasms at 20 years of follow-up (data not shown); however, at 30 years, there was a clear trend toward female dominance (4.53% [SE, 1.00%] for men vs 8.51% [SE, 1.62%] for women; $P = .06$). This association held for carcinoma incidence (2.14% [SE, 0.72%] for men vs 5.52% [SE, 1.35%] for women; $P = .07$). There was also a trend toward alkylating agent treatment (4.41% [SE, 0.95%] for alkylating agents vs 1.43% [SE, 0.64%] for no alkylating agents; $P = .08$). However, these trends did not reach statistical significance at the $P = .05$ level.

TABLE 4 shows the updated results of risk factor analyses conducted in patient cohorts treated during the modern treatment era (Total Therapy studies X to XIII B). Nineteen new secondary neoplasms were diagnosed in these groups since publication of the studies, but in each analysis the risk factors retained their original importance.

COMMENT

Previous studies have demonstrated a low incidence of secondary neoplasm during the first 10 to 15 years after the treatment of childhood acute lymphoblastic leukemia.^{9-11,27} Data on the longer-term incidence of secondary neoplasms has been limited by relatively incomplete and short follow-up times in the majority of published studies.^{9-11,27} We demonstrate herein that the cumulative incidence of secondary neoplasms in patients remaining in complete remission does not reach plateau at 20 years but continues to increase.

The majority of these late-onset secondary neoplasms are low-grade tumors (meningioma and basal cell carcinomas), although a substantial proportion consist of more aggressive solid tumors, such as soft tissue sarcomas and carcinomas.

Compared with the results from the Children's Cancer Group (CCG)¹⁰ or Berlin-Frankfurt-Münster (BFM) study group,¹¹ in which meningioma and basal cell carcinoma accounted for less than 4% of all secondary neoplasms, the proportion of such tumors is considerably higher (approximately 15%) in our patient population. This discrepancy likely reflects the longer follow-up time in our study (median, 18.3 years) compared with theirs (median, 5-6 years) and the failure of most cancer registries to report low-grade tumors on a routine basis.²⁸

Although meningioma is generally considered a curable neoplasm, it frequently causes neurological and neuro-

Table 4. Updated Results of Previously Published St Jude Total Therapy Studies X-XIII B on Risk Factors for Secondary Neoplasms

Study and Secondary Neoplasm Type*	Secondary Neoplasms in Original Study/Updated	Significant Risk Factors in Multivariate Analysis	Cumulative Incidence Among Specified Patient Groups at Specified Year, % (SE) [P Value]	
			Original Estimate†	Updated Estimate
Study XII Central nervous system ^{22,24}	6/10‡	CRT TPMT defect in patients who received CRT	8 y: CRT (n = 52) vs no CRT (n = 101): 12.8 (5.0) vs 0 [P < .001] Defective TPMT (n = 7) vs wild-type TPMT (n = 45): 42.9 (20.6) vs 8.3 (4.7) [P = .008]	8 y: 11.5 (4.5) vs 0 [P < .001] 42.9 (20.6) vs 6.7 (3.8) [P = .06]‡
Studies X-XI Acute myeloid leukemia ²⁰	21/29	Prolonged administration of epipodophyllotoxins (weekly or twice-weekly dose) vs other schedules§	6 y: Weekly (n = 84) vs twice weekly (n = 85) vs other schedules§ (n = 39-155): 12.4 (3.9) vs 12.3 (4.1) vs 0-1.6 (1.0) [P < .01]	6 y: 8.3 (3.0) vs 7.1 (2.8) vs 0-2.0 (1.2) [P = .02]
Study XIII A (high risk) Acute myeloid leukemia ²¹	4/11	L-asparaginase given immediately before etoposide	2 y: Study XIII A (high risk; n = 154) vs study XI (n = 186): 5.4 (2.9) vs 1.1 (0.8) [P = .05]	2 y: 2.6 (1.3) vs 1.1 (0.8) [P = .01]
Studies XIII A-B Acute myeloid leukemia ²³	20/20	CRT and G-CSF	6 y: CRT and no G-CSF (n = 44) vs G-CSF and no CRT (n = 85) vs CRT plus G-CSF (n = 14) vs neither (n = 269): 12.3 (5.3) vs 11.0 (3.5) vs 7.1 (7.2) vs 2.7 (1.3) [P = .02]	6 y: 11.5 (4.9) vs 10.9 (3.4) vs 7.1 (7.2) vs 2.0 (0.9) [P = .002]

Abbreviations: CRT, cranial/craniospinal irradiation; G-CSF, granulocyte colony-stimulating factor; TPMT, thiopurine methyltransferase.

*Results for key findings presented in the original articles' abstracts were updated using the same methods as the original article, with the exception of applying the approach of Fine and Gray²⁶ in the updated analysis for Pui et al.²⁰ The method of Fine and Gray is the analog to Cox proportional hazards models for modeling survival times in the presence of competing risks. For Relling et al.²² and Walter et al.²⁴ the first comparison is according to CRT and the second comparison is according to TPMT using the test of Gray.²⁵ For Pui et al.²¹ the P value is based on the Gray test²⁵; for Relling et al.²³ the protocol-stratified Gray test²⁵; and for Pui et al.²⁰ the multivariable proportional hazard regression model of Fine and Gray.²⁶ See Pui et al.²⁰ Pui et al.²¹ Relling et al.²² Relling et al.²³ and Walter et al.²⁴ for further details of the analysis for a specific study.

†P values are rounded from the originally reported numbers.

‡All 4 new cases occurred after 9 years, which yielded 10-year cumulative incidences of 42.9% (SE, 20.6%) and 15.8% (SE, 5.6%) for those with defective and wild-type TPMT, respectively (P = .06).

§Other schedules received no epipodophyllotoxins or received epipodophyllotoxins only in remission induction or every 2 weeks during continuation treatment.

||The 5-year cumulative incidence was 6.5% (SE, 2.0%) and 1.6% (SE, 0.9%) for studies XIII A (high risk) and XI, respectively (P = .01).

cognitive deficits,²⁹ and the treatment results may vary depending on whether the tumor arises before or after therapy for another malignancy. Secondary meningioma tends to have aggressive biological behavior and to recur.³⁰ Moreover, if a patient survives secondary meningioma, the probability of subsequent tumor may be increased. In our series, 4 patients (17%) with meningioma as a secondary neoplasm had a third cancer, and 1 of them (with hepatocellular carcinoma) died of a progressive tumor. Likewise, basal cell carcinomas are often locally invasive, and their multiple occurrence is common.²⁸ Indeed, the clinical significance of these “low-grade” tumors occurring as secondary neoplasms should not be underestimated. Among the 41 patients who developed secondary neoplasms after 15 years, 14 had histologically aggressive tumors (Table 2). Although most of them were not high-grade tumors and the prognosis after secondary neoplasms was favorable (10 of 14 were alive at the time of analysis), this patient population also had high morbidity.

All higher-grade tumors observed after 15 to 20 years of follow-up in this series were either carcinomas or sarcomas. One might argue that such late-occurring tumors are not necessarily secondary to acute lymphoblastic leukemia but could be expected because of the increased incidence of cancer in the older population. However, as demonstrated by SIR analysis, the risk of solid tumor development was still 2.4-fold higher than in the age- and sex-matched general population after 2 decades of follow-up. The median age of patients with these solid tumors in our cohort was 26.2 years (range, 12.6-39.7 years), considerably younger than the expected ages for the development of most carcinomas and sarcomas. In fact, a recent report from the Childhood Cancer Survivor Study³¹ indicates that young survivors of childhood cancers have increased risk of developing carcinomas that typically present in later adulthood. Interestingly, we did not observe a high incidence of cancers common in mid and

late adulthood, such as colon, breast, and lung cancers, which could reflect the relatively young age of our cohort (median, 24.8 years [range, 6.1-52.5 years]). Longer follow-up is needed to determine if acute lymphoblastic leukemia therapy confers an excess risk of developing the carcinomas that commonly present in adulthood.

For several reasons, we analyzed the risk factors associated with secondary neoplasm development according to the era in which the patients were treated. First, a meaningful analysis is difficult when we must account for the effects of multiple treatment regimens over 30 years (eg, epipodophyllotoxins were not used in Total Therapy studies I-IX). Second, too few patients enrolled in protocols of contemporary risk-based therapy have attained 20 to 30 years of follow-up to justify their inclusion in studies of factors influencing the longer-term development of secondary neoplasms,²⁰⁻²⁴ leading us to update rather than repeat these analyses. Third, given that the 5-year event-free survival rate before Total Therapy Study X was only 40%, there are few long-term survivors to assess (and, therefore, fewer secondary neoplasms and small risk-factor subgroup sizes at later years of follow-up), thus limiting the investigation of risk factors in the early era.

Some limitations to the current study should be noted. Although our follow-up contact rate is comparable with other cooperative group studies,¹⁰ 24% did not have contact in the last 2 years. We observed that the percentage with contact in the last 2 years differed according to age and study, reflecting the difficulty of maintaining contact with aging survivors, which introduces a potential bias. However, it should be noted that only 3.3% did not have follow-up in the last 5 years, which is considered “lost to follow-up” by most cancer registries. Additionally, in the recent era, our survivors had a shorter duration of follow-up (median, 15.9 years [range, 2.4-26.2 years]). Many of these patients may have not been observed long enough for development of late-occurring second malignancies, but a number of them de-

veloped early second malignancies (Table 4). Also, our analyses address the effects of frontline pretransplantation therapy on the occurrence of secondary neoplasm in first complete remission, so the impact of transplantation and salvage therapies was not assessed. Finally, although our analyses include all patients with acute lymphoblastic leukemia enrolled in St Jude studies between 1962 and 1998, some of our estimates, particularly those investigating temporal trends, are based on small sample sizes and have wide confidence intervals, which indicates lack of precision requiring careful interpretation.

It was also possible to assess the effect of cranial/craniospinal irradiation on the cumulative incidence of secondary neoplasms in relation to the US general population by stratifying patients according to receipt or no receipt of cranial/craniospinal irradiation (Table 3). In the subgroups with CNS tumors or carcinomas (excluding meningiomas and basal cell or squamous cell carcinomas), only patients who did receive cranial/craniospinal irradiation had SIRs that were significantly different from those in the general population, reinforcing the results shown in Table 4. In the current St Jude frontline protocol for acute lymphoblastic leukemia, cranial/craniospinal irradiation is no longer given prophylactically but is reserved for patients who develop CNS relapse. We anticipate that this conservative therapeutic approach will significantly reduce the incidence of radiation-associated secondary neoplasms. Nonetheless, the incidence of secondary neoplasms in patients who received cranial/craniospinal irradiation in the early era has not attained a plateau after 3 decades, and lifelong monitoring is necessary in this cohort. Our recent elimination of epipodophyllotoxins for all patients but those at very high risk of relapse should limit the cases of secondary AML.

Despite the persistent influence of therapeutic factors such as cranial/craniospinal irradiation,^{22,24} epipodophyllotoxins,²⁰ and alkylating agents⁸ on secondary neoplasm induction, the

pathogenesis of these cancers is almost certainly multifactorial. Indeed, the significance of host-related genetic risk factors for secondary neoplasm was recognized recently using gene expression profiles for the diagnostic bone marrow specimens.^{32,33} Patients found to have high genetic susceptibility to secondary neoplasms will likely receive special consideration and long-term follow-up in the future.

In conclusion, the cumulative incidence of secondary neoplasm after treatment for childhood acute lymphoblastic leukemia does not attain a plateau at 15 to 20 years but continues to increase over 30 years. Although the majority of these late-occurring secondary neoplasms are low-grade tumors such as meningioma and basal cell carcinoma, the health care issues they raise may be critical. The risk for high-grade tumors, especially carcinomas, significantly exceeds the risk in the general population, underscoring the need for continued careful follow-up of acute lymphoblastic leukemia survivors.

Author Contributions: Dr Hijiya and Ms Lensing had full access of all the data in this study and take responsibility of integrity of the data and accuracy of data analysis.

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Obtained funding: Evans, Relling, Pui.

Administrative, technical or material support: Hijiya, Hudson, Lensing, Zacher.

Study supervision: Hijiya.

Financial Disclosures: None reported.

Funding/Support: This work was supported in part by National Institutes of Health grants CA-21765, CA-51001, CA-36401, CA-78224, CA-71907, CA-60419, and GM-61393 and by the American Lebanese Syrian Associated Charities. Dr Pui is an American Cancer Society professor.

Role of the Sponsor: The funding agencies/sponsors had no involvement in the design and conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, and approval of the manuscript.

Previous Presentation: This study was presented in part at the 41st Annual Meeting of the American Society of Clinical Oncology, May 14, 2005, Orlando, Fla.

Acknowledgment: We thank John Gilbert for scientific editing (compensated for his work). We also thank from St Jude Children's Research Hospital: Michael Hancock, Cheng Cheng, PhD, Yinmei Zhou, Deqing Pei, and Stan Pounds, PhD, for suggestions and assistance in the statistical analysis; Joseph Khoury, MD, for discussions regarding histological classification; Annette Stone and Pam Hays for data collection; Julie Groff for assistance with figures; and Jeana Cromer for administrative assistance. We are indebted to the medical staff, the patients, and their parents for participation in the clinical trials, without whom this study would not have been possible. We dedicate this article to the late Charles Pratt, MD, who made substantial contributions in the study of subsequent malignancies in pediatric cancer survivors.

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