Table I. Cumulative doses of selected chemotherapeutic agents and radiation of ALL trials L84-11 to L99-15 according to risk groups.

Risk Group by protocol	Patients (n)	Anthracycline (mg/m^2)						CPM (mg/m^2)	VP-16 (mg/m^2)	IV MTX (g/m^2)	Maintenance (weeks)	MTXIT	CRT (Gy)	CRT rate (%)	10-year OS (%)
		DNR	DOX	THP	ACR	MIT	Total								
L84-11	484													100	74·3 ± 2·0
SR (A/B arm)†	194	0	0	0	0	0	0	0	0	2/3·5	172	9/15	18	100	
HR (A/B arm)†	244	180	0	0	150	0	224	6800/6000	0	1/2·5	172	5/11	24	100	
HEX	48	75	100	0	0	0	162	4000	0	0	96	11	24	100	
L89-12	418													80	73·5 ± 2·2
SR (A/B arm)†	142	0	100/0	100/150	0	0	160/90	0	900	9	91	9/9	0 vs 18	44	
IR	100	0	0	210	60	0	135	3100	2400	6	91	7	18	100	
HR	146	0	0	240	60	20	210	3600	2400	6	87	6	18	100	
L92-13	347													44	77·9 ± 2·2
SR	124	0	0	150	0	20	170	0	0	6	24	8	0	0	
HR (A/B arm)†	122	0	0	100	0	20	140	1000	1200	6/0	22	10	0 vs 12/18	47	
HEX	101	0	0	100	0	40	220	1000	1200	0	16	9 (6)	18	100	
L95-14	597													44	82·0 ± 1·6
SR	231	0	0	100	0	0	60	2000	0	10·6	54	11	0	0	
HR (A/B arm)†	129	0	0	220	0	0	132	4000	0	10/1	54	8	0 vs 12/18	18	
HEX	237	100	200	220	0	0	415	4000	0	1	54	8	18	100	
L99-15/L04-1502	1007													8·6	87·6 ± 1·2‡
SR	381	100	0	0	0	0	83	2000	0	13·15	104	11	0	0	
HR (A/B arm)†	404	100	100	120	0	0	245	4000/5000	0	10	52	10/11	0	0	
HEX	242	100	0	0	0	20	163	5600	1000	6	54	17	12/18	27·4	

SR, Standard risk; IR, Intermediate risk; HR, High risk; HEX: extremely high risk; DNR, daunorubicin; DOX, doxorubicin; THP, pirarubicin; ACR, acracinomycin; MIT, mitoxantrone; Total, DOX-equivalent dose; CPM, cyclophosphamide; VP-16, etoposide; MTX, methotrexate; CRT, cranial irradiation; IT, intrathecal; OS, overall survival.

†(A/B arm): cumulative doses of A arm/B arm; Additional details of treatment regimen are provided as supplemental information.

‡4-year overall survival rate.

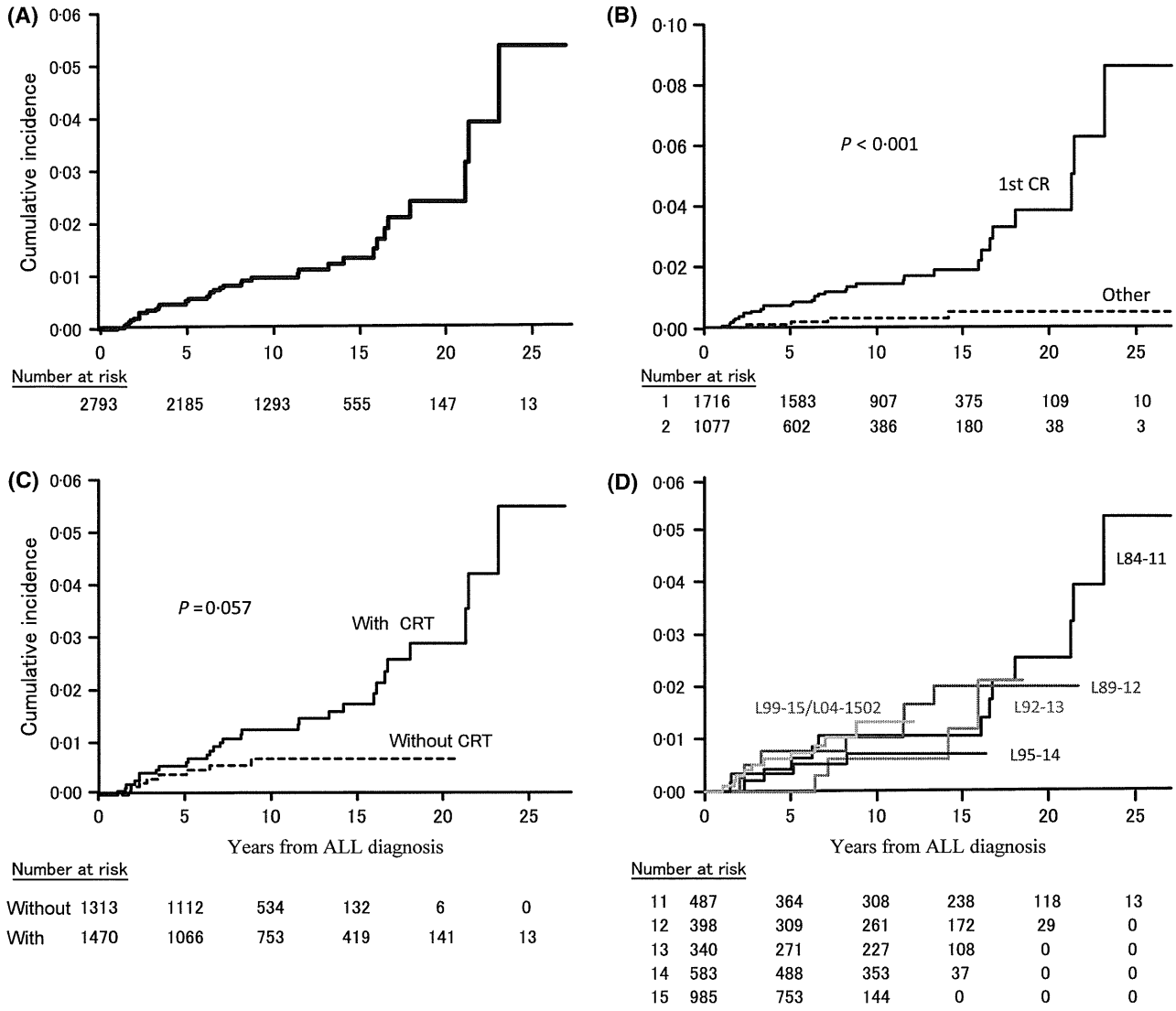

Fig 2. Cumulative incidence of secondary cancers. Shown are the cumulative incidences of secondary cancers as a function of time since primary ALL diagnosis over a maximum follow-up of 27 years. (A) Overall cumulative incidence of secondary cancer among the total patient cohort. (B) Overall cumulative incidence of patients remaining in first complete remission (1st CR) compared to others. (C) Overall cumulative incidence according to treatment with or without cranial radiation therapy (CRT). (D) Overall cumulative incidence according to treatment protocols: L84-11 (black line), L89-12 (red line), L92-13 (green line), L95-14 (purple line), and L99-15/L04-1502 (blue line). The numbers of patients at risk at a specific time point are indicated below each of the four plots.

other carcinoma tended to develop more commonly in children that were older at ALL diagnosis. There was no difference between types of secondary cancers with regard to initial WBC, immunophenotype and risk classification of the primary ALL. The median latency period from ALL diagnosis to secondary cancers was 6 years (range 1–23 years) and varied by type of secondary cancer (Fig 3). The median time to diagnosis for haematological cancers (AML, MDS and NHL) was shortest (median 3·0 years), followed by brain tumours (median 11·5 years) and other solid carcinoma (median 16·3 years). Haematological cancers developed most commonly during the first 10 years followed by brain tumours from 15 to 20 years (Fig 3A, B). The age distributions at diagnosis of secondary cancers are shown in (Fig 3C). Median age at diagnosis of secondary was earlier for haematological cancers than brain tumour (median 14 years) and other carcinomas (median 19 years). Among AML, the most common morphological type was M5 (3 had t (9;11) (p22;q23) with *MLL-MLLT3* translocation). Four MDS cases showed chromosomal abnormality. Lymphoma and solid tumours did not show any chromosomal abnormalities.

As for the characteristics related to the treatment of primary ALL, the secondary cancers with the highest proportions of patients who underwent CRT were MDS, brain tumour and other carcinoma, while the haematological cancers showed elevated cumulative anticancer drug doses. Among a total of 621 SCT that had been performed for the primary ALL during the observation period of the study population, only 3 patients

Table II. Clinical characteristics of patients with secondary cancers.

	AML	MDS	NHL	Brain tumour	Other carcinoma
Total number of secondary cancers	11	5	2	13	6
Gender (Male:Female)	3:8	1:4	2:0	8:5	3:3
Primary ALL					
Age at diagnosis of ALL (years)	5 (1–14)	5 (2–13)	4 (2–6)	8 (2–12)	11 (3–14)
Initial WBC count ($\times 10^9$/l)	20·5 (1·9–168)	11·2 (2·9–70)	8·7 (3·4–14)	12·6 (1·9–112)	4·9 (2·1–163)
Immunophenotype (B:T:Other)	7:0:4	3:0:2	2:0:0	7:1:5	6:0:0
Risk group (SR:IR:HR)	1:8:2	1:2:2	2:0:0	1:10:2	2:4:0
Secondary cancer (SC)					
Incubation time to SC (years)	3·3 (1·6–11·6)	2·3 (1·0–6·3)	3·1 (2·8–3·4)	11·5 (2·3–23·2)	16·3 (7·2–21·4)
Diagnosis on therapy	4/11 (36%)	2/5 (40%)	1/2 (50%)	0/13 (0%)	0/6 (0%)
Age at diagnosis of SC (years)	9·0 (6·4–21·3)	11·1 (4·0–14·5)	7·5 (5·3–9·7)	18·5 (10·3–27·7)	23·9 (18·8–32·6)
Sub-classification	M4: 2, M5: 7, M7: 1, Unknown: 1	RAEB: 1, CMML: 2, Unknown: 2	Diffuse large B-cell lymphoma: 1, Burkitt lymphoma: 1	Glioma: 8, Meningioma: 3, Other: 2	Oral cancer: 2, parotid cancer: 2, breast cancer: 1, thyroid cancer: 1
Treatment for primary ALL					
Protocol (11:12:13:14:15)	1:3:0:2:5	2:1:0:1:1	0:0:0:0:2	6:3:1:1:1	3:0:2:0:1
Cranial irradiation	6/11 (55%)	5/5 (100%)	0/2 (0%)	13/13 (100%)	5/6 (83%)
Dose of cranial irradiation (Gy)	18 (0–28)	18 (18–24)	24 (18–36)	0	18 (0–24)
Anthracyclines (DOX equivalent)	230 (50–330)	72 (0–190)	112 (82–142)	120 (0–190)	47 (0–230)
Cyclophosphamide ($\times 10^3$ g)	4·0 (3·1–6·0)	4·0 (0–5·6)	1·0 (0–2·0)	4·0 (0–6·8)	1·1 (0–6·0)
Etoposide ($\times 10^3$ g)	0 (0–2·4)	0 (0–2·4)	0 (0–2·4)	0	0 (0–1·2)
Duration of maintenance (weeks)	52 (28–172)	96 (62–172)	96 (22–175)	78 (52–104)	112 (0–172)
Stem cell transplantation	0	0	0	1/13 (8%)	2/6 (33%)
Treatment for secondary cancer (SC)					
Surgery	0	0	0	9	6
Radiation	0	0	0	7	3
Chemotherapy	11	4	2	6	3
Stem cell transplantation	8	1	0	0	0
Median survival duration (years)	1·7 (0·2–4·3)	4·6 (0·9–11·1)	3·6 (0·5–6·7)	2·0 (0·1–11·3)	3·0 (0·8–10·4)
4 year survival rate (%)	24%	60%	50%	50%	83%
Standardized incidence ratio (SIR) and absolute excess risk (AER)					
No. observed/expected	16/0·64	2/0·52	13/0·36	6/2·45	
SIR (95%CI)	25 (14–41)	3·8 (0·5–14)	36 (19–62)	2·5 (0·9–5·3)	
AER/100 000 person-years	118	9·4	90	26	

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; RAEB, refractory anaemia with excess blasts; CMML, chronic myelomonocytic leukaemia NHL, Non-Hodgkin lymphoma; WBC, white blood cell; SR/IR/HR, standard/intermediate/high risk; DOX, doxorubicin; 95% CI, 95% confidence interval.
Numbers shown as median (range; minimum-maximum).

developed a secondary cancer (1 brain tumour and 2 other cancers). All 3 cases received total body irradiation-containing conditioning regimens, two of 3 developed tongue carcinoma whilst suffering from chronic graft-versus-host disease after allogeneic SCT. SCTs were common among secondary AML patients as treatment. Kaplan–Meier OS curves for the patients with secondary cancers are shown in (Fig 3D). The lowest survival probabilities were observed for patients with AML/MDS/NHL compared to patients with brain tumours and other carcinoma (P = 0·045 by log-rank test).

SIR and AER

We compared the incidence of secondary cancers in our cohort with that of the general population using the regional cancer registration database of the National Cancer Centre Hospital in Japan. As shown in Table II, the SIR was 25 (95% CI, 14–41) for AML/MDS, 3·8 (95% CI, 0·5–14) for lymphoma, 36 (95% CI, 19–62) for brain tumours and 2·5 (95% CI, 0·9–5·3) for other solid carcinoma. This represents a 9·3-fold (95% CI, 6·5–12·8) increase risk of all secondary cancers during a total of 27 658 person-years of observation. The total AER for secondary cancers was 256 per 100 000 person-years.

Risk factors for secondary cancers

The unadjusted analyses comparing patients with and without secondary cancers showed differences in age at ALL diagnosis, risk classification, CPM and CRT, while there were no statistically significant differences with respect to gender,

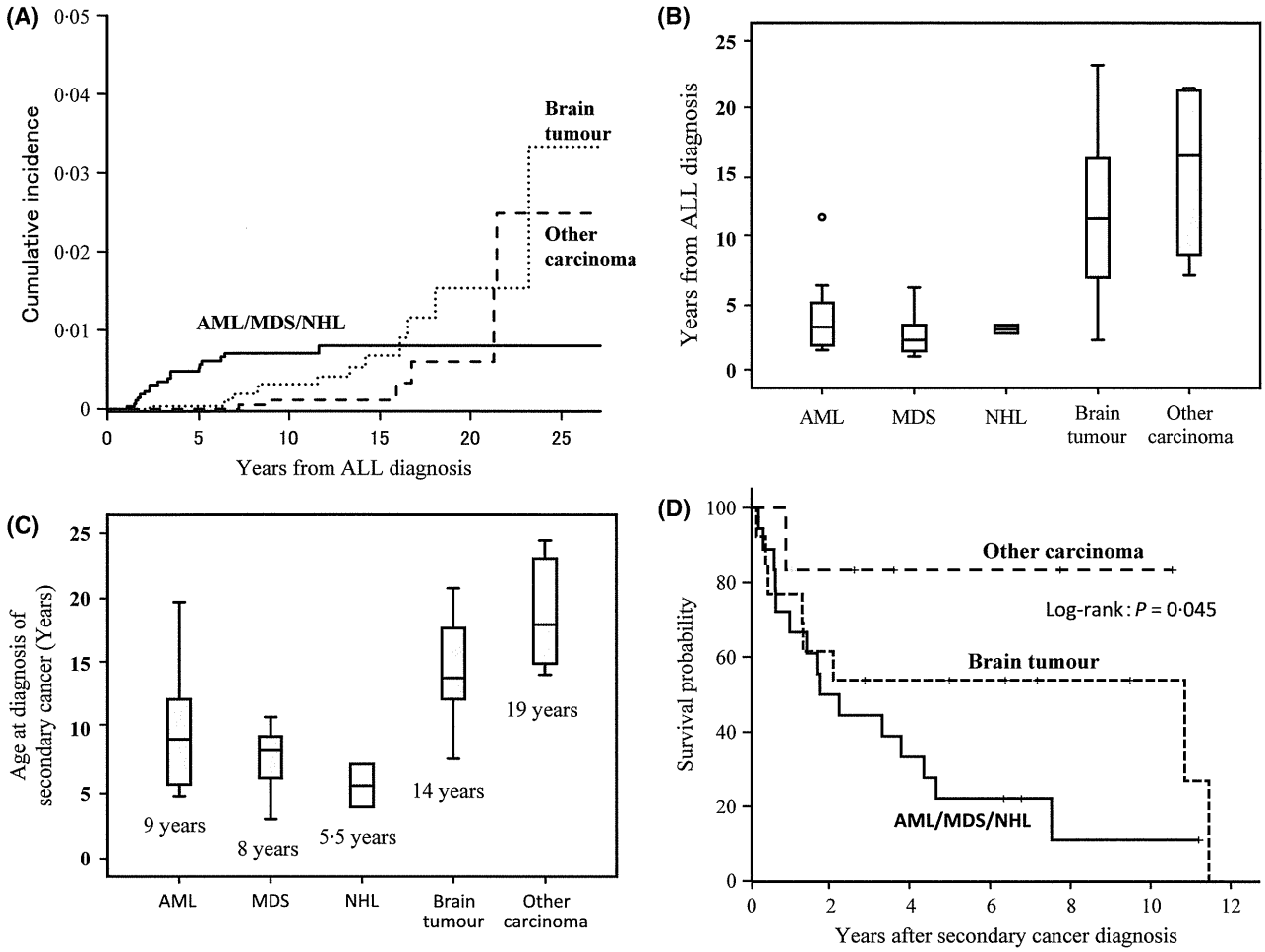

Fig 3. Clinical characteristics according to types of secondary cancer. (A) Cumulative incidence by years since ALL diagnosis of specific secondary cancers including AML/MDS/NHL (solid line), brain tumour (dotted line), and other carcinoma (dashed line). (B) The median latency period from diagnosis of ALL to development of specific secondary cancers. The median time for haematological cancers (AML, MDS and NHL) was shortest, followed by brain tumours and other solid carcinoma. (C) Age at diagnosis of secondary cancers; generally, the median age of haematological cancers was younger compared to brain tumours and other carcinomas. (D) Overall survival of secondary cancer patients are shown using Kaplan–Meier survival curves. Survival probabilities were the lowest for patients with AML/MDS/NHL. Actuarial survival at 4 years from diagnosis of secondary cancers depend on the type; AML/MDS/NHL 33%; brain tumours 54%; other carcinoma 83%. AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma.

initial WBC, immunophenotype, anticancer agents (with the exception of CPM) and maintenance duration of the primary ALL (Table III and Figure S2). Because protocol and anticancer drugs were highly correlated, we were unable to effectively evaluate them in the same multivariate regression analysis. Thus, results using Cox regression adjusting for covariates including treatment protocol (but not anticancer drug) (Table III) showed that CRT was associated with a 6-fold increased risk of secondary cancers compared to patients not receiving CRT (HR = 6·02, 95% CI 1·46–24·8). When CRT was categorized into 3 groups based on dose (i.e. no CRT, 18 Gy, and >24 Gy), similarly increased risks were observed for the moderate and high dose categories (data not shown). Age at ALL diagnosis >7 years (versus 3 years or younger, HR = 3·01, 95% CI 1·14–7·94) and inclusion in the more recent TCCSG L99-15/L04-1502 protocol (versus L84-11, HR = 8·15, 95% CI 1·03–64·7) were independently associated with an increased risk of secondary cancers. The same model, but replacing treatment protocol with the anticancer drugs (i.e. CPM, yes versus no; etoposide, yes versus no; high-dose methotrexate, yes versus no) showed an attenuated risk estimate for CPM (HR = 1·84, 95 CI 0·32–10·4), despite it being statistically significant in the unadjusted analysis (OR = 3·05, 95% CI 1·06–8·76).

Discussion

The risk of secondary cancers in childhood ALL survivors may be influenced by genetic predisposition, but growing evidence shows therapeutic regimen to be another major contributing factor. The risk of developing secondary cancers should be interpreted in the context of the survival

Table III. Cox-regression analysis evaluating the association between select characteristics of the primary ALL diagnosis and risk of developing a secondary cancer.

Intention to treat analysis group (n = 2807)	Patients with Secondary cancer	Patients without Secondary cancer	Crude HR (95%CI)	Adjusted HR (95%CI)	P-value
Protocol					
L84-11	12	476	Reference	Reference	
L89-12	7	392	1·00 (0·37–2·69)	1·35 (0·47–3·84)	0·576
L92-13	4	336	0·78 (0·24–2·56)	3·64 (0·45–29·1)	0·224
L95-14	4	584	0·56 (0·17–1·91)	4·47 (0·46–43·6)	0·198
L99-15/L04-1502	10	982	1·12 (0·42–3·01)	8·15 (1·03–64·7)	0·047
Risk classification					
Standard risk	7	1021	Reference	Reference	
Intermediate risk	20	956	3·42 (1·44–8·08)	2·70 (0·84–8·69)	0·096
High risk	10	771	2·67 (1·02–7·03)	1·01 (0·21–4·84)	0·992
Age at ALL diagnosis					
3 years or younger	8	986	Reference	Reference	
4–7 years	12	965	1·63 (0·67–3·98)	1·76 (0·71–4·40)	0·224
8 years or older	17	888	3·10 (1·34–7·21)	3·01 (1·14–7·94)	0·026
Gender: Male/Female	18/19	1530/1207	1·29 (0·68–2·46)	1·37 (0·71–2·62)	0·347
Attained age ≥20 years: No/Yes	20/17	2054/685	0·89 (0·42–1·90)	0·46 (0·19–1·12)	0·089
Cranial irradiation: No/Yes	8/29	1310/1445	2·57 (1·15–5·75)	6·02 (1·46–24·8)	0·013
Maintenance >1·5 years: No/Yes	15/22	1547/1209	1·16 (0·57–2·36)	3·19 (0·55–18·4)	0·194
Anticancer drugs					
Anthracycline: No/Yes	4/33	182/2574	1·32 (0·45–3·89)	N/A	N/A
Cyclophosphamide: No/Yes	4/33	448/2308	3·05 (1·06–8·76)	N/A	N/A
Etoposide: No/Yes	24/13	1910/846	1·30 (0·65–2·60)	N/A	N/A
High-dose Methotrexate: No/Yes	15/22	793/1963	0·77 (0·23–2·54)	N/A	N/A

ALL, acute lymphoblastic leukaemia; HR, hazard ratio; 95% CI, 95% confidence interval; N/A, not available.
Total number of patients may not equal 2807 for all variables due to missing data.

probability for a given treatment protocol, as low survival will result in fewer secondary cancers. Although the lifetime incidence of secondary cancers has not yet been defined, within the first 20 years of initial diagnosis of childhood ALL, previous studies conducted the U.S. and Europe have estimated it to be between 2% and 5%. To our knowledge, our study is the first conducted among an Asian population to report estimates of the cumulative incidence of secondary cancers in childhood ALL survivors. We found that the cumulative incidence of any secondary cancers in ALL survivors was 1·0% at 10 years and 2·4% at 20 years, respectively.

The previous reports on secondary cancers in childhood ALL survivors are summarized in Table IV. In 1991, the Children's Cancer Group (CCG) evaluated 9720 cases of ALL diagnosed since 1972 (Neglia *et al*, 1991) with a more recent update reported by Bhatia *et al*(2002) The CCG report showed a cumulative incidence of 1·3% at 10 years after ALL diagnosis, whereas the Berlin-Frankfurt-Munster (BFM) study (Loning *et al*, 2000) observed an overall cumulative incidence of secondary cancers at 15 years of 3·3% and 2·9% (95% CI: 1·6%–4·2%) among patients in first CR. In 1991, a Norwegian study found an overall cumulative incidence of 2·9% by 20 years after diagnosis in a group of 895 patients treated between 1958 and 1985 (Nygaard *et al*, 1991). In the St. Jude study reported by Hijiya *et al* (2007) a comparatively higher cumulative incidence of 4·2% at 15 years and 11% at 30 years was found. Our study of Japanese patients resulted in cumulative incidence and SIR estimates that are consistent with these results reported by the CCG, BFM, and Norwegian studies.

Previous reports from the CCSS and BCCSS (Mody *et al*, 2008; Reulen *et al*, 2011) calculated cumulative incidence and SIR estimates of secondary cancers within cohorts of childhood cancer patients that have survived at least 5 years. The distribution of secondary cancer types reported by those studies appeared to be different compared to ours and other prospective clinical studies (Table IV). As shown previously and in our study, most AML and MDS developed within 5 years after diagnosis of ALL. Thus, studying 5 year childhood cancer survivors probably influenced the comparatively fewer numbers of AML/MDS secondary cancers observed in the CCSS and BCCSS (Table IV).

Our results are also consistent with previous studies with respect to the median latency period by secondary cancer type (shortest for AML/MDS/NHL)(Loning *et al*, 2000; Bhatia *et al*, 2002; Hijiya *et al*, 2007) over-representation of females (Neglia *et al*, 2001; Bhatia *et al*, 2002; Meadows *et al*, 2009) in secondary AML/MDS, and CRT as a strong risk factor for secondary cancer development.(Neglia *et al*, 1991; Nygaard *et al*, 1991; Loning *et al*, 2000; Borgmann *et al*,

Table IV. Previous reports on the incidence of secondary cancers among survivors of childhood ALL.

Authors	Group	Total ALL patients (n)	Treatment Year	Follow-up, years Total person-years (P-Y)	Patients with secondary cancer (n)	Type of secondary cancer	Cumulative incidence	SIR (95%CI)
Neglia *et al* (1991)	CCG	9720	1972–88	4·7 (0·2–16) 43 446 P-Y	43	10 leukeamia/lymphoma, 24 brain tumours, 9 other tumours	0·3% (0·2–0·5) at 5 years 1·5% (1·1–2·1) at 10 years 2·5% (1·7–3·4) at 15 years	42/6·1 = 6·85
Bhatia *et al* (2002)	CCG	8831	1979–95	5·5 (0–16·1) 54 883 P-Y	70	14 AML/MDS, 6 NHL, 2 HL, 19 brain tumours, 4 sarcoma, 4 thyroid cancers, 4 parotid tumours, 4 other tumours	1·3% (0·8–1·5)at 10 years 2·1% (1·4–2·8) at 15 years	7·2 (5·5–9·1)
Nygaard *et al* (1991)	Norway (NOPHO)	895	1958–85	10·5 7·2 (4·3–26·5) 6295 P–Y	8 (6)	3 brain tumours, 2 basal cell carcinoma, 1 thyroid cancer, 2 sarcoma	2·9% (SE 1·4) at 20 years	5·9 (2·2–12·9)
Kimball Dalton *et al* (1998)	DFCI	1597	1972–95	7·6 (0–24·0)	13	3 leukaemia/lymphoma, 5 brain tumours, 5 other solid tumours	2·7% (0·7–4·7)	N/A
Loning *et al* (2000)	BFM	5006	1979–95	5·7 (1·5–18) 28 605 P-Y	52	16 AML, 1 CML, 6 lymphoma, 13 brain tumours, 3 thyroid cancers, 13 other solid tumours	0·5% (0·4–0·6) at 5 years 1·5% (1·3–1·9) at 10 years 3·3% (1·6–5·1) at 15 years	14·1 (11–18)
Hijiya *et al* (2007)	St. Jude	2169	1962–98	18·7 (2·4–41·3) 29 179 P-Y	123	45 AML, 2 CML, 10 MDS, 6 lymphoma, 48 brain tumours, 9 sarcoma, 48 other solid tumours	4·2% (SE 0·5) at 15 years 10·9% (SE 1·3) at 30 years	13·5 (11–17)
Schmiegelow *et al* (2009)	NOPHO	1614	1992–01	10·4 (50% range: 8·0–12·6)	20	8 AML, 8 MDS, 1 brain tumour, 1 oral cancer, 1 LPD after SCT, 1 thyroid cancer	1·6% (SE 0·4) at 12 years	N/A
Mody *et al* (2008)	CCSS	5760	1970–86	21·2 (5–35)	185 (199)	4 AML, 7 NHL, 106 brain tumours, 11 breast cancer, 16 thyroid cancers, 13 sarcomas, 9 skin cancer, 26 others	5·2% (4·3–6·1) at 25 years	5·0 (4·1–6·0)
Reulen *et al* (2011)	BCCSS	No. of leukaemia patients was not available Total 17 981	1940–91	24·3 (50% range: 17·9–32·4) 80 028 P-Y	115 all leukaemias (not limited ALL)	7 leukaemia, 3 lymphoma, 27 brain tumours, 17 thyroid cancers, 61 other solid tumours	N/A	4·3 (3·6–5·2)
This study	TCCSG	2807	1984–05	9·5 (0·2–27) 27 658 P-Y	37	11 AML,5 MDS, 2 lymphoma, 13 brain tumours, 6 other solid tumour	1·0% (0·7–1·4) at 10 years 1·4% (0·9–2·0) at 15 years 2·4% (1·5–3·7) at 20 years	9·3 (6·5–12·8)

CCG, Children's Cancer Group; NOPHO, Nordic Society for Paediatric Haematology and Oncology; DFCI, Dana-Farber Cancer Institute; BFM, Berlin-Frankfürt-Münster; St. Jude, St. Jude Children's Research Hospital, St.Jude; CCSS, Childhood Cancer Survivor Study; BCCSS, British Childhood Cancer Survivor Study; TCCSG, Tokyo Children's Cancer Study Group; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CML, chronic myeloid leukaemia; LPD, lymphoproliferative disease; SCT, stem cell transplantation; SE, standard error; SIR, standardized incidence ratio; 95%CI, 95% confidence interval; N/A, not available.

2008; Schmiegelow *et al*, 2009) Another important finding in the present study is that no marked difference was observed in cumulative incidence between the five TCCSG protocols, but the multivariate analysis adjusting for confounders including CRT resulted in a statistically significant increased risk of secondary cancers in patients treated with the recent protocol (Table III). Because of the relatively short follow-up duration for patients included in the recent protocol and potentially complex interplay with treatment, at this point we consider this finding preliminary and it will be followed-up in future studies. Despite considerable reduction in the use of CRT over time, particularly for the more recent treatment protocols, we observed no evidence of a reduction in incidence of secondary cancers among children with ALL (Fig 2D). One explanation may be that CRT is probably linked mainly to secondary brain tumours, which only comprise approximately a third of all the secondary cancers. Furthermore, examination of the data showed that secondary brain tumours were diagnosed in patients enrolled in the earlier treatment protocols, a time when CRT was still commonly administered. Secondary cancers diagnosed in patients enrolled in the more recent treatment protocols were predominantly haematological. Given that the latency for secondary brain tumours is generally longer than that of haematological cancers, it is possible that a longer follow-up period may be needed to observe the effects of the reduction in CRT use. Finally, considering the poor prognosis of secondary AML/MDS (Fig 3D), it is important to identify the associated factors and minimize the development of secondary haematological cancers.

Therapy-related secondary cancers have been identified in patients receiving radiotherapy, chemotherapy, or combined modality therapy for ALL. Our study identified CRT as a strong risk factor, which was also found in the BFM study. (Loning *et al*, 2000; Borgmann *et al*, 2008) The cumulative incidence of secondary cancer for the irradiated group continued to increase with time even after more than 15 years following ALL diagnosis, possibly suggesting a long-term effect of irradiation on the rates of secondary cancers (Fig 2C). Even among the patients treated with more recent non-irradiated protocol, it is currently unknown whether the cumulative risk will remain constant, or whether secondary cancers might arise after a longer latency period. Multi-agent chemotherapy as part of multimodality therapy for cancers has increased the difficulty of assessing which agents might play a causative role in the development of secondary cancers. Alkylating agents, and more recently DNA-topoisomerase II inhibitors, have been linked to the development of secondary AML and MDS.(Hawkins *et al*, 1992; Le Deley *et al*, 2003) In contrast to previous reports, we were not able to demonstrate a clear relationship between the anthracyclines, etoposide or methotrexate and the occurrence of secondary cancers or specific types of secondary cancers.(Relling *et al*, 1999) The crude HR of CPM showed an increased risk of secondary cancers, but adjustment for confounders in multivariate analyses resulted in an attenuated and non-statistically significant finding.

Lastly, we found that cumulative incidence of secondary cancers in patients remaining in first CR was significantly higher than the patients who experienced a relapse of their primary ALL, changed treatment regimen, were lost to follow-up or died during first CR unexpectedly (Fig 2B). This finding was unexpected as it could be hypothesized that, because relapsed patients usually receive additional therapeutic exposures, they may potentially be at a higher risk of developing of secondary cancers. Nevertheless, a few studies provide some supportive data for our observations, including Borgmann *et al* (2008) who reported that the cumulative incidence of secondary cancers was unexpectedly low (1·3% at 15 years) despite repeated exposure to intense frontline and relapse treatment using BFM ALL-REZ Study data. In the St. Jude study (Hijiya *et al*, 2007), secondary neoplasms were observed in 123 out of 2,169 (5·7%) patients with continued first CR and in 45 out of 879 patients (5·1%) with relapse. In contrast, however, Bhatia *et al* (2002) demonstrated that the 10-year cumulative incidence of second malignancy was 0·91% in the patients with continued first CR compared with 1·2% in the entire cohort. The interpretation of these inconsistent results is difficult. It could be partially influenced by differences in OS among the patients with continued first CR and patients with relapse across the various studies.

One strength of the current study is that treatment of patients according to TCCSG therapeutic protocols ensured uniform access to standard therapy, giving us the opportunity to explore risk factors associated with secondary cancers in this cohort. Secondly, the follow-up duration was relatively long compared to previous prospective clinical studies and allowed us to describe the incidence of secondary cancers among patients treated on contemporary therapeutic protocols.

The results of this study should be interpreted in the context of acknowledged limitations. One major limitation is that this study was smaller than some previous studies, such as the CCG, CCSS and BCCSS, which may have affected our statistical power for certain analyses. Although all the patients in our cohort were treated according to therapeutic protocols, we do not have detailed information regarding actual cumulative exposures doses after relapse, which potentially could have influenced the development of second cancers. To address this concern, we conducted a sensitivity analysis (per protocol analysis) that included only patients who had completed all planned treatment leading to first CR. These results were largely consistent with the primary analyses (Table S1). Also, we were unable to compare the clonal phenotypes and genotypes between the primary ALL in L84-11/L89-12 and certain secondary ALL candidates. The difficulty in distinguishing between the primary and secondary type of recurrence using current standard techniques is well-recognized. In both of these events, some clonal markers

are maintained between the original diagnosis and recurrence but others can be altered.(Szczepanski *et al*, 2001; Zuna *et al*, 2007) Thus, they were not included in the analysis.

In conclusion, we showed that cumulative incidence of secondary cancer after TCCSG-ALL therapy is relatively low (1·0% at 10 years and 2·4% at 20 years) compared to the previous reports, although it is still 9 times higher than in the general population. We confirm that CRT is a strong risk factor of secondary cancer, but we did not observe evidence for a decrease in incidence despite the marked reduction in CRT treatment in the more recent protocols. In view of the long latency periods and long life expectancy of ALL patients treated in childhood, long and careful follow-up of these patients is warranted. Efforts to identify the causative carcinogenic factors should continue, and future treatment protocols should take these factors into account to maximize the chances of a long and healthy life, while preserving the efficacy of ALL treatment.

Acknowledgements

We sincerely thank Kaori Itagaki for preparing the TCCSG-ALL data, and Ryota Hosoya for his careful supervision. The authors thank the members of the ALL Committee of the TCCSG: Atsushi Manabe, Kei-ichi Isoyama, Akitoshi Kinoshita, Takehiko Kamijo, Masa-aki Kumagai, Hiromasa Yabe, Yasuhide Hayashi, Tsuyoshi Morimoto, Miho Maeda, Ken-ichi Sugita, Yasushi Noguchi, Takashi Kaneko, Kanji Sugita, Manabu Sotomatsu, Michiko Kajiwara, Takeyuki Sato, Yuri Okimoto, Setsuo Ohta, Masahiro Saito, Hiroyuki Takahashi, and Koichiro Ikuta.

Authorship and Disclosures

Conception and design: Yasushi Ishida (YI) and Miho Maeda (MM); Financial support: YI and Akira Ohara (AO); Administrative support: MM, Masahiro Tuchida(MT) and AO; Provision of study patients: YI, MM, Chikako Kiyotani, Yuki Aoki, Yoko Kato, Shoko Goto, Sachi Sakaguchi, Kenichi Sugita, Mika Tokuyama (MT), Naoya Nakadate, Eizaburo Ishii, MT and AO; Collection and assembly of data: YI, MM and MT; Data analysis and YI, MM, and Kevin Urayama (KU); Data interpretation: YI, MM, MT and AO; Manuscript writing: YI and KU, Final approval of manuscript: All authors.

Financial Disclosure

This study was supported in part by a grant from the Children's Cancer Association of Japan and a research grant from the St. Luke's Life Science Institute. The authors indicated no potential conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Schemas of the TCCSG (Tokyo Children's Cancer Study Group) protocols.

Fig. S2. Cumulative incidence of secondary cancers according to therapy of primary ALL.

Table S1. Cox- regression analysis limited to per protocol group evaluating the association between select characteristics of the primary ALL diagnosis and risk of developing a secondary cancer.

References

Bhatia, S., Sather, H.N., Pabustan, O.B., Trigg, M.E., Gaynon, P.S. & Robison, L.L. (2002) Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukaemia after 1983. *Blood*, **99**, 4257–4264.

Borgmann, A., Zinn, C., Hartmann, R., Herold, R., Kaatsch, P., Escherich, G., Moricke, A., Henze, G. & von Stackelberg, A. (2008) Secondary malignant neoplasms after intensive treatment of relapsed acute lymphoblastic leukaemia in childhood. *European Journal of Cancer*, **44**, 257–268.

Friedman, D.L., Whitton, J., Leisenring, W., Mertens, A.C., Hammond, S., Stovall, M., Donaldson, S.S., Meadows, A.T., Robison, L.L. & Neglia, J.P. (2010) Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute*, **102**, 1083–1095.

Gooley, T.A., Leisenring, W., Crowley, J. & Storer, B.E. (1999) Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Statistics in Medicine*, **18**, 695–706.

Hasegawa, D., Manabe, A., Ohara, A., Kikuchi, A., Koh, K., Kiyokawa, N., Fukushima, T., Ishida, Y., Saito, T., Hanada, R. & Tsuchida, M. & Tokyo Children's Cancer Study, G. (2012) The utility of performing the initial lumbar puncture on day 8 in remission induction therapy for childhood acute lymphoblastic leukaemia: TCCSG L99-15 study. *Pediatric Blood & Cancer*, **58**, 23–30.

Hawkins, M.M. & Robison, L.L. (2006) Importance of clinical and epidemiological research in defining the long-term clinical care of pediatric cancer survivors. *Pediatric Blood & Cancer*, **46**, 174–178.

Hawkins, M.M., Wilson, L.M., Stovall, M.A., Marsden, H.B., Potok, M.H., Kingston, J.E. & Chessells, J.M. (1992) Epipodophyllotoxins, alkylating agents, and radiation and risk of secondary leukaemia after childhood cancer. *BMJ*, **304**, 951–958.

Hijiya, N., Hudson, M.M., Lensing, S., Zacher, M., Onciu, M., Behm, F.G., Razzouk, B.I., Ribeiro, R.C., Rubnitz, J.E., Sandlund, J.T., Rivera, G.K., Evans, W.E., Relling, M.V. & Pui, C.H. (2007) Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukaemia. *JAMA*, **297**, 1207–1215.

Igarashi, S., Manabe, A., Ohara, A., Kumagai, M., Saito, T., Okimoto, Y., Kamijo, T., Isoyama, K., Kajiwara, M., Sotomatsu, M., Sugita, K., Sugita, K., Maeda, M., Yabe, H., Kinoshita, A., Kaneko, T., Hayashi, Y., Ikuta, K., Hanada, R. & Tsuchida, M. (2005) No advantage of dexamethasone over prednisolone for the outcome of standard- and intermediate-risk childhood acute lymphoblastic leukaemia in the Tokyo Children's Cancer Study Group L95-14 protocol. *Journal of Clinical Oncology*, **23**, 6489–6498.

Japanese National Cancer Centre Hospital (2013) The regional cancer registry, Available at: http://ganjoho.jp/professional/statistics/monita.html. [Accessed July 13, 2013].

Kanda, Y. (2013) Free statistical software: EZR (Easy R) on R commander. Available at: http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html. [Accessed April 1, 2013].

Kimball Dalton, V.M., Gelber, R.D., Li, F., Donnelly, M.J., Tarbell, N.J. & Sallan, S.E. (1998) Second malignancies in patients treated for childhood acute lymphoblastic leukaemia. *Journal of Clinical Oncology*, **16**, 2848–2853.

Le Deley, M.C., Leblanc, T., Shamsaldin, A., Raquin, M.A., Lacour, B., Sommelet, D., Chompret, A., Cayuela, J.M., Bayle, C., Bernheim, A., de Vathaire, F., Vassal, G., Hill, C., Societe Francaise d'Oncologie, P. (2003) Risk of secondary leukaemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Societe Francaise d'Oncologie Pediatrique. *Journal of Clinical Oncology*, **21**, 1074–1081.

Loning, L., Zimmermann, M., Reiter, A., Kaatsch, P., Henze, G., Riehm, H. & Schrappe, M. (2000) Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukaemia in childhood: significantly lower risk without cranial radiotherapy. *Blood*, **95**, 2770–2775.

Manabe, A., Tsuchida, M., Hanada, R., Ikuta, K., Toyoda, Y., Okimoto, Y., Ishimoto, K., Okawa, H., Ohara, A., Kaneko, T., Koike, K., Sato, T., Sugita, K., Bessho, F., Hoshi, Y., Maeda, M., Kinoshita, A., Saito, T., Tsunematsu, Y. & Nakazawa, S. (2001) Delay of the diagnostic lumbar puncture and intrathecal chemotherapy in children with acute lymphoblastic leukaemia who undergo routine corticosteroid testing: Tokyo Children's Cancer Study Group study L89-12. *Journal of Clinical Oncology*, **19**, 3182–3187.

Meadows, A.T., Friedman, D.L., Neglia, J.P., Mertens, A.C., Donaldson, S.S., Stovall, M., Hammond, S., Yasui, Y. & Inskip, P.D. (2009) Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *Journal of Clinical Oncology*, **27**, 2356–2362.

Mody, R., Li, S., Dover, D.C., Sallan, S., Leisenring, W., Oeffinger, K.C., Yasui, Y., Robison, L.L. & Neglia, J.P. (2008) Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study. *Blood*, **111**, 5515–5523.

Neglia, J.P., Meadows, A.T., Robison, L.L., Kim, T.H., Newton, W.A., Ruymann, F.B., Sather, H.N. & Hammond, G.D. (1991) Second neoplasms after acute lymphoblastic leukaemia in childhood. *New England Journal of Medicine*, **325**, 1330–1336.

Neglia, J.P., Friedman, D.L., Yasui, Y., Mertens, A.C., Hammond, S., Stovall, M., Donaldson, S.S., Meadows, A.T. & Robison, L.L. (2001) Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *Journal of the National Cancer Institute*, **93**, 618–629.

Nygaard, R., Garwicz, S., Haldorsen, T., Hertz, H., Jonmundsson, G.K., Lanning, M. & Moe, P.J. (1991) Second malignant neoplasms in patients treated for childhood leukaemia. A population-based cohort study from the Nordic countries. The Nordic Society of Pediatric Oncology and Hematology (NOPHO). *Acta Paediatrica Scandinavica*, **80**, 1220–1228.

Pui, C.H., Campana, D., Pei, D., Bowman, W.P., Sandlund, J.T., Kaste, S.C., Ribeiro, R.C., Rubnitz, J.E., Raimondi, S.C., Onciu, M., Coustan-Smith, E., Kun, L.E., Jeha, S., Cheng, C., Howard, S.C., Simmons, V., Bayles, A., Metzger, M.L., Boyett, J.M., Leung, W., Handgretinger, R., Downing, J.R., Evans, W.E. & Relling, M.V. (2009) Treating childhood acute lymphoblastic leukaemia without cranial irradiation. *New England Journal of Medicine*, **360**, 2730–2741.

Relling, M.V., Rubnitz, J.E., Rivera, G.K., Boyett, J.M., Hancock, M.L., Felix, C.A., Kun, L.E., Walter, A.W., Evans, W.E. & Pui, C.H. (1999) High incidence of secondary brain tumours after radiotherapy and antimetabolites. *Lancet*, **354**, 34–39.

Reulen, R.C., Frobisher, C., Winter, D.L., Kelly, J., Lancashire, E.R., Stiller, C.A., Pritchard-Jones, K., Jenkinson, H.C. & Hawkins, M.M. & British Childhood Cancer Survivor Study Steering, G. (2011) Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA*, **305**, 2311–2319.

Schmiegelow, K., Al-Modhwahi, I., Andersen, M.K., Behrendtz, M., Forestier, E., Hasle, H., Heyman, M., Kristinsson, J., Nersting, J., Nygaard, R., Svendsen, A.L., Vettenranta, K., Weinshilboum, R., Nordic Society for Paediatric, H. & Oncology (2009) Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukaemia: results from the NOPHO ALL-92 study. *Blood*, **113**, 6077–6084.

Szczepanski, T., Willemse, M.J., Kamps, W.A., van Wering, E.R., Langerak, A.W. & van Dongen, J.J. (2001) Molecular discrimination between relapsed and secondary acute lymphoblastic leukaemia: proposal for an easy strategy. *Medical and Pediatric Oncology*, **36**, 352–358.

Toyoda, Y., Manabe, A., Tsuchida, M., Hanada, R., Ikuta, K., Okimoto, Y., Ohara, A., Ohkawa, Y., Mori, T., Ishimoto, K., Sato, T., Kaneko, T., Maeda, M., Koike, K., Shitara, T., Hoshi, Y., Hosoya, R., Tsunematsu, Y., Bessho, F., Nakazawa, S. & Saito, T. (2000) Six months of maintenance chemotherapy after intensified treatment for acute lymphoblastic leukaemia of childhood. *Journal of Clinical Oncology*, **18**, 1508–1516.

Tsuchida, M., Ohara, A., Manabe, A., Kumagai, M., Shimada, H., Kikuchi, A., Mori, T., Saito, M., Akiyama, M., Fukushima, T., Koike, K., Shiobara, M., Ogawa, C., Kanazawa, T., Noguchi, Y., Oota, S., Okimoto, Y., Yabe, H., Kajiwara, M., Tomizawa, D., Ko, K., Sugita, K., Kaneko, T., Maeda, M., Inukai, T., Goto, H., Takahashi, H., Isoyama, K., Hayashi, Y., Hosoya, R. & Hanada, R. & Tokyo Children's Cancer Study, G. (2010) Long-term results of Tokyo Children's Cancer Study Group trials for childhood acute lymphoblastic leukaemia, 1984-1999. *Leukaemia*, **24**, 383–396.

Tsunematsu, Y., Kikuchi, K. & Koide, R. (1974) Severe hyponatremia in two cases of childhood acute myeloid leukaemia–syndrome of inappropriate secretion of antidiuretic hormone secondary to vincristine therapy (author's transl). *Rinsho Ketsueki*, **15**, 1149–1155.

Zuna, J., Cave, H., Eckert, C., Szczepanski, T., Meyer, C., Mejstrikova, E., Fronkova, E., Muzikova, K., Clappier, E., Mendelova, D., Boutard, P., Schrauder, A., Sterba, J., Marschalek, R., van Dongen, J.J., Hrusak, O., Stary, J. & Trka, J. (2007) Childhood secondary ALL after ALL treatment. *Leukaemia*, **21**, 1431–1435.

VOLUME 31 · NUMBER 19 · JULY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Second Malignant Neoplasms After Treatment of Childhood Acute Lymphoblastic Leukemia

Kjeld Schmiegelow, Mette Frandsen Levinsen, Andishe Attarbaschi, Andre Baruchel, Meenakshi Devidas, Gabriele Escherich, Brenda Gibson, Christiane Heydrich, Keizo Horibe, Yasushi Ishida, Der-Cherng Liang, Franco Locatelli, Gérard Michel, Rob Pieters, Caroline Piette, Ching-Hon Pui, Susana Raimondi, Lewis Silverman, Martin Stanulla, Batia Stark, Naomi Winick, and Maria Grazia Valsecchi

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on May 20, 2013.

Supported by Grant No. IG 5017 from the Associazione Italiana per la Ricerca sul Cancro (M.G.V.); St Anna Kinderkrebsforschung; Deutsche Krebshilfe; Fördergemeinschaft Kinderkrebszentrum Hamburg; Grants No. CA098543 and U10 CA98413 from the Children's Oncology Group; Grant No. 5 P01CA068484 from the National Cancer Institute; The European Organisation for Research and Treatment of Cancer Charitable Trust and the Schröder Foundation; Direction Recherche Clinique-Assistance Publique-Hôpitaux de Paris; Centre de Recherche en Oncologie, Hematologie et Pediatrie Association; Israel Cancer Association; Hayim Association for Children with Cancer in Israel; Ministry of Health, Labour and Welfare of Japan; Children's Cancer Association of Japan; Grant No. R40-A2154 from the Danish Cancer Society; Danish Childhood Cancer Foundation; Swedish Childhood Cancer Foundation; Grant No. CA-21765 from the National Institutes of Health; American Lebanese Syrian Associated Charities; Childhood Cancer Foundation Taiwan; and the Medical Research Council (UK).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Kjeld Schmiegelow, MD, Department of Paediatric and Adolescent Medicine, University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark; e-mail: kschmiegelow@rh.dk.

0732-183X/13/3119w-2469w/$20.00

DOI: 10.1200/JCO.2012.47.0500

ABSTRACT

Purpose
Second malignant neoplasms (SMNs) after diagnosis of childhood acute lymphoblastic leukemia (ALL) are rare events.

Patients and Methods
We analyzed data on risk factors and outcomes of 642 children with SMNs occurring after treatment for ALL from 18 collaborative study groups between 1980 and 2007.

Results
Acute myeloid leukemia (AML; n = 186), myelodysplastic syndrome (MDS; n = 69), and nonmeningioma brain tumor (n = 116) were the most common types of SMNs and had the poorest outcome (5-year survival rate, 18.1% ± 2.9%, 31.1% ± 6.2%, and 18.3% ± 3.8%, respectively). Five-year survival estimates for AML were 11.2% ± 2.9% for 125 patients diagnosed before 2000 and 34.1% ± 6.3% for 61 patients diagnosed after 2000 ($P < .001$); 5-year survival estimates for MDS were 17.1% ± 6.4% (n = 36) and 48.2% ± 10.6% (n = 33; $P = .005$). Allogeneic stem-cell transplantation failed to improve outcome of secondary myeloid malignancies after adjusting for waiting time to transplantation. Five-year survival rates were above 90% for patients with meningioma, Hodgkin lymphoma, thyroid carcinoma, basal cell carcinoma, and parotid gland tumor, and 68.5% ± 6.4% for those with non-Hodgkin lymphoma. Eighty-nine percent of patients with brain tumors had received cranial irradiation. Solid tumors were associated with cyclophosphamide exposure, and myeloid malignancy was associated with topoisomerase II inhibitors and starting doses of methotrexate of at least 25 mg/m^2 per week and mercaptopurine of at least 75 mg/m^2 per day. Myeloid malignancies with monosomy 7/5q− were associated with high hyperdiploid ALL karyotypes, whereas 11q23/*MLL*-rearranged AML or MDS was associated with ALL harboring translocations of t(9;22), t(4;11), t(1;19), and t(12;21) ($P = .03$).

Conclusion
SMNs, except for brain tumors, AML, and MDS, have outcomes similar to their primary counterparts.

J Clin Oncol 31:2469-2476. © 2013 by American Society of Clinical Oncology

INTRODUCTION

As many as one third of all deaths in childhood acute lymphoblastic leukemia (ALL) are caused by toxicities or second malignant neoplasms (SMNs).[1-4] Previously reported cumulative incidences of SMNs have varied from less than 1% to 10% or more because of differences in antileukemic therapy and in duration, accuracy, and completeness of follow-up.[1,2,5-18] Partly because of their rarity, little is known about the etiology of SMNs or about the treatment options that offer the best chances of cure.[1]

With the goal of improving overall survival in childhood ALL and providing guidelines for treatment, the international Ponte di Legno consortium of ALL study groups has studied uncommon subgroups of childhood ALL.[19-23] This is the largest study of SMNs after therapy for childhood ALL reported to date, and it presents new potential risk factors and provides survival rates for distinct subsets.

PATIENTS AND METHODS

Review of Patient Data

In the February 2010 issue of *Leukemia*, 16 cooperative study groups from Europe, North America, and Asia reported clinical outcomes, including the occurrence of

SMNs, of 54,068 children and adolescents up to 21 years of age with newly diagnosed ALL enrolled onto controlled clinical trials between 1980 and 2007.[5-17,24-26] From these 16 groups as well as from FRALLE (French Acute Lymphoblastic Leukaemia Study Group) and the childhood leukemia branch of the European Organisation for Research and Treatment of Cancer (EORTC), we collected data on individuals with SMNs to form a common database with predefined variables comprising clinical and biologic data (including cytogenetic characteristics for myeloid neoplasias) as well as outcomes (Appendix Table A1, online only). Furthermore, we recorded clinical and biologic characteristics of their primary ALL as well as treatment given and status at latest follow-up. The data available for this study were retrieved from the groups' central ALL databases. If patient data on drug doses were unavailable, the patients were assigned the drugs and doses listed in the ALL protocols onto which they were enrolled. Accrual of data for patients with ALL who did not develop SMNs was not part of the study. The study was approved according to regional institutional review board requirements. All data were compiled at Rigshospitalet (Copenhagen, Denmark), and the database was approved by the Danish Data Protection Authorities.

Statistical Analysis

Differences in distribution of individual parameters among subsets were analyzed by using nonparametric tests.[27] Since accrual of data for patients with ALL who did not develop SMNs was not part of this study, odds ratios for SMNs in relation to specific exposures are not included. Instead, we analyzed patterns of ALL characteristics and therapy by subsets of SMNs to determine whether certain ALL subtypes or drug exposures were more prevalent within specific subsets of SMNs. Survival after an SMN was defined as time from diagnosis of the SMN to death as a result of any cause or to last follow-up. The Kaplan-Meier method was used to estimate survival rates with SEs calculated according to Greenwood.[28] Differences in survival rates were compared with the log-rank test.[29] The Cox proportional hazard model was used for selected analysis of survival after SMNs.[30] Two-sided *P* values below .05 were regarded as significant.

RESULTS

In all, 659 patients diagnosed with ALL between 1980 and 2007 were registered with a malignant neoplasm or a CNS tumor as the first event after diagnosis of ALL. Seventeen SMNs reported as ALL (n = 12), acute undifferentiated leukemia (n = 2), or myeloid malignancies with monosomy 7 (n = 1) or t(9;22)(q34;q11.2) (n = 2) at diagnosis of both ALL and the subsequent SMNs were excluded because the clonal relationship to the original leukemia could not be confidently verified, leaving a total of 642 study patients.

Table 1 reports clinical information on the 642 SMNs by subtype. The interval between diagnosis of ALL and occurrence of SMNs was significantly associated with the subtype of SMN, being shortest for hematologic malignancies and longest for carcinomas and meningiomas ($P < .001$; Fig 1 and Table 1). Thus, among the 48 SMNs diagnosed more than 15 years from the diagnosis of ALL, 35% were meningiomas (n = 15) or other CNS tumors (n = 2); 31% were non–skin carcinomas (n = 15), including six thyroid cancers; 15% were melanomas (n = 4) or other skin cancers (n = 3); and 17% were hematologic malignancies (n = 5); sarcomas (n = 2); or testicular cancer (n = 2). Eight patients with cancer-predisposing diseases are described in Appendix Table A2 (online only).

Patterns of SMNs by ALL-Presenting Features

Although distribution of sex, age, and WBC count at diagnosis of ALL varied significantly among the major categories of SMNs for the entire cohort (Table 1), this was not the case for the subset of 201 patients who were not irradiated and did not undergo hematopoietic stem-cell transplantation during first-line ALL treatment ($P > .45$ for all analyses; Appendix Table A3, online only).

Immunophenotype

Of the 186 patients with AML and 69 patients with myelodysplastic syndrome (MDS), the ALL lineage (B-cell precursor or T-cell lineage) was available for 217 patients. When analyzing only the 192 patients who did not receive irradiation and did not receive transplantation but who did have ALL immunophenotype available, the prevalence of T-cell ALL did not differ significantly among the categories of hematologic malignancies, CNS tumors, carcinomas, and other tumors (7.8%, 10.0%, and 16.7%, respectively; $P = .38$), but 26.6% of all patients with AML (42 of 158) and 8.5% of all patients with MDS (five of 59) initially had T-cell ALL. Patients with AML were overall more likely than those with other hematologic malignancies (n = 136) to have had T-cell ALL (26.6% *v* 13.2%; $P = .005$) with the same trend (10.0% *v* 5.6%; $P = .33$) in the subsets of patients who did not receive irradiation and did not receive transplantation. The interval between diagnosis of ALL and SMN was significantly shorter for the 11 patients who did not receive irradiation and did not receive transplantation but who had T-cell ALL than for the 130 patients with B-cell precursor ALL who had developed hematologic malignancies (median, 1.6 *v* 3.0 years; $P = .001$). Finally, 91% (10 of 11) of the patients who developed Langerhans cell histiocytosis had T-cell ALL compared with 20.4% among the other SMNs ($P < .001$).

Karyotype and Therapy-Related Myeloid Neoplasias

The time to develop AML was shorter than the time to develop MDS (median, 2.7 *v* 3.3 years; $P = .01$), reflecting a higher proportion of 11q23/*MLL* rearrangements with short latency (median, 2.5 years) in patients with AML (58% *v* 5% of patients with MDS with an aberrant karyotype; $P < .001$). By contrast, treatment-related myeloid neoplasia (t-MN; ie, AML or MDS) with monosomy 7 (median interval, 3.7 years) occurred in 22% of patients with AML and in 50% of patients with MDS with an aberrant karyotype ($P = .002$).

Among the 44 patients with t-MN with monosomy 7, 5q−, or 11q23/*MLL* rearrangements (one t-MN with both monosomy 7 and 11q23/*MLL* rearrangements was excluded) and an available karyotype for the ALL clone, the cytogenetic aberrations of their ALL and t-MN were highly correlated. Thus, among the 25 patients who developed 11q23/*MLL*-rearranged t-MN, 13 had ALL with classical recurrent translocations—t(9;22)(q34;q11.2) (n = 1), t(1;19)(q23;p13.3) (n = 2), t(12;21)(p13;q22) (n = 8), or 11q23/*MLL* rearrangements (n = 2 [different 11q23/*MLL* rearrangement in the two clones]—and six had a high hyperdiploid ALL karyotype (modal chromosome number above 50), and six had other structural and/or numeric aberrations. In contrast, among the 19 patients who developed t-MN with 5q− or monosomy 7, 10 had a high hyperdiploid ALL karyotype, three had ALL clones with one of the above-listed classical translocations, and six had other aberrations ($P = .03$ by likelihood-ratio χ^2 test).

Patterns of SMNs by ALL Therapy

The pattern of SMNs was significantly influenced by the preceding ALL therapy (Table 2). The 12 patients with CNS tumors who had not received CNS irradiation were diagnosed at significantly shorter intervals after ALL than the 97 patients with CNS tumors that occurred after CNS irradiation (median, 6.6 *v* 9.1 years; $P = .01$).

Table 1. Clinical Characteristics and 5-Year Overall Survival of 642 Patients With SMNs by Major Categories and Subtype

Type of SMN	Total		Males		ALL Immunophenotype* (n = 555)		Age at ALL (years)		WBC at ALL ($\times 10^9$/L)		Interval to SMN (years)		Age at SMN (years)		5-Year Survival Rate After SMN (%)
	No.	%	No.	%	BCP	%	Median	50% Range	Median	50% Range	Median	50% Range	Median	50% Range	
Total	642		346	53.9	434	78.2	5.2	3.2-10.3	11.4	4.7-45.0	4.8	2.6-8.9	12.6	7.8-17.5	40.4 ± 2.1†
Hematologic	345	53.7	198	57.4	234	79.6	5.2	3.2-11.2	9.0	4.2-37.0	2.9	2.0-4.5	9.4	6.5-15.2	35.2 ± 2.7
Acute myeloid leukemia	186		106	57.0	116	73.4	5.6	3.3-11.2	11.6	4.2-45.0	2.7	1.8-4.5	9.5	6.4-15.0	18.1 ± 2.9
Myelodysplastic syndrome	69		32	46.4	54	91.5	5.2	3.1-12.2	6.0	3.8-12.7	3.3	2.6-4.6	9.7	6.9-15.9	31.1 ± 6.2
Chronic myeloid leukemia	9		4	44.4	7	100.0	12.5	4.2-15.1	9	4.0-28.5	4.1	3.5-7.2	18.0	17.4-19.3	62.2 ± 17.8
Non–Hodgkin lymphomas	56		39	69.6	39	83.0	4.7	3.0-8.6	11.2	4.3-31.8	2.3	1.5-4.0	7.8	5.5-12.1	68.5 ± 6.4
Hodgkin disease	25		17	68.0	18	78.3	4.2	3.0-9.2	7.4	5.0-45.0	4.1	2.6-5.3	10.2	6.9-14.9	91.1 ± 6.0
CNS tumor	138	21.5	67	48.6	94	78.3	4.2	2.6-8.7	15.7	6.1-59.0	8.6	6.8-11.2	14.7	11.0-19.2	25.9 ± 4.2
Nonmeningioma CNS tumor	116		53	45.7	79	77.5	4.4	2.7-8.7	18.7	6.9-82.8	8.1	6.5-9.8	13.9	10.5-16.5	18.3 ± 3.8
Meningioma	22		14	63.6	15	83.3	3.5	2.3-8.5	9	5.1-30.0	16.2	12.3-18.3	21.7	17.8-25.4	90.9 ± 8.7
Carcinoma	78	12.1	34	43.6	62	84.9	5.8	3.3-10.6	12.3	4.0-45.6	10.1	6.7-14.5	17.5	12.4-22.2	82.2 ± 4.9
Nonthyroid carcinoma	46		19	41.3	35	81.4	8.4	3.9-13.0	12.9	3.6-38.5	10.2	6.1-15.0	18.0	12.4-25.8	67.3 ± 8.2
Thyroid carcinoma	32		15	46.9	27	90.0	5.0	3.1-6.5	12.1	4.3-58.5	10.1	7.8-13.5	15.5	12.1-18.3	100
Other	81	12.6	47	58.0	44	64.7	5.7	4.0-10.4	14.0	4.9-79.9	6.8	3.4-10.0	14.1	8.2-17.9	55.3 ± 6.1
Soft tissue sarcoma	29		14	48.3	14	60.9	6.0	4.1-10.4	19.8	7.3-66.0	5.4	3.3-9.6	13.3	8.0-17.2	43.9 ± 9.7
Bone tumor	22		13	59.1	14	77.8	5.3	2.9-8.1	7.0	3.1-30.9	7.8	5.2-11.4	14.4	11.9-17.9	61.9 ± 11.6
Melanoma	11		6	54.6	9	90.0	10.0	5.7-13.9	10.0	4.7-30.9	10.0	6.3-17.8	19.2	16.7-24.3	85.7 ± 13.2
Germ cell tumor	4		4	100.0	3	100.0	12.7	8.1-15.2	7.8	2.6-13.2	12.3	8.4-19.8	22.9	20.2-31.4	100
Histiocytosis	12		9	75.0	2	16.7	4.2	2.5-5.5	141.0	40.4-248.5	2.3	1.4-3.9	6.9	6.0-8.2	48.6 ± 14.8
Other	3		1	33.3	2	100.0	9.9	4.1-12.3	4.0	2.2-148.0	7.6	3.3-9.8	15.5	13.9-17.5	33.3 ± 27.2

Abbreviations: ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; SMN, second malignant neoplasm.
*In all, 87 patients were excluded because immunophenotype was not reported (n = 75) or was not specified as either BCP or T-cell ALL (n = 12).
†Ten-year survival rate was 38.7% ± 2.2%.

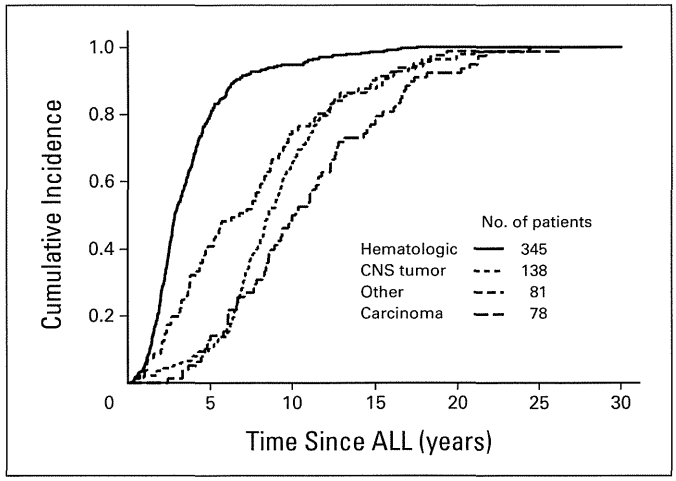

Fig 1. Kaplan-Meier estimates of the interval between diagnosis of acute lymphoblastic leukemia (ALL) and development of the four major categories of second malignant neoplasms.

Thirty-eight (76.0%) of 50 patients with t-MN with an aberrant karyotype and previous exposure to epipodophyllotoxins had 11q23/*MLL* rearrangements, whereas only four (8.0%) had monosomy 7 and none had 5q–. In contrast, among the 46 patients with t-MN (52.2%) who had not been exposed to epipodophyllotoxins, 24 developed monosomy 7 (n = 20) or 5q– (n = 4) t-MN, and only 13 (28.3%) had 11q23/*MLL* rearrangements ($P < .001$).

Among patients who did not receive irradiation, 44 (79%) of 56 patients with solid tumors had previously received cyclophosphamide compared with 82 (57%) of 143 patients with hematologic malignancies or CNS tumors ($P = .005$).

Among the patients who did not receive transplantation for whom data on maintenance therapy methotrexate (n = 431) and mercaptopurine dosage (n = 422) were available, the patients who developed t-MN received higher starting doses of methotrexate and mercaptopurine than did patients who developed other SMNs ($P < .001$ for both drugs), and this was the case for both CNS patients who received irradiation ($P < .001$ and $P = .001$, respectively) and those who did not ($P = .007$ and $P = .02$, respectively). Thus, compared with patients with other SMNs, the patients who developed t-MNs were more likely to have received methotrexate starting doses of at least 25 mg/m^2 per week (45% *v* 28%; $P < .001$) and mercaptopurine starting doses of at least 75 mg/m^2 per day (52% *v* 29%; $P < .001$).

Neither the distribution of the four major categories of SMNs ($P = .37$) nor the time interval to SMN ($P = .84$) differed significantly between patients with low (n = 13; 10 by genotype and three by phenotype) versus normal (n = 114) thiopurine methyltransferase activity. Among the 413 patients who did not undergo transplantation but who did have data on the total duration of therapy, 65 (31.3%) of the 208 patients with t-MN and 36 (17.6%) of the 205 patients with solid tumors had received ALL therapy for 2.5 years or longer ($P = .001$).

Transplantation during first remission of ALL had been performed in 29 (5.7%) of the 510 ALL patients with available information. One (1.4%) of 74 patients with CNS tumors and seven (3.6%) of 193 patients with t-MN had received transplantation compared with nine (28.1%) of 32 patients with carcinomas and eight (15.4%) of 52 with other SMNs ($P < .001$).

Survival After SMNs

The median follow-up after diagnosis of an SMN was 4.9 years for the 292 patients who were alive at their latest follow-up. In all, 350 patients died within 20.6 years from diagnosis of an SMN (median, 0.75 years; 25th to 75th percentile: 0.4 to 1.4). The overall cumulative probability of death as a result of any cause was 59.6% ± 2.1% at 5 years and 61.3% ± 2.2% at 10 years after an SMN (Table 1 and Fig 2). The 10-year cumulative incidence of death as a result of the second (n = 236) or third (n = 1) cancer was 41.1% ± 2.1%; it was 5.6% ± 1.0% for relapsed ALL (n = 31), 10.4% ± 1.3% for treatment-related toxicities among patients who received a transplantation (n = 39) and those who did not (n = 20), and 4.2% ± 0.9% for unknown causes (n = 23; Fig 3). The 10-year probability of survival was 18.9% ± 6.9% (n = 33) for patients whose SMN occurred before 1990 (n = 54), 34.8% ± 2.8% (n = 296) for patients with SMNs diagnosed between 1990 and 1999, and 40.9% ± 6.3% (n = 313) for patients diagnosed from 2000 onward ($P < .001$).

Hematologic Malignancies

Survival remained consistently lower for patients with AML compared with those who had MDS ($P < .001$). The 5-year survival estimate for AML was 11.2% ± 2.9% for 125 patients diagnosed before 2000 and 34.1% ± 6.3% for 61 patients diagnosed after 2000 ($P < .001$). For MDS, the 5-year survival was 17.1% ± 6.4% for 36 patients diagnosed before 2000 and 48.2% ± 10.6% for 33 patients diagnosed after 2000 ($P = .005$). In a Cox regression model, adjusting for sex and age at diagnosis of SMNs and the use of CNS irradiation for ALL treatment, the improved outcome after 2000 was confirmed for both AML (estimated hazard ratio [HR], 0.62; 95% CI, 0.42 to 0.90; $P = .01$) and MDS (HR, 0.30; 95% CI, 0.15 to 0.60; $P < .001$). The hazard of death after t-MN decreased by approximately 10% for every additional year of interval between ALL and AML (HR, 0.88; 95% CI, 0.80 to 0.96; $P = .004$) with a similar trend for MDS (HR, 0.92; 95% CI, 0.80 to 1.06; $P = .23$).

For 185 patients with available information on transplantation after t-MN, the 5-year survival was 30.3% ± 4.4% for the 119 patients who received a transplantation and 11.4% ± 4.0% for the 66 who did not ($P < .001$). However, with a landmark at the median waiting time to transplantation of 4.1 months from SMN diagnosis, the 5-year survival estimates for patients who had received a transplantation and those who had not did not differ (26.7% ± 4.2% and 27.2% ± 7.7%, respectively),[28,31] and this was also the case for 78 patients with t-MN diagnosed in 2000 or later (42.0% ± 7.6% *v* 46.9% ± 11.5%). Among the patients with t-MN who received a transplantation, the 10-year survival for 30 patients with 11q23/*MLL* rearrangements (24.7% ± 8.3%) did not differ significantly from that of 26 patients with monosomy 7 (28.0% ± 9.0%).

Only two of the 25 patients with Hodgkin lymphoma died, both of whom were diagnosed with Hodgkin lymphoma in the 1980s. Excluding patients who received transplantation as part of their ALL therapy, the 5-year survival was 70.5% ± 7.9% for the 34 patients with non-Hodgkin lymphoma diagnosed in the 1990s and 65.4% ± 10.8% for the 22 patients diagnosed later ($P = .64$). The 5-year survival was 76.9% ± 8.3% for the 27 patients who had developed mature B-cell non-Hodgkin lymphoma.

Table 2. Pattern of SMNs in Relation to Their First-Line ALL Treatment in Patients Who Did Not Receive Hematopoietic Stem-Cell Transplantation

					Cyclophosphamide*				6-Mercaptopurine†			
	CNS Irradiation* (n = 432)		Epipodophyllotoxin* (n = 446)		CNS Irradiation (n = 228)		No CNS Irradiation (n = 199)		CNS Irradiation (n = 230)		No CNS Irradiation (n = 192)	
Type of Second Cancer	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Total	230	202	185	261	186	42	126	73	53	177	94	98
Hematologic SMN	79	145	105	127	67	11	82	61	25	50	76	61
t-MN was AML or MDS	64	109	84	96	54	9	60	47	22	38	61	43
CNS tumors	97	12	48	63	76	20	7	5	24	68	5	7
Non-CNS solid tumors	54	45	32	79	43	11	37	7	4	49	13	30

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; SMN, second malignant neoplasm; t-MN, therapy-related myeloid neoplasia.
*Only patients who did not receive transplantation who had available information on their therapy are included.
†Dose ≥ 75 mg/m^2.

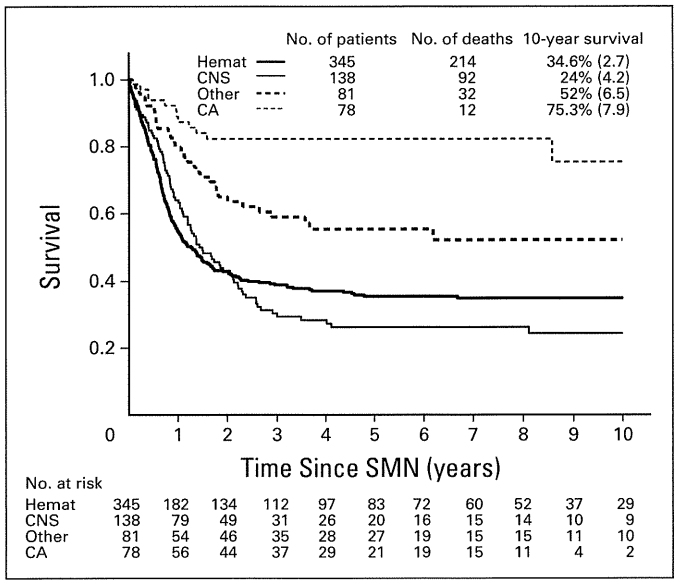

Fig 2. Survival curves according to the four major categories of second malignant neoplasms (SMNs). Hemat, hematologic; CA, carcinoma.

CNS Tumors

Although only one of 22 patients with meningioma died, the 5-year survival was very poor for the remaining 116 patients with brain tumors (18.3% ± 3.8%), including eight patients with low-grade tumors (45.0% ± 18.8%), 76 with high-grade tumors including medulloblastomas and supratentorial primitive neuroectodermal tumors (6.5% ± 3.6%), and 13 unspecified glial tumors (8.5% ± 8.2%). Overall survival after nonmeningioma brain tumor did not improve over time, with 5-year estimates of 19.6% ± 5.5% before 2000 and 16.6% ± 5.3% afterward ($P = .76$).

Nonthyroid Carcinomas

All seven patients with basal cell carcinoma and nine with parotid gland tumors survived, and the 5-year survival for the nine patients with squamous cell carcinoma was 71.4% ± 17.1%. In contrast, the overall survival for the 18 patients with other carcinomas (five, breast; four, gastrointestinal; three, liver; and one each, peritoneal, pancreas, lung, cervix uteri, urinary tract, and nasopharyngeal) was only 40.1% ± 13.7% at 5 years and 0% at 10 years ($P < .001$).

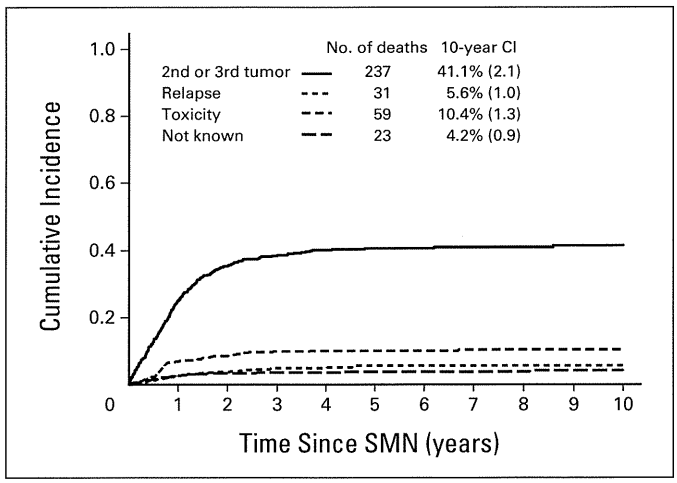

Fig 3. Cause-specific cumulative incidences (CIs) of death after development of a second malignant neoplasm (SMN).

DISCUSSION

In this study, the largest reported to date, patients with t-MN or nonmeningioma brain tumor had a poor prognosis, whereas patients with secondary meningioma, Hodgkin lymphoma, thyroid carcinoma, basal cell carcinoma, and parotid gland carcinoma had a 5-year survival exceeding 90%.

This study had some limitations since it did not allow calculations of HRs by ALL characteristics or therapy components, and it could not identify exposures that had equal influence on the risk of all major categories of SMNs. In addition, the data must be interpreted cautiously, since the completeness of recording of SMNs was influenced by the individual study groups' frequency and duration of follow-up,[1] screening strategies for thyroid carcinomas, meningiomas, or breast cancer in irradiated patients,[32-34] and linkage with population-based nationwide cancer registries.[18] The impact of such differences will be limited for secondary hematologic malignancies but will be more profound for SMNs that have long latency such as carcinomas and meningiomas. Furthermore, hematologic SMNs can be misinterpreted as relapse of ALL, and some cases of ALL and SMNs may have a common clonal origin.[35,36] Thus, an association between T-cell ALL and histiocytosis has previously been reported,[35,36] and patients with early T-cell precursor ALL have been shown to have genetic profiles similar to those of patients with myeloid malignancies,[37] which could indicate a common ancestral clone for the primary and second malignancies.

The observed association between high-hyperdiploid ALL and the development of t-MN with monosomy 7/5q– has been observed in a much smaller study,[2] although the association between ALL with specific chromosomal translocations (ie, t(9;22)(q34;q11.2), t(1;19)(q23;p13.3), t(12;21)(p13;q22)) and t-MN with 11q23/*MLL* rearrangements has hitherto not been reported. The more frequent use of topoisomerase II inhibitors such as epipodophyllotoxins in high-risk ALL cases with specific chromosomal translocation might have contributed to the development of t-MN with 11q23/*MLL* rearrangements. However, the unique gene expression profiles of ALL blast from those patients who subsequently developed SMNs, including t-MN, could also reflect inherited genetic variants[38] that could influence drug disposition (eg, glutathione S-transferases, cytochrome P-450 enzymes, quinone oxidoreductase, or the folate pathway[39,40]) or be related to cancer predisposition syndromes. International collaboration with extensive mapping of host genomic variants could be instrumental in identifying subsets of patients with ALL with genetic predispositions for whom modification of first-line ALL therapy or individualized follow-up should be offered.

This study supports previously reported associations of t-MN with higher mercaptopurine dosages during maintenance therapy and longer duration of therapy. Some study groups that offer a maintenance therapy mercaptopurine starting dose of 75 mg/m^2 have found an association between an increased risk of SMN and low-activity thiopurine methyltransferase genotypes or phenotypes.[2,41] Notably, others who used a mercaptopurine starting dose of only 50 mg/m^2 failed to find such an association.[42] The linkage between thiopurine

therapy and risk of SMN may reflect that these anticancer agents, when given at high dosage or for an extended period, may interfere with DNA repair rather than directly induce mutations.[41,43] Accordingly, the omission or interruption of maintenance therapy for patients who received a transplantation as part of their ALL therapy may explain why very few patients with brain tumor or t-MN in this cohort had received transplantation. Overall, the risk of relapse if mercaptopurine/methotrexate-based maintenance therapy is truncated[44] is far higher than the risk of t-MN indicated by this and previous studies. The goal for future research is thus to identify patients with a clearly excessive risk of t-MN and consider treatment modification only for such a limited patient subset.

Patients with t-MN have had significant improvements in survival over the last few decades, but the cure rates are still below those obtained by the best treatment protocols for primary AML.[45] Although the survival of patients with t-MN who did not receive transplantation was only 11.4% ± 4.0%, the study did not support that hematopoietic stem-cell transplantation would be beneficial for these patients when the data were adjusted for the waiting time to transplantation. Thus, future studies of this important issue, including the impact of t-MN cytogenetics, are needed.

It is uncertain whether the extremely poor survival rate for CNS tumors, the vast majority of which developed after CNS irradiation, reflects a more aggressive biology, difficulties in performing complete tumor resection in previously irradiated regions, limitations in irradiating previously irradiated regions, or a pessimistic attitude toward curative therapy for such patients. Because this subset is the second most common SMN among survivors of childhood ALL and is overall one of the most common SMNs after a childhood cancer,[18] a review of patients' records of these tumors is needed to explore these issues in depth.

Although the cure rates for some SMNs were as favorable as those obtained for their primary cancer counterparts, future strategies should continue to focus on prevention of SMNs. Thus, the frequency of secondary brain tumor is expected to fall dramatically during the coming decades with the reduced use of CNS irradiation in first-line ALL therapy,[46] and given the few patients on contemporary protocols who are exposed to epipodophyllotoxins, the risk of 11q23/*MLL*-rearranged t-MN is likely to be lower in future childhood ALL cohorts.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Kjeld Schmiegelow, Maria Grazia Valsecchi
Collection and assembly of data: Kjeld Schmiegelow, Mette Frandsen Levinsen, Andishe Attarbaschi, Andre Baruchel, Mini Devidas, Gabriele Escherich, Brenda Gibson, Christiane Heydrich, Keizo Horibe, Yasushi Ishida, Der-Cherng Liang, Franco Locatelli, Gérard Michel, Rob Pieters, Caroline Piette, Ching-Hon Pui, Susana Raimondi, Lewis Silverman, Martin Stanulla, Batia Stark, Naomi Winick, Maria Grazia Valsecchi
Data analysis and interpretation: Kjeld Schmiegelow, Maria Grazia Valsecchi
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Hijiya N, Hudson MM, Lensing S, et al: Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. JAMA 297:1207-1215, 2007
2. Schmiegelow K, Al-Modhwahi I, Andersen MK, et al: Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia: Results from the NOPHO ALL-92 study. Blood 113:6077-6084, 2009
3. Prucker C, Attarbaschi A, Peters C, et al: Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: A population-based analysis of the Austrian Berlin-Frankfurt-Münster study group. Leukemia 23:1264-1269, 2009
4. Lund B, Åsberg A, Heyman M, et al: Risk factors for treatment related mortality in childhood acute lymphoblastic leukaemia. Pediatr Blood Cancer 56:551-559, 2011
5. Schmiegelow K, Forestier E, Hellebostad M, et al: Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. Leukemia 24:345-354, 2010
6. Kamps WA, van der Pal-de Bruin KM, Veerman AJ, et al: Long-term results of Dutch Childhood Oncology Group studies for children with acute lymphoblastic leukemia from 1984 to 2004. Leukemia 24:309-319, 2010
7. Pui CH, Pei D, Sandlund JT, et al: Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. Leukemia 24:371-382, 2010
8. Tsuchida M, Ohara A, Manabe A, et al: Long-term results of Tokyo Children's Cancer Study Group trials for childhood acute lymphoblastic leukemia, 1984-1999. Leukemia 24:383-396, 2010
9. Tsurusawa M, Shimomura Y, Asami K, et al: Long-term results of the Japanese Childhood Cancer and Leukemia Study Group studies 811, 841, 874 and 911 on childhood acute lymphoblastic leukemia. Leukemia 24:335-344, 2010
10. Silverman LB, Stevenson KE, O'Brien JE, et al: Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985-2000). Leukemia 24:320-334, 2010
11. Conter V, Aricò M, Basso G, et al: Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. Leukemia 24:255-264, 2010
12. Stary J, Jabali Y, Trka J, et al: Long-term results of treatment of childhood acute lymphoblastic leukemia in the Czech Republic. Leukemia 24: 425-428, 2010
13. Gaynon PS, Angiolillo AL, Carroll WL, et al: Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: A Children's Oncology Group Report. Leukemia 24:285-297, 2010
14. Salzer WL, Devidas M, Carroll WL, et al: Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984-2001: A report from the Children's Oncology Group. Leukemia 24:355-370, 2010
15. Möricke A, Zimmermann M, Reiter A, et al: Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia 24:265-284, 2010
16. Escherich G, Horstmann MA, Zimmermann M, et al: Cooperative study group for childhood acute lymphoblastic leukaemia (COALL): Long-term results of trials 82, 85, 89, 92 and 97. Leukemia 24:298-308, 2010
17. Mitchell C, Richards S, Harrison CJ, et al: Long-term follow-up of the United Kingdom Medical Research Council protocols for childhood acute lymphoblastic leukaemia, 1980-2001. Leukemia 24:406-418, 2010
18. Olsen JH, Möller T, Anderson H, et al: Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 101:806-813, 2009
19. Aricò M, Valsecchi MG, Camitta B, et al: Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med 342:998-1006, 2000
20. Pui CH, Gaynon PS, Boyett JM, et al: Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. Lancet 359:1909-1915, 2002
21. Nachman JB, Heerema NA, Sather H, et al: Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. Blood 110:1112-1115, 2007
22. Aricò M, Schrappe M, Hunger SP, et al: Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic

leukemia treated between 1995 and 2005. J Clin Oncol 28:4755-4761, 2010

23. Schrappe M, Hunger SP, Pui CH, et al: Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med 366:1371-1381, 2012

24. Liang DC, Yang CP, Lin DT, et al: Long-term results of Taiwan Pediatric Oncology Group studies 1997 and 2002 for childhood acute lymphoblastic leukemia. Leukemia 24:397-405, 2010

25. Stark B, Nirel R, Avrahami G, et al: Long-term results of the Israeli National Studies in childhood acute lymphoblastic leukemia: INS 84, 89 and 98. Leukemia 24:419-424, 2010

26. Schrappe M, Nachman J, Hunger S, et al: 'Educational symposium on long-term results of large prospective clinical trials for childhood acute lymphoblastic leukemia (1985-2000)'. Leukemia 24: 253-254, 2010

27. Glantz SA: Primer of Biostatistics (ed 6). New York, NY, McGraw-Hill Medical Publications, 2005

28. Marubini E, Valsecchi MG: Analysing Survival Data From Clinical Trials and Observational Studies. West Sussex, United Kingdom, John Wiley and Sons, 2004

29. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

30. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

31. Simon R, Makuch RW: A non-parametric graphical representation of the relationship between survival and the occurrence of an event: Application to responder versus non-responder bias. Stat Med 3:35-44, 1984

32. Giovanella L, Toffalori E, Tozzoli R, et al: Multiplexed immunoassay of thyroglobulin autoantibodies in patients with differentiated thyroid carcinoma. Head Neck 34:1369-1371, 2012

33. Goshen Y, Stark B, Kornreich L, et al: High incidence of meningioma in cranial irradiated survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 49:294-297, 2007

34. Nathan PC, Ness KK, Mahoney MC, et al: Screening and surveillance for second malignant neoplasms in adult survivors of childhood cancer: A report from the childhood cancer survivor study. Ann Intern Med 153:442-451, 2010

35. Trebo MM, Attarbaschi A, Mann G, et al: Histiocytosis following T-acute lymphoblastic leukemia: A BFM study. Leuk Lymphoma 46:1735-1741, 2005

36. Szczepanski T, van der Velden VH, Waanders E, et al: Late recurrence of childhood T-cell acute lymphoblastic leukemia frequently represents a second leukemia rather than a relapse: First evidence for genetic predisposition. J Clin Oncol 29:1643-1649, 2011

37. Zhang J, Ding L, Holmfeldt L, et al: The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 481:157-163, 2012

38. Hartford C, Yang W, Cheng C, et al: Genome scan implicates adhesion biological pathways in secondary leukemia. Leukemia 21:2128-2136, 2007

39. Bolufer P, Collado M, Barragan E, et al: Profile of polymorphisms of drug-metabolising enzymes and the risk of therapy-related leukaemia. Br J Haematol 136:590-596, 2007

40. Stanulla M, Dynybil C, Bartels DB, et al: The NQO1 C609T polymorphism is associated with risk of secondary malignant neoplasms after treatment for childhood acute lymphoblastic leukemia: A matched-pair analysis from the ALL-BFM study group. Haematologica 92:1581-1582, 2007

41. Relling MV, Rubnitz JE, Rivera GK, et al: High incidence of secondary brain tumours after radiotherapy and antimetabolites. Lancet 354:34-39, 1999

42. Stanulla M, Schaeffeler E, Möricke A, et al: Thiopurine methyltransferase genetics is not a major risk factor for secondary malignant neoplasms after treatment of childhood acute lymphoblastic leukemia on Berlin-Frankfurt-Münster protocols. Blood 114:1314-1318, 2009

43. Karran P, Attard N: Thiopurines in current medicalpractice:Molecularmechanismsandcontributions to therapy-related cancer. Nat Rev Cancer 8:24-36, 2008

44. Toyoda Y, Manabe A, Tsuchida M, et al: Six months of maintenance chemotherapy after intensified treatment for acute lymphoblastic leukemia of childhood. J Clin Oncol 18:1508-1516, 2000

45. Kaspers GJ, Creutzig U: Pediatric acute myeloid leukemia: International progress and future directions. Leukemia 19:2025-2029, 2005

46. Pui CH, Campana D, Pei D, et al: Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 360:2730-2741, 2009

Affiliations

Kjeld Schmiegelow and Mette Frandsen Levinsen, Rigshospitalet, Copenhagen, Denmark; Andishe Attarbaschi, St Anna Children's Hospital, Vienna, Austria; Andre Baruchel and Gérard Michel, Hôpital Saint-Louis, Paris, France; Meenakshi Devidas, University of Florida, Gainesville, FL; Gabriele Escherich, University Medical Center Eppendorf, Hamburg-Eppendorf; Christiane Heydrich and Martin Stanulla, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; Brenda Gibson, Royal Hospital for Sick Children, Glasgow, United Kingdom; Keizo Horibe, National Hospital Organization Nagoya Medical Center, Nagoya; Yasushi Ishida, St Luke's International Hospital, Tokyo, Japan; Der-Cherng Liang, Mackay Memorial Hospital, Taipei, Taiwan; Franco Locatelli, Ospedale Bambino Gesù, Rome; Maria Grazia Valsecchi, University of Milano-Bicocca, Monza, Italy; Rob Pieters, Erasmus Medical Center–Sophia Children's Hospital, Rotterdam, the Netherlands; Caroline Piette, le Centre Hospitalier Régional de la Citadelle, Liège, Belgium; Ching-Hon Pui and Susana Raimondi, St Jude Children's Research Hospital, Memphis, TN; Lewis Silverman, Dana-Farber Cancer Institute and Children's Hospital Boston, Boston, MA; Batia Stark, Schneider Children's Medical Center of Israel, Petah-Tikva, Israel; and Naomi Winick, University of Texas Southwestern Medical Center, Dallas, TX.

Acknowledgment

We thank all participating centers, data managers, and local physicians as well as patients and parents. We also thank Hester de Groot, data manager of the Dutch Childhood Oncology Group; Jane O'Brien, Leukemia Program Manager, and Kristen Stevenson, statistician (Dana-Farber Cancer Institute); Yoshifumi Kawano, MD, and Yasuto Shimomura, MD, for data collection (Japanese Pediatric Leukemia/Lymphoma Study Group); and Mats Heyman, Nordic Society of Paediatric Haematology and Oncology leukemia registry manager.

Appendix

Table A1. SMNs Reported by the Seventeen Participating Collaborative Groups

Trial Group Name	Trial Group Acronym	Trial Group Location	No. of Patients	Date of Diagnosis of First SMN	Date of Diagnosis of Last SMN	Trial Registration Numbers
Associazione Italiana Ematologia Oncologia Pediatrica	AIEOP	Italy	22	January 4, 1985	December 11, 2007	ALL-BFM 90, ALL-BFM 95, ALL-BFM 2000 (NCT00430118)
Berlin-Frankfurt-Münster	BFM	Austria	14	September 1, 1992	June 26, 2009	ALL-BFM 86, ALL-BFM 90, ALL-BFM 95, ALL-BFM 2000 (NCT00430118)
Berlin-Frankfurt-Münster	BFM	Germany	107	December 12, 1984	February 1, 2009	ALL-BFM 2000 (NCT00430118), NCI Protocol ID 68529
Cooperative Study Group for Childhood Acute Lymphoblastic Leukaemia	COALL	Germany	36	May 10, 1984	July 19, 2007	COALL 07-03, EU-205104, NCT00343369
Children's Oncology Group (includes both the US Children's Cancer Group and the Pediatric Oncology Group)	COG	USA	136	April 4, 1990	February 12, 2008	Separate list of POG and CCG protocols
Dutch Childhood Oncology Group	DCOG	Holland	18	February 26, 1991	May 30, 2008	
Dana-Farber Cancer Institute	DFCI	USA	13	August 14, 1986	March 17, 2008	DFCI ALL Consortium Protocols 85-001, 87-001, 91-001, 96-001
European Organisation for Research and Treatment of Cancer	EORTC	Belgium and France	16	June 30, 1991	June 15, 2002	EORTC 58881 study
French Acute Lymphoblastic Leukaemia Study Group	FRALLE	France	52	March 12, 1991	June 15, 2010	FRALLE protocols 83, 87-89, 93, 2000
Israel National ALL Studies	INS	Israel	11	June 16, 1993	December 15, 2008	ALL INS 89 (mod BFM 86), ALL INS 93 (mod BFM 90), ALL INS 98 (mod BFM 95)
Tokyo Children's Cancer Study Group	TCCSG	Japan	49	June 23, 1987	May 6, 2010	TCCSG L84-11, L89-12, L92-13, L95-14
Japan Association of Childhood Leukemia Study	JACLS	Japan				Tokai-POG 9104, OCLSG 94, JACLS ALL-96, JACLS ALL-97
Japanese Children's Cancer and Leukemia Study Group	JCCLSG	Japan				CCLSG ALL841, ALL851, ALL874, ALL911, ALL941
Kyushu-Yamaguchi Children's Cancer Study Group	KYCCSG	Japan				KYCCSG AL841, HR88, ALL90, ALL96
Nordic Society for Paediatric Haematology and Oncology	NOPHO	Denmark, Finland, Iceland, Norway, Sweden	53	January 15, 1986	May 15, 2010	ALL-86, ALL-92, ALL-2000
St Jude Children's Research Hospital	SJCRH	USA	69	February 9, 1982	November 18, 2002	Total Therapies 4, 5, 6, 7, 8, 9, 10, 11, 12, 13A, and 13B
Taiwan Pediatric Oncology Group	TPOG	Taiwan	19	August 5, 1987	January 13, 2007	TCALL 84; TPOG-ALL 88, 93, 97, 2002
National Cancer Research Institute Children's Leukaemia Clinical Studies Group	NCRI	United Kingdom	27	January 15, 1994	September 15, 2007	UKALLXI ISRCTN 16757172, ALL97 ISRCTN 26727615
Total			642	February 9, 1982	June 15, 2010	

Table A2. Clinical Characteristics of Patients With Cancer-Predisposing Syndromes

Predisposing Syndrome	Type of Second Cancer	Sex	Age at ALL (years)	WBC at ALL ($\times 10^9$/L)	BCP or T-Cell ALL	Interval to SMN (years)	Age at SMN (years)	Status	Survival (years)
Down syndrome	AML	Male	3.2	16.8	B	4.0	7.2	Dead	0.8
Down syndrome	AML	Female	2.0	7.8	B	5.9	7.9	Dead	1.1
Down syndrome	Mature B-cell NHL	Male	6.2	38.1	B	2.6	8.8	Alive	7.0
Down syndrome	Ewing sarcoma	Female	6.6	2.1	B	8.3	14.9	Alive	5.4
Li Fraumeni syndrome	AML	Male	12.4	6.6	B	2.5	15.0	Dead	0.6
Ataxia telangiectasia	T-cell NHL	Male	9.5	86.0	T	12.5	22.0	Dead	0.6
Noonan syndrome	MDS	Female	16.0	2.0	B	2.7	18.7	N/A	
AIDS	Mature B-cell NHL	Male	13.7	1.8	B	4.0	17.7	Alive	10.2

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCP, B-cell precursor; MDS, myelodysplastic syndrome; N/A, not available; NHL, non-Hodgkin lymphoma; SMN, second malignant neoplasm.

Table A3. Clinical Characteristics and Overall Survival of the Four Major Categories of SMNs in the Subset of 201 Patients Who Were Not Irradiated and Did Not Undergo Hematopoietic Stem-Cell Transplantation as Part of Their First-Line Treatment for ALL

Type of Second Cancer	Total		Males		ALL Immunophenotype* (n = 192)		Age at ALL (years)		WBC at ALL ($\times 10^9$/L)		Interval to SMN (years)		Age at SMN (years)		5-Year Survival Rate After SMN (%)
	No.	%	No.	%	BCP	%	Median	50% Range	Median	50% Range	Median	50% Range	Median	50% Range	
Total	201		107	53.2	173	90.1					3.6	2.3-6.6	9.0	6.5-15.1	44.1 ± 3.7
Hematologic†	145	72.1	79	54.5	130	92.2	4.3	3.0-6.5	6.1	4.0-15.3	2.9	2.1-4.3	8.2	6.0-12.7	41.1 ± 4.2
CNS tumor†	12	6.0	6	50.0	9	90.0	5.0	3.5-8.9	7.4	3.7-34.4	6.8	2.7-7.4	13.1	8.7-17.2	32.1 ± 15.0
Carcinoma†	19	9.5	7	36.8	15	83.3	4.7	3.0-8.7	6.6	3.3-38.5	11.8	6.1-16.1	16.2	10.7-23.4	77.4 ± 10.0
Other†	25	12.4	15	60.0	19	82.6	5.7	3.4-8.1	4.9	2.5-26.2	7.8	4.4-9.8	14.0	10.4-17.9	44.9 ± 11.3

Abbreviations: ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; SMN, second malignant neoplasm.

*Nine patients were excluded because immunophenotype was not reported (n = 8) or was not specified as either BCP or T-cell ALL (n = 1).

†Seventy-one acute myeloid leukemia, 38 myelodysplastic syndrome, three chronic myeloid leukemia, 23 non-Hodgkin lymphoma, 10 Hodgkin disease, 10 nonmeningioma CNS tumors, two meningioma, 10 nonthyroid carcinoma, nine thyroid carcinoma, seven soft tissue sarcoma, 12 bone tumors, one germ cell tumor, four Langerhans cell histiocytosis, one other tumor.