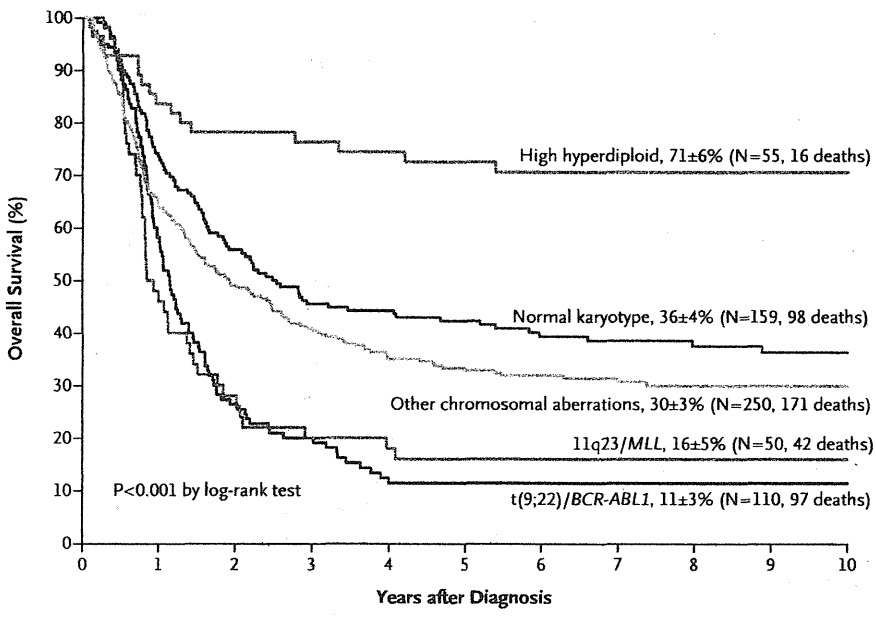

Figure 1. Kaplan–Meier Analysis of Survival in the 624 Study Patients with Induction Failure Who Had Genetic Data, According to Genetic Abnormality.

Ten-year survival estimates (±SE) are shown, along with the total numbers of patients with data and the total numbers of deaths. *MLL* denotes the mixed-lineage leukemia gene.

in the Supplementary Appendix). Patient subgroups with the worst outcomes included patients 6 years of age or older with M3 marrow (10-year survival rate, 22±5%) (Fig. 1B in the Supplementary Appendix) and patients of any age with T-cell ALL and M3 marrow (10-year survival rate, 19±4%) (Fig. 2C and Table 5 in the Supplementary Appendix).

TREATMENT AFTER INDUCTION FAILURE

Data on whether a complete remission was achieved were available for 520 patients (Table 1). The 10-year survival rate was significantly higher among the 389 patients in whom a late remission was achieved than among the 131 patients who never had a remission according to protocol criteria (48±3% vs. 14±3%, P<0.001).

EFFECT OF TRANSPLANTATION ON SURVIVAL

A total of 198 patients underwent hematopoietic stem-cell transplantation, whereas 427 received chemotherapy only. The 10-year survival rate was 43±4% among patients who underwent transplantation, as compared with 41±3% among patients who did not undergo transplantation. Patients who received a transplant were further categorized according to whether the donor was an HLA-matched, related donor or any other type of donor (because all other donor types yielded results similar to one another) (Table 6 in the Supplementary Appendix). The effect of transplantation on the outcome differed across major prognostic subgroups of patients: in children younger than 6 years of age with precursor B-cell ALL (without *MLL* rearrangement), chemotherapy alone yielded significantly higher rates of survival than did transplantation (P=0.007) (Fig. 2A). In patients 6 years of age or older with precursor B-cell ALL (without *MLL* rearrangement), receipt of a transplant from a matched, related donor appeared to improve the outcome, whereas other types of allogeneic transplantations resulted in worse outcomes (Fig. 2B), partly owing to transplantation-related death, which accounted for 6 of the 17 deaths in that group. Among patients with T-cell ALL, any type of transplantation, as compared with chemotherapy, yielded better, albeit not significantly better, rates of survival (Fig. 2C).

PROGNOSTIC FACTORS FOR SURVIVAL

In patients with precursor B-cell ALL without *MLL* rearrangement, the factors that were independently associated with a poor prognosis included a leu-

kocyte count of 100×10^9 per liter or more, an age of 6 years or older or 10 years or older, and stem-cell transplantation from other than matched, related donors (Table 2). In T-cell ALL, male sex and M3 marrow at the end of induction therapy were adverse prognostic factors, and the use of any allogeneic stem-cell transplantation was associated with a favorable trend (hazard ratio for death, 0.7; 95% confidence interval, 0.5 to 1.0; P=0.07).

In a separate Cox-regression analysis that included the 448 patients with data on transplantation and leukemic-cell genetic abnormalities, independent adverse prognostic factors were an age of at least 10 years, M3 marrow at the end of the induction phase, T-cell disease, and the presence of *MLL* rearrangement.

The outcome in infants (<1 year of age) with precursor B-cell ALL and induction failure who did not have an *MLL* rearrangement or *BCR-ABL1* fusion was similar to the outcome in children 1 to 5 years of age (10-year survival rates, 65±13% and 63±4%, respectively) (Table 5 in the Supplementary Appendix). In contrast, the 10-year survival rate among infant patients with an *MLL* rearrangement, as compared with older patients, was very poor (4±4% vs. 26±8%, P=0.06; data not shown).

TIME TRENDS IN SURVIVAL

The 10-year survival rate among patients with induction failure increased over time by approximately 10% (Table 1) but varied among patient subgroups. Among patients with precursor B-cell ALL, the 10-year survival rate improved from 34±5% before 1993 to 47±4% between 1993 and 2000 (P=0.02). This improvement was due mainly to better results with chemotherapy. Among patients with T-cell ALL, the 10-year survival rate did not improve significantly over time with chemotherapy, but in the most recent period, the rate did increase, from 20% before 1993 to 31% between 1993 and 2000 (P=0.02), probably owing to the increased use of allogeneic transplantation.

DISCUSSION

Induction failure is rare, occurring in only 2 to 3% of all patients, but it constitutes one of the most unfavorable outcomes in pediatric ALL. In our large retrospective series of patients with induction failure, we observed great clinical and biologic heterogeneity. Among these patients, as compared with an unselected population of children and

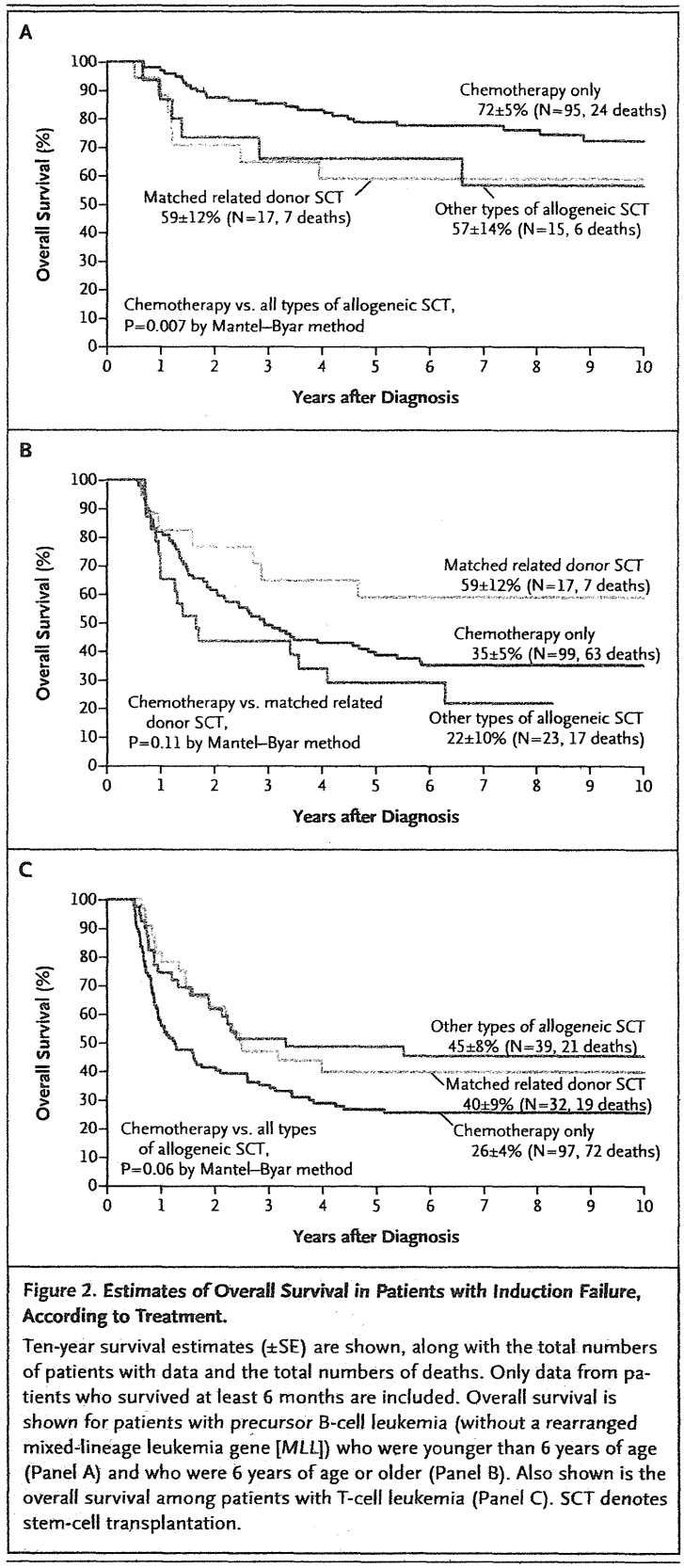

Figure 2. Estimates of Overall Survival in Patients with Induction Failure, According to Treatment.

Ten-year survival estimates (±SE) are shown, along with the total numbers of patients with data and the total numbers of deaths. Only data from patients who survived at least 6 months are included. Overall survival is shown for patients with precursor B-cell leukemia (without a rearranged mixed-lineage leukemia gene [*MLL*]) who were younger than 6 years of age (Panel A) and who were 6 years of age or older (Panel B). Also shown is the overall survival among patients with T-cell leukemia (Panel C). SCT denotes stem-cell transplantation.

Table 2. Prognostic Factors for Survival, According to Hazard Ratio for Death.*

Prognostic Factor†	No. of Patients	Hazard Ratio for Death (95% CI)	P Value
B-cell lineage, t(9;22)(*BCR-ABL1*)–negative patients‡			
M3 bone marrow at the end of induction	97	0.9 (0.6–1.3)	0.62
Leukocyte count ≥100×10^9 per liter	49	1.7 (1.1–2.5)	0.01
Age 6–9 yr	56	2.4 (1.5–3.8)	0.001
Age ≥10 yr	103	2.6 (1.8–4.0)	<0.001
SCT with matched, related donor	35	1.0 (0.6–1.8)	0.97
Other allogeneic SCT	38	2.1 (1.3–3.5)	0.003
T-cell lineage, t(9;22)(*BCR-ABL1*)–negative patients§			
M3 bone marrow at the end of induction	99	1.6 (1.1–2.2)	0.01
Male sex	143	1.4 (1.0–2.0)	0.05
Any allogeneic SCT	86	0.7 (0.5–1.0)	0.07
All patients with cytogenetic data¶			
M3 bone marrow at the end of induction	163	1.5 (1.2–2.0)	0.002
MLL	43	1.9 (1.2–2.8)	0.004
T-ALL	165	1.6 (1.2–2.2)	0.001
Age ≥10 yr	150	1.4 (1.0–1.8)	0.03
High hyperdiploidy	51	0.7 (0.4–1.2)	0.23
SCT with matched, related donor	61	0.8 (0.5–1.2)	0.28
Other allogeneic SCT	43	1.3 (0.8–1.9)	0.27

* Only patients with information on whether they had undergone stem-cell transplantation (SCT) are included. *MLL*-positive patients are excluded because the *MLL* status was available for less than 46% of the patients. In the Cox regression, the following features were explored as possible prognostic factors in the model: age (<1 year, 6 to 9 years, and ≥10 years), leukocyte count (<20×10^9 per liter, >50×10^9 per liter, and ≥100×10^9 per liter), sex, involvement of the central nervous system or lymph nodes, enlargement of liver and spleen, presence of mediastinal mass, presence of cytogenetic aberrations (*MLL* rearrangement, high hyperdiploidy with modal chromosomal number of 50 or more), treatment period (years during which patients were treated), study groups (in three strata according to treatment results), and time to transplantation as a time-dependent variable. CI denotes confidence interval.

† In each case, the comparator group is the obverse of the noted criterion. For age 6 to 9 years and age 10 years or older, the comparison is with age 1 to 5 years. For SCT with matched, related donor, other allogeneic SCT, and any allogeneic SCT, the comparison is with chemotherapy.

‡ A total of 297 patients had B-cell lineage, t(9;22)(*BCR-ABL1*)–negative status and known SCT status, with a 10-year-survival rate of 47±3%.

§ A total of 225 patients had T-cell lineage, t(9;22)(*BCR-ABL1*)–negative status and known SCT status, with a 10-year-survival rate of 28±3%.

¶ A total of 448 patients had cytogenetic data and known SCT status, with a 10-year survival estimate (±SE) of 36±2%.

adolescents with ALL, the conventional adverse prognostic factors such as high leukocyte count, older age, positivity for t(9;22)(*BCR-ABL1*), and T-cell phenotype were more prevalent and conferred an even worse prognosis.[6,12,18,35-39] Indeed, the clinical and biologic characteristics of the patients in our study and the course of the disease were similar to those in patients with relapse during receipt of therapy, another group of patients with a highly unfavorable prognosis.[40-44]

The patient subgroup with the best outcomes comprised patients with precursor B-cell ALL and either an age of less than 6 years or high hyperdiploidy. Together, these factors accounted for approximately 25% of all patients with induction failure and were associated with a 10-year survival rate above 50%. Although the favorable prognosis of high hyperdiploidy is well recognized in unselected patients with precursor B-cell ALL,[18,45-47] this association has not been reported in patients with induction failure. Why did patients with high hyperdiploidy have a relatively favorable prognosis despite the failure of remission-induction therapy? It is unlikely that many of these patients were misdiagnosed as having induction failure, because hematogones (benign immature B-cell precursors that may be mistaken for leukemic cells) should not preferentially occur in patients with high hy-

perdiploidy. The relatively favorable outcome in patients with high hyperdiploidy may be due to the increased sensitivity of the blast cells to methotrexate and mercaptopurine,[45,48] drugs that are generally not used during remission induction but are used at high doses after remission.

The time at which the response was evaluated in these patients also did not have a prognostic effect, most likely because the number of patients in each study group was too small to show a statistical difference (Tables 1 and 2 in the Supplementary Appendix). The Dana–Farber Cancer Institute Consortium has reported that outcomes are not adversely affected by a hypocellular bone marrow at the end of induction therapy or by a delay in reaching complete remission (defined as normal cellular M1 marrow, a neutrophil count of $>1\times10^9$ per liter, a platelet count of $>100\times10^9$ per liter, and no extramedullary disease).[21] Our current analysis showed that among patients with induction failure, the patients with an M3 marrow, as compared with those with an M1 or M2 marrow, had a poor outcome. The degree of leukemic involvement in bone marrow at the end of the induction phase was inversely correlated with the rate of subsequent complete remission (81% in patients with M1 or M2 marrow but only 61% in those with M3 marrow) and with 10-year survival rates (41±3% with M1 or M2 marrow vs. 26±3% with M3 marrow). Patients who did not have a complete remission after a brief course of additional therapy, as specified in the treatment protocol, (i.e., 25% of all patients with initial induction failure) had an extremely poor prognosis (Table 1).

The extremely poor prognosis of patients with t(9;22)(*BCR-ABL1*) and induction failure in the era before imatinib therapy was available has been described.[21,23,25,49] A recent study[34] showed improved early outcomes with intensive chemotherapy and imatinib treatment in patients with ALL who were positive for t(9;22)(*BCR-ABL1*); the nine patients who were positive for t(9;22)(*BCR-ABL1*) and had induction failure had a rather favorable outcome. However, the long-term efficacy of this treatment approach as compared with allogeneic transplantation still needs to be determined. It is conceivable that further improvement can be made if the most effective chemotherapy is combined with a new generation of tyrosine kinase inhibitors and if transplantation in special subgroups is guided by minimal residual disease level.[50-52]

Modifications of chemotherapy have reduced the rate of recurrence among patients with high-risk ALL but have not yet been shown to improve the outcomes in patients with induction failure.[53] Several studies have shown that matched-donor transplantation improved the outcomes in patients with induction failure,[23,24,35,54] but the number of patients in each of these studies was too small to determine which patient subgroups had the greatest benefit from transplantation.

Our retrospective analysis has the advantage of including large numbers of patients but is limited by the heterogeneity of the protocols guiding the patients' treatment. Thus, unmeasured variables could influence the findings. However, our data suggest that allogeneic transplantation may be associated with improved outcomes in patients with T-cell ALL who have not had a complete remission with induction chemotherapy. This observation is consistent with prior reports of improved outcomes in patients with high-risk T-cell ALL receiving transplantation after the first remission.[55,56] The number of patients with *MLL* rearrangement in whom induction therapy failed is too small in our study to allow us to determine the role of allogeneic transplantation in this subgroup. Allogeneic transplantation failed to improve the outcome in patients with 11q23–*MLL* rearrangement in a previous large study from our intergroup collaboration[26] but showed some benefits in high-risk subgroups of infants younger than 1 year of age with *MLL* rearrangement in the Interfant-99 study (ClinicalTrials.gov number, NCT00015873).[57] Finally, our analysis showed no benefit of allogeneic transplantation in patients younger than 6 years of age who had precursor B-cell ALL and induction failure and no high-risk cytogenetic features — an observation with considerable clinical implications, since transplantation is generally considered to be the standard of care for such patients.

This work is dedicated to James B. Nachman, M.D. (1948–2011), who contributed, with a truly global view and outstanding personal dedication, to this and many other important scientific papers in the field of pediatric leukemia.

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APPENDIX

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Second Malignant Neoplasms After Treatment of Childhood Acute Lymphoblastic Leukemia

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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.

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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%.

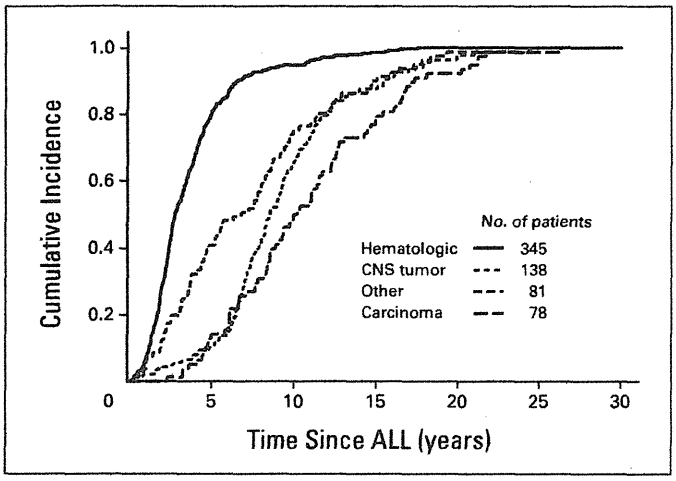

Fig 1. Kaplan-Meier estimates of the interval between diagnosis of acute lymphoblastic leukemia (ALL) and development of the four major categories of second malignant neoplasms.

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.

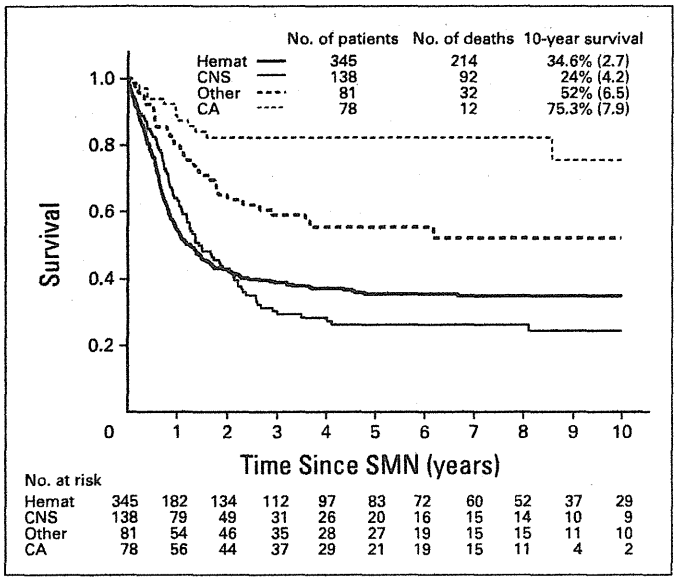

Fig 2. Survival curves according to the four major categories of second malignant neoplasms (SMNs). Hemat, hematologic; CA, carcinoma.

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 ($P < .001$).

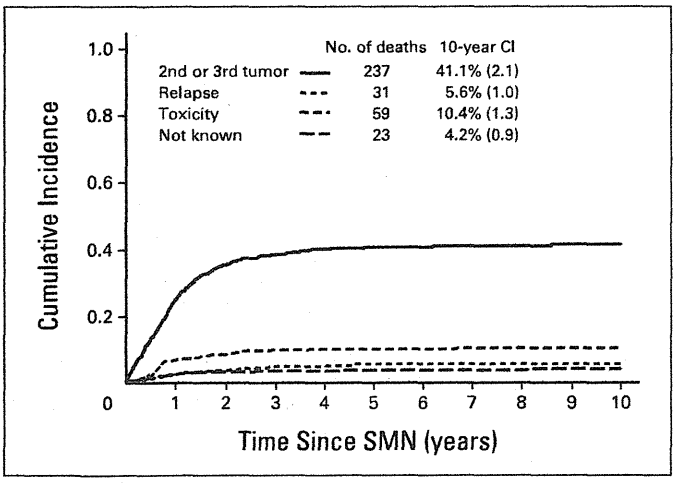

Fig 3. Cause-specific cumulative incidences (CIs) of death after development of a second malignant neoplasm (SMN).

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.

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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.

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ALL-2 急性リンパ性白血病

小児ALLの治療方針

堀部敬三

Key words : Childhood, Acute lymphoblastic leukemia, Risk-adapted therapy, Minimal residual disease

はじめに

小児急性リンパ性白血病（ALL）は，日本小児血液学会疾患登録の集計では小児期腫瘍性血液疾患の47%を占め，年間550～600例の新規発生があると考えられる[1]。その治療成績は，過去50年間の治療の進歩，とりわけ，リスク層別化による化学療法の強化と適正化，および支持療法の進歩によって5年無イベント生存率（EFS）が約80%，5年全生存率が90%に達している[2]。今後の課題は，難治例に対する治療戦略の確立と，良好な成績を維持しつつ長期的影響を含めた合併症の低減を図るためのより緻密な層別化治療の確立である。近年，ゲノムワイドに網羅的遺伝子解析が可能となり[3,4]，腫瘍および宿主のゲノム情報に基づいた個別化治療の時代も遠くないと思われる。なお，日本小児血液学会編「小児白血病・リンパ腫の診療ガイドライン2011年版」に最新の小児ALLの治療指針が掲載されているので参照されたい[5]。

診断分類に基づく治療選択

治療方針を立てるには，正確な診断と分類が必要である。ALLの臨床診断は，臨床的にはミエロペルオキシダーゼ（MPO）陰性の芽球が一律的に骨髄に増殖する疾患を総称しており，リンパ腫様白血病の場合は，骨髄の芽球比率が25%を超えるかそれ以下かで白血病とリンパ腫に分ける。WHO分類第4版では，ALLは，細胞の系統発生によってPrecursor lymphoid neoplasmの中でB lymphoblastic leukemia/lymphoma，T lymphoblastic leukemia/lymphomaに分類される[6]。成熟B細胞性ALLは，mature B neoplasmのカテゴリーの中でBurkitt leukemia/lymphomaに分類される。

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成熟B細胞性ALLは，小児ALLの1～2%を占め，細胞回転が速く，耐性獲得が速いため以前は早期に再発をきたす予後不良な疾患であった。現在は，成熟B細胞性リンパ腫と同様に短期間のブロック型化学療法（維持療法なし）の有効性が確立し，80%以上の5年EFSが期待できる[7]。成熟B細胞性ALLは，他のALLと治療戦略が異なるため迅速な細胞系統診断と適切な治療選択が重要である。

T細胞性（T-）ALLは，高リスク群として強化された治療が行われ，Lアスパラギナーゼ（ASP）の多用が有効である[8]。それにより予後良好因子として抽出されるまでになった[9]。T-ALLは，特有の生物学的特徴を有し，MTXの活性化代謝物が蓄積しにくく[10]，骨髄微小残存病変（MRD）の動態もB前駆細胞性（BCP-）ALLと異なる[11]。さらに，ネララビンなどT-ALLに選択的に有効性のある薬剤が開発されたことから独自の治療研究が進められている[12]。一方，最近，通常のT-ALLと異なる免疫学的表現型や遺伝子のプロファイルを示す予後不良な一群として早期前駆細胞性T-ALL（EPT-ALL）が明らかにされた[13,14]。

BCP-ALLにおいても，さまざまな予後と関連した染色体・遺伝子異常が明らかにされてきた。t(12;21)/*ETV6-RUNX1*や高2倍体（>50本，HHD）が予後良好因子である一方，フィラデルフィア染色体（Ph）/t(9;22)/*BCR-ABL*や11q23染色体異常/MLL遺伝子再構成は従来の治療では予後不良である。さらに，低2倍体染色体（<44本）[15]，t(17;19)(q22;p13.3)/*TCF3*（*E2A*）-*HLF*[16]，iAML21[17]も予後不良因子と考えられている。t(1;19)/*TCF3-PBX1*[18]は，治療の強化で予後の改善が得られている。Ph陽性ALLは，*BCR-ABL*の機能を特異的に抑えるチロシンキナーゼ阻害薬（TKI）イマチニブを化学療法に併用して長期投与することで劇的な予後の改善が得られたことで治療戦略が一変した[19]。これまで

絶対適応とされた同種造血幹細胞移植（SCT）の成績と有意差がなく，治療の初期反応性やMRDの評価を打ち消す効果が示唆されている[19]。また，網羅的な遺伝子解析によってALLのさまざまな遺伝子異常が明らかにされ，中でも*IKZF1*領域の欠失[20]，*CRLF2*の高発現[21]や*P2RY8-CRLF2*[22]，*JAK2*遺伝子変異[21]が新たな予後因子および治療の分子標的として注目されている。

このようにALLは，ヘテロな集団であり，今後，分子病態の解明の進歩によって病型の細分化が一層進み，病型特異的な治療戦略が追究されていくと思われる。

そのほか，リンパ系と骨髄系のマーカーを発現するambiguous lineage leukemiaにおいて，MPO陰性の場合はALLとして取り扱われる。biphenotypic leukemia，とりわけ*ETV6-RUNX1*陽性例は予後良好であるが，bilinealやlineage switchを示す例は，予後不良であり，同種SCTの適応がある[23]。

リスク層別化治療

小児ALLの治療は，高い治癒率を維持しつつ過剰な副作用を避けるために再発予測を厳格に行って精緻なリスク分類に基づいて層別化して行う（図1）。リスク分類は，年齢，白血球数，免疫学的マーカーなどによって標準リスクと高リスクの2群に分けられていたが[24]，その後，初期治療反応性や白血病細胞の染色体・遺伝子型を考慮して3群に分類された。さらに，現在は，寛解導入療法中および後のMRDが初期リスクの変更，とりわけ，SCTの適応の判断に用いられる。個々の予後因子の重要性は，治療レジメンに影響を受けるため，治療レジメンによって層別化基準が異なることがある。とりわけ，MRDは，治療依存性であり，治療レジメン，解析方法や解析時期によって判断基準が異なる。

1）年齢因子の意義

年齢は，以前からALLの強力な予後因子とされてきた。年齢が高くなるほど再発リスクが高くなるが，一方で1歳未満は，とりわけ予後不良であり，わが国では80年代後半から乳児ALLプロトコールが作られて独自に治療開発が行われてきた[25]。乳児ALLの予後不良の主な要因は，80％の症例に認められる*MLL*遺伝子再構成である。実際，乳児ALLの治療成績を*MLL*遺伝子再構成の有無で比較すると，*MLL*遺伝子再構成を伴わない例は，ほとんどがCD10陽性のBCP-ALLであり，強化された化学療法で90％以上の長期寛解生存が期待できる[26]。一方，*MLL*遺伝子再構成を伴う例は，ほとんどがCD10陰性のBCP-ALLであり，同種SCTを併用しても5年全生存率は50％に留まっている[25, 27]。生存率向上に限界がある上に移植後生存例において成長障害を半数以上に認めるなど，晩期合併症が回避できないことも課題であり，さらに層別化した治療開発が必要と考えられる[27]。

小児ALLは，2～5歳に発症ピークがあり，その年齢層に予後良好な分子異常である*ETV6-RUNX1*とHHDが多くみられ，予後良好群を形成している[2]。一方，年齢が6歳以上[28]，10歳以上[24]は予後不良とされてきた

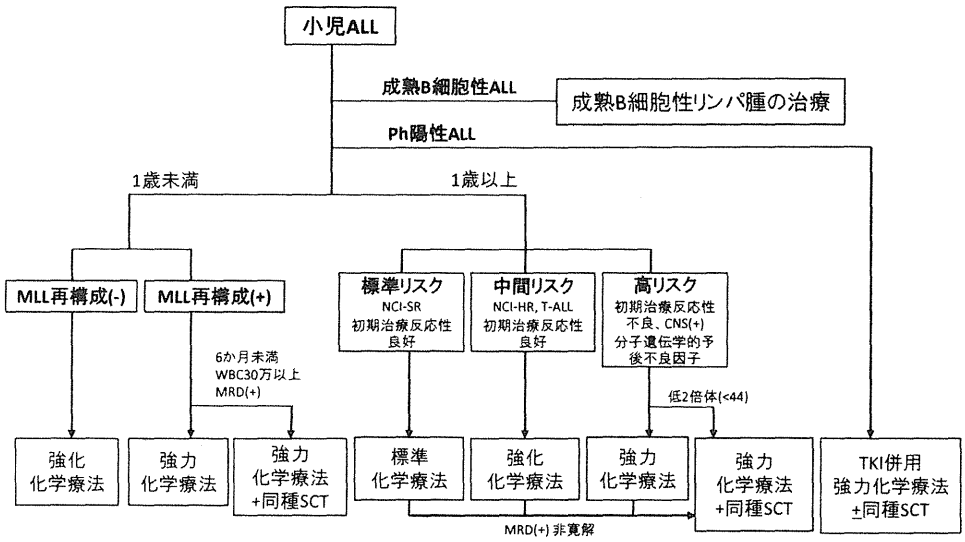

図1 小児ALLの治療選択アルゴリズム
日本小児血液学会編小児白血病・リンパ腫の診療ガイドライン2011版[5]を引用（一部改変）

が，治療を強化することで予後の改善が得られている。

思春期 ALL は，T-ALL の割合が高く，予後良好な *ETV6-RUNX1* や HHD が少なく，予後不良な Ph 陽性例や t(4;11)/*MLL-AF4*，低 2 倍体，寛解導入療法後の MRD 陽性例が漸増する[29, 30, 31]。しかし，10 代前半と後半の ALL に生物学的要因の分布はほぼ同じである。15 歳以上の多くは血液内科で診療されるが，15～21 歳の思春期・若年成人（AYA-）ALL は，欧米の多くの後方視的研究で，小児プロトコールの治療成績が成人プロトコールの成績よりよいことが示されている[32]。

2）初期治療反応性と MRD 評価の意義

初期治療反応性の評価法は，欧州と米国の研究グループ間で異なる。Berlin-Frankfurt-Munster（BFM）グループでは，プレドニゾン/プレドニゾロン（PSL）7 日間と MTX 髄注後の day8 の末梢血の芽球比率が用いられる[28]。PGR（day8 の末梢血芽球数が 1,000/μl 未満）が PSL 反応良好群，PPR（day8 の末梢血芽球数が 1,000/μl 以上）が PSL 反応不良群であり，2000 年前後からわが国に取り入れられるようになり，現在，日本小児白血病リンパ腫研究グループ（JPLSG）の臨床試験においても採用されている。一方，米国 Children's Oncology Group（COG）では，day8 と day15 の骨髄芽球比率と day29 の骨髄 MRD が用いられる[33]。RER（day8 で M1 marrow かつ day29 で MRD 陰性（0.1％未満），または day8 で M2/M3 marrow で day15 で M1 marrow かつ day29 で MRD 陰性）を初期反応良好群，SER（day15 で M2/M3 marrow または day29 で MRD 陽性（0.1％以上）を初期反応不良群として治療層別している。

MRD の測定法もさまざまな手法があるが，免疫グロブリン遺伝子と T 細胞受容体を標的とした（Ig/TCR-）PCR 法に基づく欧州グループで標準化された方法（PCR-MRD）が最も信頼性が高い[34]。PCR-MRD の場合，地固め療法開始時（5 週後，TP1）および中間維持療法開始時（12 週後，TP2）の評価を組み合わせて治療層別に用いられる。AIEOP-BFM グループは，年齢と白血球数による層別化から PSL 反応性と MRD に基づいた層別法に切り替えた臨床試験を行ってその有用性を検証した[35]。その結果，TP2 が最も重要であり，10^{-3} 以上の MRD が残存する場合は予後不良であり同種 SCT が推奨される[36]。近年，欧州で MRD 測定法とその解釈を標準化するための組織（ESG-MRD-ALL）が設立され，国際共同臨床試験における MRD 測定が厳密に標準化された[37]。JPLSG の MRD 測定施設（責任者：堀壽成，愛知医科大学）も 2010 年から正式参加している。一方，転座で生じる融合遺伝子を RT-PCR 法で検出する方法は，感度が高く，比較的簡便であるが，汎用性に難点がある。しかし，Ph 陽性 ALL においては，Ig/TCR-PCR 法と *BCR-ABL* の RT-PCR 法とは結果が相関せず，BCR-ABL 陽性検体の 20％が Ig/TCR-PCR 法で陰性になるとされており，二つの方法で測定して経過観察するのが望ましいとされている[38]。また，フローサイトメトリー法による MRD 測定（FCM-MRD）技術も確立しており，感度はやや低いものの day15 の初期反応性や寛解判定の評価に優れており，COG プロトコールのリスク分類にも採用されている[39～41]。

3）宿主要因

宿主因子は治療効果に影響を与える。抗がん剤の薬物代謝に個体差があるため効果の減弱や毒性の増強が起こりうる。6-メルカプトプリン（6MP）の代謝酵素であるチオプリンメチル化転移酵素（TPMT）や多くの抗がん剤の不活化に関係するグルタチオン S 転移酵素などの遺伝子多型が治療効果や急性および晩期の毒性に影響が強いことが知られている[42, 43]。また，Down 症児は MTX の活性型代謝物が蓄積しやすいためホリナートの投与や MTX 大量投与時の投与量の調節が必要である[44]。

小児 ALL の治療骨格と各治療相の考え方

小児 ALL の標準的治療骨格は，寛解導入療法，地固め療法，中間維持療法，後期強化療法（再寛解導入療法），維持療法からなり，縦断的に中枢神経系（CNS）白血病予防治療が行われる（図 2，図 3）。

1）寛解導入療法

寛解導入療法は，99％以上の白血病細胞を根絶させて正常造血を回復させるのが目標である。副腎皮質ステロイド，ビンクリスチン（VCR），ASP の 3 剤が基本であるが，高リスクでは，アントラサイクリン系薬剤を加えた 4 剤で治療される。BFM 型レジメン（図 2）ではすべてのリスクで 4 剤治療が標準である。アントラサイクリン系薬剤は急性のみならず晩期の心筋障害が問題となるため標準危険群では控えるのが望ましく，BFM 型レジメンでは標準リスクで投与回数削減が試みられている[28]。成人 ALL では，シクロホスファミド（CPA）を入れた 5 剤で治療されることが多いが，小児でも T-ALL をはじめとする高リスクで CPA が追加される場合がある。また，CNS 白血病の予防治療として寛解導入療法中に MTX の髄注が 2～3 回行われる。CNS 陽性例には，髄注を追加して CNS の寛解をめざす。

副腎皮質ステロイドの選択は古くて新しい問題である。PSL とデキサメタゾン（DEX）の比較試験が多く行われたが，投与量も結果もまちまちで結論が出ていな