Table II. Clinical characteristics of 91 patients treated with TCCSG NHL B9604 protocol.

Registration period	April 1996 – January 2001
Observation period	0 – 103 months (median 60 months)
Sex (Male/Female)	64/27
Age range	0.9 – 16.8 years (median 9.4 years)
Pathological diagnosis	Burkitt, 45
	Large cell, 26
	B-ALL, 9
	B-NHL not further specified, 6
	Others, 5
Primary site	Head and neck: 32; chest: 3
	Abdomen: 36; bone: 8
	B-ALL: 9; others: 3
Disease stage	I: 5; II: 23; III: 25; VI: 38
Risk group	A: 3; B: 25; C: 46; D:17

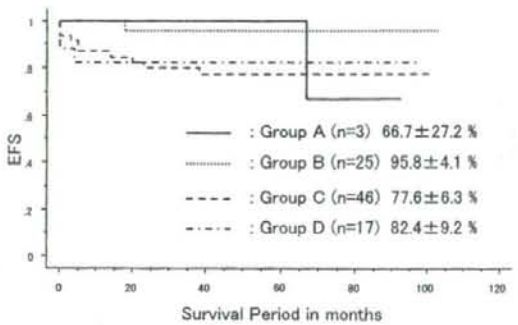

Figure 2. EFS according to the risk groups. EFS was 66.7% ± 27.2% in Group A ($n=3$), 95.8% ± 4.1% in Group B ($n=25$), 77.6% ± 6.3% in Group C ($n=46$) and 82.4% ± 9.2% in Group D ($n=17$).

patients were rescued with further chemotherapy for B-LBL. These relapses were considered due to inadequate treatment duration rather than drug resistance. In Group A, one patient (UPN 100) whose primary site was the tonsils developed diffuse large B-cell lymphoma at the cecum 5 years after initial diagnosis. Although we could not determine whether this lesion was relapse or secondary neoplasm, the EFS of Group A patients became low because of this rare event. Such a late relapse as in this case was also reported in the SFOP study [8]. Aside from these three cases, the 12 event cases consisted of three induction failures, five relapses, two toxic deaths and two second malignant neoplasm. All three induction failures and four BM involved relapsed patients died of disease progression in spite of further chemotherapy or stem cell transplantation. These cases may have required a quite different treatment concept for the first-line therapy based on stratification with tumor biology profiling. One patient (UPN 44) showed massive ICH at initial presentation and died 2 days after

Table III. Event cases in TCCSG NHL B9604 protocol.

UPN	Age	Sex	Stage	Group	Histology (central review)	Event	Remission period	Outcome	Cause of death	Survival period
11	15	F	III	C	DLBCL (DLBCL)	Secondary malignancy	14	Alive	N.A.	88+
22	5	F	III	C	Burkitt (Burkitt)	Induction failure	0	Dead	Disease progression	9
39	14	M	III	C	Burkitt (Burkitt)	Relapse (BM)	3	Dead	Disease progression	6
44	9	M	IV	D	ALL	ICH	0	Dead	ICH	0
57	11	M	IV	D	Burkitt (Burkitt)	Relapse (BM)	4	Dead	Disease progression	6
58	3	F	IV	C	Burkitt (Burkitt)	Induction failure	0	Dead	Disease progression	6
74	15	M	III	C	Burkitt (Burkitt)	Relapse (BM + local)	6	Dead	Disease progression	7
100	13	F	I	A	DLBCL (DLBCL)	Relapse (cecum)	67	Alive	N.A.	71+
102	10	F	IV	C	ALL	Relapse (BM)	6	Dead	Disease progression	11
103	2	M	III	C	Burkitt (Burkitt)	Sepsis	0	Dead	Sepsis	0
132	7	M	II	B	DLBCL (B-LBL)	Relapse (BM)	33	Alive	N.A.	66+
141	14	M	III	C	Medium (N.D.)	Relapse (local)	20	Alive	N.A.	77+
146	7	F	IV	C	DLBCL (B-LBL)	Relapse (local)	23	Alive	N.A.	60+
149	15	M	III	C	MLBCL (MLBCL)	Secondary malignancy	38	Alive	N.A.	62+
154	8	M	IV	D	Burkitt (Burkitt)	Induction failure	0	Dead	Disease progression	10

DLBCL, diffuse large B cell lymphoma; MLBCL, mediastinal large B-cell lymphoma; ICH, intracranial hemorrhage; N.A., not applicable; N.D., not done.
Age is shown in years. Remission period and survival period are shown in months. A plus sign indicates that the patient is still alive.

admission. We do not think this was therapy-related toxic death. Toxic death was reported in another patient (UPN 103) who died of sepsis during remission induction therapy. Although Grade 4 non-hematological toxicity was noted in four cases in addition to this patient, this intensified treatment regimen was well tolerated. Two second malignant neoplasm (myelodysplastic syndrome and acute myeloid leukemia) were observed 14 and 38 months after diagnosis. These patients survived with BM transplantation from unrelated donors. As we used a relatively larger dose of chemotherapeutic drugs in this study, we have to cautiously observe the development of a second malignant neoplasm among patients treated with this protocol.

In recent childhood lymphoma studies, international collaborations are essential because large scale studies are needed to prove improved outcome compared with current good one. To participate in these international studies, it is important for us (Japanese or Asian people) to confirm short, intensive chemotherapy for B-NHL and B-ALL is safe and effective regardless of racial differences. We elucidated such short, intensive chemotherapy for B-NHL and B-ALL was safe and effective for Japanese children. Treatment reduction is a main theme of childhood B-NHL therapy. Recently, Patte et al. [13] reported results of FAB/LMB96 trial for intermediate risk B-NHL patients. In this report, they elucidated a four-course treatment is enough for these patients with initial good response. Several studies for B-NHL have attempted therapy reduction to decrease toxicity, however, the dose reduction is associated with an inferior outcome for advanced stage disease so far [14,15].

The TCCSG NHL B9604 protocol achieved an excellent treatment outcome, especially in patients with the most advanced disease (Group D: high BM blast cell burden and/or CNS involvement). Although we have to cautiously observe the development of late adverse effects in treated patients, several study attempts have not succeeded in appropriate therapy reduction without jeopardizing survival and intensified regimen is, at least tentatively, needed for a good prognosis for advanced stage patients.

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Significance of the complete clearance of peripheral blasts after 7 days of prednisolone treatment in children with acute lymphoblastic leukemia: the Tokyo Children's Cancer Study Group Study L99-15

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ABSTRACT

Background

Treatment response has become one of the most important prognostic factors in childhood acute lymphoblastic leukemia. We evaluated the significance of the complete clearance of peripheral leukemic blasts on survival in children with acute lymphoblastic leukemia.

Design and Methods

Seven hundred and fifty-four children diagnosed with acute lymphoblastic leukemia, consecutively enrolled from 1999 to 2003 in the TCCSG L99-15 study, were eligible for analysis. Patients were stratified into three risk groups based on presenting features, such as age and the leukocyte count before starting the treatment, followed by reclassification into three categories 7 days after prednisolone monotherapy based on the peripheral blast count; 0/μL (*Day8NoBlasts*), 1-999/μL and ≥ 1,000/μL.

Results

After 7 days of prednisolone monotherapy, 249 patients (33%) were classified as *Day8NoBlasts*, 392 patients (52%) had blast counts of 1-999/μL, and 113 patients (15%) had blast counts ≥ 1,000/μL. The event-free survival for all patients was 79.6±1.6 (SE)% at 4 years, whereas that for patients with *Day8NoBlasts* was 90.4±2.0% (n=249) and the event-free survival for the other patients was 74.2±2.2% (n=504) (log rank $p<0.001$). The event-free survival for *Day8NoBlasts* patients with B-lineage acute lymphoblastic leukemia and T-cell acute lymphoblastic leukemia was 89.8±2.1% (n=226) and 95.7±4.3% (n=23), respectively. In a multivariate analysis, age at diagnosis, the initial white blood cell count, immunophenotype, and gender did not remain as independent risk factors for treatment failure, whereas *Day8NoBlasts* and marked hyperdiploidy (more than 50 chromosomes) became statistically significant.

Conclusions

Children with *Day8NoBlasts* constituted one third of all the cases with childhood acute lymphoblastic leukemia with an excellent outcome, and should be candidates for curative management with less intensive treatment.

Key words: lymphoblastic leukemia, children, clearance of blasts, steroid response.

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Introduction

Early treatment response is one of the most useful prognostic indicators in childhood acute lymphoblastic leukemia (ALL). This response depends on numerous variables, including the clinicobiological features of the disease, chemotherapy dosages, and also the ability of individual patients to metabolize antileukemic drugs.[1,2] The level of circulating lymphoblasts after 1 week of chemotherapy is associated with the risk of relapse.[3-7] The Berlin-Franfurt-Münster (BFM) group has traditionally employed the response to prednisolone for 7 days and one dose of intrathecal methotrexate to stratify patients: a cut-off peripheral blood blast count of 1,000/μL is used to assign patients into two groups; that is, prednisolone good responders and prednisolone poor responders.[3,8] The utility of this method has been well appreciated and is now employed by other study groups.[9-11]

We analyzed the results of the L89-12 study of the Tokyo Children's Cancer Study Group (TCCSG), and found that a cut-off of 1,000 blasts/μL after a 7-day course of prednisolone monotherapy was useful for stratifying patients.[12] We also found that patients without detectable blasts in the peripheral blood had an even better prognosis (*unpublished data*). In the 99-15 study, we employed a cut-off of 0 blasts in addition to 1,000 blasts to stratify children with ALL. Here, we report the treatment outcome of the study, in which the utility of the above-mentioned stratification of the patients was examined.

Design and Methods

Patients

Seven hundred and seventy children (1 to 18 years of age) diagnosed with ALL were consecutively enrolled from February 1999 to July 2003 in the TCCSG L99-15 study. Children less than 1 year of age were excluded from this study and treated with an infant ALL protocol. Sixteen patients were not evaluable; therefore, 754 patients (male: female; 428 : 326) were eligible for analysis. Their median age was 5 years (range, 1-17). Written informed consent was obtained from parents or guardians and from the patients as appropriate for their age and conceptual ability.

The diagnosis of ALL was based on morphological, biochemical, and flow cytometric features of leukemic cells, including lymphoblast morphology on May- or Wright-Giemsa-stained bone marrow smears, negative staining for myeloperoxidase, and reactivity with monoclonal antibodies to B- or T-lineage-associated lymphoid differentiation antigens. Remission was defined as the presence of fewer than 5% blasts with the recovery of hematopoiesis.

Day 8 risk classification

The patients were stratified into three risk groups based on presenting features (age and the leukocyte count before starting the treatment) and then reclassified into three categories 7 days later according to the sensitivity to oral prednisolone monotherapy, the dose of which was 30-60 mg/m^2/day (Table 1). A total dose of at least 210 mg/m^2 of prednisolone was to be administered in this 7-day prephase period. A diagnostic lumbar puncture was performed and initial intrathecal methotrexate was given on day 8.[12] The dividing counts of 0 blasts/μL and 1,000 blasts/μL were used to stratify patients. To count blasts in the peripheral blood, 200 cells were morphologically assessed under a microscope.

Day 43 risk classification

The patients were finally stratified based on the bone marrow status examined between 43 and 50 days after the initiation of remission induction therapy and on cytogenetic findings. Patients who did not achieve remission and those with the Philadelphia chromosome or 11q23 rearrangements were allocated to the high risk group and underwent allogeneic stem cell transplantation, and those initially at standard risk who showed t(1;19) were switched into the intermediate risk group. The median follow-up period of patients was 3.8 years.

Treatment protocol

The protocol was approved by the institutional review boards of the participating institutions or the equivalent organization. Treatment regimens are detailed in Table 2. A proportion of patients in the high risk group underwent stem cell transplantation in first

Table 1. Risk stratification.

		B-lineage ALL	
Initial risk WBC (×10^9/L)	1-6 years	7-9 years	>10 years
<20	SR	IR	IR
20-50	IR	IR	IR
50-100	IR	IR	HR
≥100×10^9/L	HR	HR	HR
		Day 8 risk (final risk)	
Day 8 PB Blasts	0	1-999	≥1,000/μL
Day 1 SR	SR	SR	IR
Day 1 IR	IR	IR	HR
Day 1 HR	IR	HR	Allo-SCT
		T-ALL	
Day 8 PB blasts	0	1-999	≥1,000/μL
All patients*	IR	HR	Allo-SCT

*WBC: white blood cell count; PB: peripheral blood; SR: standard risk; IR: intermediate risk; HR: high risk; allo-SCT: allogeneic stem cell transplantation; *in T-ALL, patients were stratified only based on the day 8 PB blast count regardless of age and initial WBC. Patients with ALL, from 1 to 18 years of age at diagnosis. Philadelphia chromosome and MLL rearrangement: Allo-SCT, t(1;19): Shifted to IR if in SR. Cranial irradiation: patients with initial WBC > 100×10^9/L: 12 Gy for those aged 1-6 years, 18 Gy for the others.*

remission according to the protocol (n=58). Prophylactic cranial irradiation was given only to patients with an initial leukocyte count exceeding 100×10^9/L. The dose of irradiation was 12 Gy for patients aged between 1 and 6, and 18 Gy for the others. A maintenance phase, consisting of 6-mercaptopurine and methotrexate, was continued until week 146 in the standard risk group and until week 104 in the intermediate risk group, whereas no maintenance therapy was given to patients in the high risk group.

Two randomizations were performed. The first randomization concerned the schedule of L-asparaginase in the remission induction phase in the standard and intermediate risk groups: two doses a week *vs.* three doses a week for a total number of nine doses in both groups. The second randomization involved only intermediate risk patients: high-dose cytarabine at 2 g/m^2 8 times *vs.* cytarabine at 75 mg/m^2 15 times accompanied by cyclophosphamide at 1,000 mg/m^2 and 6-mercaptopurine at 60 mg/m^2 21 times in the post-remission induction intensification phase. No differences in event-free survival had been documented previously;[15] we, therefore, analyzed the randomized patients as a single subset. The detailed results of these randomizations will be reported separately.

Table 2. **Treatment regimens.**

Standard risk
Induction: Pred 60 mg/m^2×5 weeks, VCR 1.5mg/m^2 x 5, Pirarubicin 20mg/m^2×2, L-asp 6,000U/m^2×9 (2 times/week *vs.* 3 times/week, randomized)
Intensification 1: CY 1,000 mg/m^2, Ara-C 75 mg/m^2×15, 6MP 60mg/m^2×21
Intensification 2: MTX 3 g/m^2×3
Interim maintenance: 6 MP 60 mg/m^2×14, MTX 25 mg/m^2×3
Reinduction: Pred 60 mg/m^2×14, VCR 1.5 mg/m^2×3, Pirarubicin 20 mg/m^2×3, L-asp 10,000U/m^2×4
Late intensification 1: CY 1,000 mg/m^2, Ara-C 75 mg/mm^2×10, 6MP 60 mg/m^2× 14
Late intensification 2 (3 cycles): MTX 500 mg/m^2, PSL/VCR/L-asp (2 wks)
Maintenance: 6 MP/MTX until week 146.
Total number of IT therapies: 11

Intermediate risk
Induction: Pred 60 mg/m^2×5 wks, VCR 1.5 mg/m^2×5, DNR 25 mg/m^2×4, CY 1,000 mg/m^2×2, L-asp 6000U/m^2×9 (2 times a week *vs.* 3 times a week)
Intensification 1 (Randomized): High-dose Ara-C (2 g/m^2×8), L-asp (10,000U/m^2) *vs.* CY 1,000 mg/m^2, Ara-C 75 mg/m^2×15, 6 MP 60 mg/m^2×21
Intensification 2: MTX 3 g/m^2×3
Interim maintenance: 6 MP 60 mg/m^2×14, MTX 25 mg/m^2×3
Reinduction 1: DEXA 6 mg/m^2×14, VCR 1.5 mg/m^2×4, DXR 25 mg/m^2×4, L-asp 10,000U/m^2×4
Late intensification 1: CY 1,000 mg/m^2, Ara-C 75mg/m^2×10, 6MP 60 mg/m^2× 14
Late intensification 2 (2 cycles): Ara-C 2 g/m^2×4 with L-asp 10,000U/m^2×1, MTX 500 mg/m^2
Reinduction 2: Pred 60 mg/m^2×14, VCR 1.5 mg/m^2×3, Pirarubicin 20 mg/m^2× 3
L-asp 10,000 U/m^2 × 4
Late intensification 3: CY 1,000 mg/m^2, Ara-C 75 mg/m^2 x 10, 6MP 60 mg/m^2 x 14
Maintenance: 6MP/MTX until week 104.
Total number of IT therapies: 10 or 11

High risk
Induction: Pred 60 mg/m^2×5 weeks, VCR 1.5mg/m^2×5, DNR 25 mg/m^2×4, CY 1,000 mg/m^2×2, L-asp 6,000U/m^2×9
Intensification 1: High-dose Ara-C (2 g/m^2×8) with L-asp (10,000 U/m^2) CY 1,000 mg/m^2, Ara-C 75mg/m^2×15, 6MP 60 mg/m^2×21
Intensification 2 (2 cycles): Ara-C 3 g/m^2×6, Etoposide 100mg/m^2×5, Mitoxantrone 10 mg/m^2
Allogeneic SCT if indicated. If not, proceed to the followings:
Intensification 3: high-dose MTX 3 g/m^2, CY 200 mg/m^2×5, VCR 1.5 mg/m^2
Repeat Intensification 2 twice, then repeat Intensification 3
Intensification 4 (2 cycles): Ara-C 3 g/m^2×4, L-asp 10,000 U/m^2
Cranial irradiation with 6MP 60 mg/m^2×14
No maintenance: Treatment stopped at week 48
Total number of IT therapies: 9-17

Statistical analysis

The duration of event-free survival was defined as the time from the initiation of therapy to either treatment failure (relapse, death, or diagnosis of secondary cancer) or to the last day when the patient was confirmed to be in remission. In those patients who did not achieve complete remission after the first induction phase or who died before the confirmation of remission, treatment was considered to have failed at day 0. The probability of event-free survival was estimated by the Kaplan-Meier method, and was tested for significance using the log-rank test.

For multivariate analysis, the Cox proportional hazards model was employed to assess independent effects of risk factors on event-free survival. All calculations were performed by PC-SAS (SAS Institute Inc., PC-SAS, version 8, 2000, Cary, NC, USA).

Results

The numbers of peripheral leukemic blasts on day 8

The number of leukemic blasts was assessed in all patients (Table 3). Prephase prednisolone was administered to all the patients except six in whom vincristine and/or cyclophosphamide was used before day 8 because of insufficient cytoreduction. Overall, blasts were not detectable in 249 patients (33.0%) (*Day8NoBlasts*), 392 patients (52.0%) had a blast count of 1-999/μL, and 113 patients (15.0%) had a blast count ≥ 1,000/μL. In the subset of 90 patients with T-ALL, 23 (25.6%) fell in the *Day8NoBlasts* group, whereas 226 (34.0%) out of the 664 patients with B-lineage ALL belonged to the *Day8NoBlasts* group. Of note, 15

Table 3. The number of patients stratified by peripheral blood leukemic blast count on day 8.

Immunophenotype	*The number of peripheral blood leukemic blasts per μL*		
	0	*1-999*	*≥1,000*
B-lineage ALL			
Initial SR group	132*	148	22
Initial IR group	88	175	34
Initial HR group	6	34	25
T-ALL	23	35	32

*SR: standard risk; IR: intermediate risk; HR: high risk. *The numbers of patients in each category are shown.*

patients (9 with T-ALL and 6 with B-lineage ALL) in the initial high risk group achieved the status of *Day8NoBlasts*, despite high initial leukocyte counts exceeding 50,000/μL.

Subsets of patients with abnormal karyotypes were further analyzed: 25 (35.7%) of the 70 patients with *TEL/AML1* rearrangement achieved *Day8NoBlasts*, as did 69 (37.9%) of the 182 patients with high hyperdiploidy (more than 50 chromosomes), 3 (8.1%) of the 37 patients with *E2A/PBX1* rearrangement, 4 (36%) of the 11 patients with *MLL* rearrangement, and 2 (11.8%) of the 17 patients with the *BCR/ABL* fusion.

Treatment outcome

Remission was achieved in 736 (97.6%) of the 754 patients: non-T ALL: 98.6%, T-ALL: 94.4%. The probability of event-free survival for all patients was 79.6±1.6% (SE) % at 4 years, whereas the event-free survival rates for patients with B-lineage ALL and T-ALL were 80.5±1.7% (n=664) and 66.0±5.1% (n=90), respectively (Figure 1). The event-free survival for patients stratified finally on day 43 (T-cell ALL included) were as follows: 92.4±1.8% in the standard risk group (n=262), 80.3±2.6% in the intermediate risk group (n=313), and 57.8±4.1% in the high risk group (n=179). The event-free survival for patients with *Day8NoBlasts* was 90.4±2.0% (n=249), which was significantly better than that for the other patients (74.2±2.2%; $p<0.01$) (Figure 2). The event-free survival for *Day8NoBlasts* patients with T-ALL (n=23) was 95.7±4.3%, which was comparable with that of patients with B-lineage ALL (n=226), 89.8±2.1% ($p=0.45$. Figure 3).Treatment failed in only one patient with T-ALL with *Day8NoBlasts* because of death due to pancreatitis during remission induction. The event-free survival for patients with *Day8NoBlasts* and blast counts of 1-999/μL in the initial standard risk group with B-lineage ALL did not differ (90.5±2.6% *vs.* 92.5±2.5%; $p=0.82$), whereas there was a significant difference in the initial intermediate risk group with B-lineage ALL (89.4±3.6% *vs.* 72.7±3.9%; $p=0.004$). Lastly, in the initial high risk group with B-lineage ALL, five out of six patients with *Day8NoBlasts* had a good outcome.

Multivariate analysis

The significance of *Day8NoBlasts* was further analyzed using a Cox proportional hazards model. The results of the multivariate analysis are shown in Table 4. Age at diagnosis, the initial white blood cell count, immunophenotype (T-ALL *vs.* non T-ALL), and gender did not remain as statistically significant independent factors. Only *Day8NoBlasts* and high hyperdiploidy were statistically significant. We also assessed the prognostic value of *Day8NoBlasts* by dividing the counts into three categories; 0/μL, 1-999/μL, and ≥1000/μL. No difference was observed between the 1-999/μL and ≥1000/μL categories in the univariate analysis; the risk ratio for ≥1000/μL against 1-999/μL was 1.23 (95% CI: 0.98-1.56) whereas the risk ratio for ≥1000/μL against 0/μL was 0.46 (95% CI: 0.33-0.62). The results were similar when this prognostic factor was used as a three-category term in the multivariate analysis. These results led to the use of this prognostic factor as a two-category factor for simplicity and convenience for use in other studies.

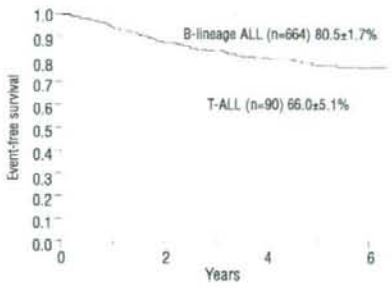

Figure 1. Kaplan-Meier plots of event-free survival according to immunophenotype (B-lineage ALL and T-ALL).

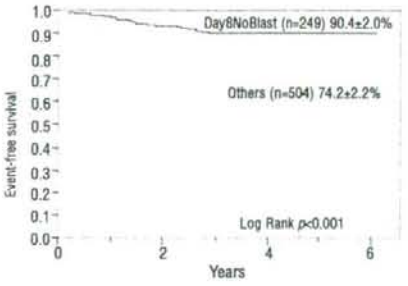

Figure 2. Kaplan-Meier plots of event-free survival of patients with no detectable blasts on day 8 and the other patients: the difference between the two curves at 4 years was highly significant ($p<0.001$ by the log-rank test).

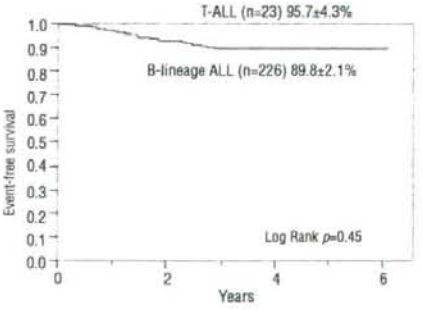

Figure 3. Kaplan-Meier plots of event-free survival of patients with no detectable blasts on day 8 divided according to the immunophenotype: the event-free survival at 4 years for *Day8NoBlasts* patients with T-ALL was comparable to that of patients with B-lineage ALL ($p=0.45$ by the log-rank test).

Discussion

The concept that an early response to treatment is strongly predictive of relapse has been overwhelmingly emphasized. Here, we added novel information that patients whose peripheral blood blasts disappeared after 7 days of prednisolone monotherapy had an excellent prognosis, that is, a 4-year event-free survival of 90%. Of note, such patients constituted one third of all children with ALL, thus being quite a large group. *Day8NoBlasts* was also an independent prognostic factor when assessed by multivariate analysis. Of interest, a substantial proportion of patients with *TEL/AML1* rearrangement and high hyperdiploidy achieved *Day8NoBlasts* (36% and 38%, respectively), while a very small proportion (6%) of patients with *E2A/PBX1* did so, suggesting that the kinetics of reduction in leukemic blasts may be different in subsets of patients defined by genetic changes.

One of the limitations of our study was that the enumeration of blasts in the peripheral blood was done by microscopic evaluation, which is a subjective method. The results might, therefore, not be reproducible with confidence; however, the percentages of patients with blast counts of 0/μL, 1-999/μL and ≥ 1000/μL on day 8 in the present L99-15 study (33%, 52%, 15%, respectively) were almost identical to those of our most recent L99-1502 study (31%, 53%, 16%, respectively). On the other hand, there remains a possibility that patients having been staged down by this stratification system to less intensive treatment could even have fared better (i.e. over 90%) if treated according to the older stratification system. In the next study, we plan to employ more objective methods, such as flow cytometry.[14]

In this study, we confirmed the importance of the sensitivity of leukemic blasts to steroids. Since we did not administer intrathecal therapy until day 8, our assessment of the reduction of leukemic cells in peripheral blood on day 8 should exclusively reflect an early response of leukemic blasts to steroids.[12] Steroids function as antileukemic agents mostly by inducing ALL cells to undergo apoptosis, but little was known about critical molecules involving steroid-induced apoptosis of leukemic cells. Many investigators have addressed this issue by using gene expression profiling and several candidate genes, which might be able to predict steroid sensitivity, have been identified:[15-18] apoptotic pathway-associated genes (*MCL-1, DAPK1, CASP8A2, TXNIP, ZBTB16*), carbohydrate metabolism-associated genes, MAPK pathway-associated genes, and NF-κB-associated genes. Of these genes, *CASP8A2*, a caspase 8-related molecule, was identified as a crucial molecule differentially expressed by leukemic cells at diagnosis between patients who had high and low levels of minimal residual disease in bone marrow 18 and 45 days after the initiation of induction therapy, and it can predict both *in vitro* cell growth and prognosis.[16] One could identify the new molecule, which determines steroid sensitivity, using a similar methodology, for example, comparing gene expression patterns of leukemic cells from patients with *Day8NoBlasts* with those of patients with a classic poor response to steroid.

Table 4. The results of the multivariate analysis.

Factor	Risk ratio	95% CI	p value
No blasts 0 at day 8	0.46	0.33-0.62	<0.001
High hyperdiploidy	0.66	0.51-0.84	<0.001
TEL-AML1	0.85	0.61-1.13	0.27
T-ALL	0.89	0.71-1.13	0.34
Male	0.97	0.82-1.16	0.75
Age at presentation >10 years old	1.00	0.82-1.25	0.96

The early response to steroids has been utilized to stratify children with ALL as a tradition by the BFM group since the early 1980s.[3,8] This group uses the cut-off of 1,000 blasts/μL, among other cut-offs, to identify the approximately 10% of patients with a very high risk of relapse;[19] however, the cut-off of 0 blasts has never been used.[20] We demonstrated that one-third of patients with a better prognosis could be identified by the use of this new cut-off of 0 blasts/μL. In this study, patients with no blasts on day 8 were identified not only in the initial low risk group but also in the initial higher risk groups: 94 of 362 patients with B-lineage ALL in the intermediate and high risk groups and 23 of 90 patients with T-ALL. Generally, children with T-ALL have a poorer outcome than those with B-lineage ALL and need more intensive treatment. We, however, showed that patients with T-ALL as well as those with B-lineage ALL had a favorable outcome if circulating leukemia cells could not be detected on day 8 of therapy. By using the cut-off of 0 blasts, we could select patients, including those with B-lineage ALL in the initial higher risk groups and those with T-ALL, who could be targeted for treatment reduction, as some previous studies showed that a subset of patients with ALL could be cured with less intensive regimens.[21,22]

Authorship and Disclosures

AM and AO designed the research, analyzed data and wrote the paper; DH analyzed the data and reconstructed the text; KI, RH and MT designed the research; AO, KK, TS, NK, AK, HT and YH analyzed the data; MT is a chairman of the TCCSG.

The authors reported no potential conflicts of interest.

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総　説

小児がん経験者の長期フォローアップ

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Long-Term Follow-Up for Childhood Cancer Survivors

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Abstract The literature review of cumulative survival and cause-specific mortality revealed that the mortality of childhood cancer survivors has been significantly high even after 5 years have passed (the standardized mortality ratio was 4-17). The 5-year survivors of childhood cancer have also a high rate (60-70%) of chronic burden of disease from various late effects. The cumulative incidence of second malignant neoplasmas was 3.5-4.7% at 25 years and the standardized incidence ratio was 3.6-6.38. These results confirm the requirement of life-long follow-up of children with cancer. I introduced the models of long-term care for childhood cancer survivors (advantages and disadvantages of various types), and explained the follow-up programs which were proposed in the United States of America, the United Kingdom, Germany, Italy and so on. Lastly I discussed the issues about long-term follow-up for childhood cancer in Japan.

要　旨　累積生存率と原因別の死亡解析を文献レビューした結果，診断後5年が経過した後でも小児がん経験者の死亡率は統計学的に有意に高く，標準化死亡比は4～17であった．また5年以上生存した小児がん経験者の多く（60～70%）は，種々の晩期合併症による後遺症を抱えていた．二次がんの累積発症率は，診断後25年で3.5～4.7%とされており，標準化発生比は3.6～6.38であった．以上の結果から，小児がん経験者においては一生にわたるフォローが必要と考えられる．小児がん経験者の長期フォローアップのモデルに関して，それぞれの長所と短所を紹介した．アメリカ合衆国，イギリス，ドイツ，イタリアなどで施行・提唱されている長期フォローアッププログラムを解説し，最後に本邦における問題点について述べた．

Key words:　long-term follow-up, childhood cancer survivors, late effects, mortality, secondary cancer

I. はじめに

小児期に発症するがんの治療成績の進歩は顕著で，最近の5年寛解生存率は70～80%に及び，本邦にも数万人以上の小児がんの長期生存者（以下小児がん経験者）が存在し，成人期を迎えた小児がん克服者の数は若年成人の400～1,000人に1人にあたるといわれている[1,2]．

小児がんは身体的・精神的に成長途上に発病するため，成人のがんとは違い，疾患のみの影響だけではなく治療の影響を強く受けることが予想される．また治療終了後にも40～50年にわたる長期の生命予後が期待され，復学や社会復帰と就労に加えて，結婚および出産などを含めた数多くのイベントを迎えるため，自立支援を含めた長期経過観察の重要性が高まっている．長期フォローアップ（以下FU）に関しては欧米に比べて本邦では整備された体制がないために，治療終了後は各施設医師個人の努力に依存しているのが現状であり，残念ながら本邦では晩期合併症の実態すらも十分に把握されていない．

本邦の小児がん治療が欧米のグループスタディを参考にしながら進歩してきたことを考えると，人種差があるとはいえ，欧米の実態に近いものではないかと予想される．小児がん経験者の治療終了後の問題に関しては，以前に本誌の総説で前田が身体的晩期合併症とQuality of life（QOL）の問題[3]，小澤がPost traumatic stressの問題[4]

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を取り上げているので，本稿では重複を避けて小児がん経験者の長期生命予後，晩期合併症の頻度と二次がんの問題を取り上げ，小児がんの長期 FU に対する欧米各国の取り組みの現状について紹介し，本邦の問題点に関して考察する．

II. 小児がんの長期生存率（Table 1, Fig. 1, 2）

これまでに診断後 5 年以上生存した小児がん経験者の長期生命予後に関しては多くの報告があり，そのおもなものを Table 1 にまとめた[5-12]．発表年やフォローアップ期間などにより多少数字にはばらつきはあるものの，共通しているのは長期生存の割合は 86～92%であり，死亡症例は 10%前後で，標準化死亡比（標準化死亡比＝実死亡数/期待死亡数×100）は 8～17 と，同年齢コントロールに比較すると約 10 倍であること，死亡原因の第 1 位は原発がんの再発であり，約 60～70%を占めること，二次がんによる死亡は観察期間が長くなるに従い増加するが，7～20%であり，心合併症を含めた二次がん以外の晩期合併症によると考えられる死亡の割合は 4～15%であることなどである．

その中の代表として，北米の CCSS（Childhood Cancer Survivor Study）の同年齢のアメリカ人男女（コントロール群）と比較した生存曲線を Fig. 1 に示した[7,11]．小児がん経験者の生存率は 30 年後には約 80%に低下すると予想される結果であり，年間死亡は 1,000 患者・年あたり 8.4 で，診断後 20 年以上たってからもコントロール群と差が広がり続けている．全体では女性の生存率がやや高いが，年齢構成により調整した死亡率である標準化死亡比では，小児がん女性が 13.2（95% CI: 12.5～14.0）と，男性の 6.6（95% CI＝6.3～7.0）に比べて約 2 倍高かった．また治療内容としては手術・放射線照射・化学療法の集学的治療を行った症例の標準化死亡比が 10.1（95% CI＝9.5～10.8）と高値であった[7,11]．

Fig. 2 にその死亡原因別の経時的な累積を示したが，原病の再発が全体死亡原因の中では 58%ともっとも多いものの，再発自体は約 15 年後からはプラトーに近くなるのに対し，15 年以後に死亡原因として問題になってくるのは心合併症（死亡原因全体の 7.0%），呼吸器合併症（同 1.8%），二次がん（同 14.8%），その他（同 16.7%）などのいわゆる晩期合併症で，とくに悪性度の高い二次がんが多くを占めている[7,11]．それぞれの標準化死亡比は，二次がんが 12.8，心疾患が 5.7，呼吸器疾患が 7.6 という結果であった．これに関連して，Castellino らは長期生命予後に対する人種差を調査しているが，晩期累積死亡率，二次がんの累積罹患率などについては

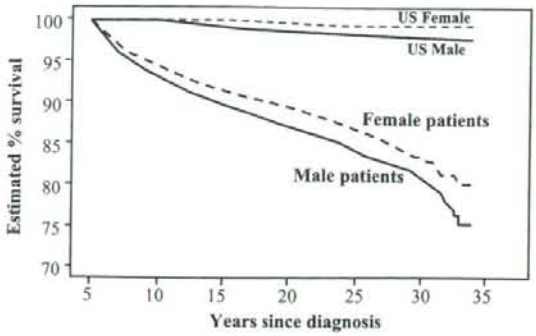

Fig. 1　Cumulative survival of 5-year childhood cancer survivors（sex-specified）

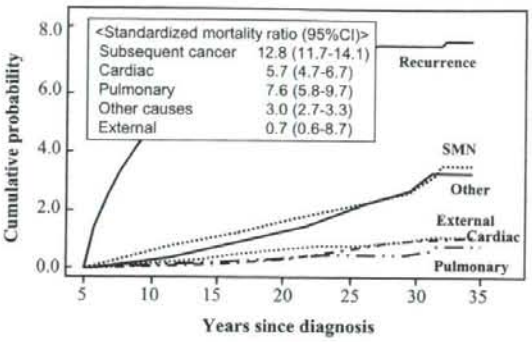

Fig. 2　Cumulative cause-specific mortality of 5-year childhood cancer survivors

大きな差がなかったと報告している[7,11]．また最近 Lawless らは，15 年以上生存した小児がん経験者 565 人のその後の死亡原因を調査しているが，それによると死亡原因の第 1 位は二次がんで 39%（15/38）を占め，原病の再発（8/38＝21%）を上回る結果であった[13]．

2007 年のアメリカ臨床癌学会で，CCSS から Wasilewski-Masker によって小児がん経験者の再発率に関するデータが報告された．それによると，5 年以上生存していた 12,948 人の小児がん経験者のコホートにおいて，5～28.9 年（中央値 7.9 年）の経過観察で 670 人（5.2%）に再発がみられた．20 年の統計学的累積再発率（95% CI）は，白血病 4.9%（4.3～5.6），脳腫瘍 10.8%（9.4～12.5），悪性リンパ腫 4.0%（3.3～4.8），ウィルムス腫瘍 0.9%（0.5～1.7），神経芽腫 2.4%（1.6～3.6），ユーイング肉腫 13.2%（10.1～17.3），軟部腫瘍 4.8%（3.9～5.9）であった．多変量解析による晩期再発の危険因子は，原疾患としてはユーイング肉腫（HR＝2.3）と脳腫瘍（HR＝2.7），10 歳以上の発症（HR＝1.4），化学療法（HR＝1.5）と放射線治療（HR＝1.4）であった．

Table 1 Comparison of data for 5-year survivors of childhood and adolescent cancer[5-12]

Leading author (published year)	Robertson[5] (1994)	Hudson[6] (1997)	Mertens[7] (2001)	Moller[8] (2001)	Cardous-Ubbink[9] (2004)	Dama[10] (2006)	Mertens[11] (2007)	MacArthur[12] (2007)
Country	Britain	USA	USA (CCSS)	Nordic	Netherland	Italy	USA (CCSS)	Canada
Type of study	Population	Hospital	Hospital	Population	Hospital	Population	Hospital	Population
Period of diagnosis	1971–85	1962–83	1970–86	1960–89	1966–96	1967–99	1970–86	1970–95
Age (y) at diagnosis	0–14	0–19	0–20	0–19	0–18	0–14	0–20	0–19
Last follow-up	1990/12/31	1993/12	1996/12/31	1995/12/31	1998/1	2004/6/30	2002/12/31	2000/12/31
No. of the survivors	9,080	2,053	20,227	13,711	1,378	1,698	20,690	2,354
Alive	8,287 (91.3%)	1,795 (87.4%)	18,197 (90.0%)	12,289 (89.6%)	1,258 (91.3%)	1,554 (91.5%)	17,867 (86.40%)	2,173 (92.3%)
Dead	793	258	2,030	1,422	120	144	2,823	181
Causes of death (%)								
Primary cancer	72.9	61.5	67.4	68.6	74.2	62.2	57	69.1
Second cancer	6.6	20.2	12.7	7.0	15.8	12.5	15	7.7
Cardiovascular	—	3.1	4.5	—	2.5	1.4	7	—
Other causes	15.3	7.0	4.1	11.3	1.7	8.3	6	12.2
Non-cancer related	2.5	8.1	11.3	11.7	5.8	15.4	15	—
(accidents)	(1.3)	(7.4)	(5.1)	—	(3.3)	(5.6)		
Unknown	1.5			1.4				11.0
Standardized mortality ratio (95% CI)	4.0 (3.0–5.0)	15.0 (12–19)	10.8 (10.3–11.3)	10.8 (10.3–11.5)	17.0 (14.3–20.6)	9.3 (7.8–10.9)	8.2 (7.9–8.5)	9.1 (7.8–10.5)

また再発症例の51.6%の症例は最終観察日までに死亡していた[14]。

III. 小児がんの晩期合併症の頻度

1. 北米CCSSの報告（Fig. 3）

Oeffingerらは，身体的な晩期合併症の程度を，Common Terminology Criteria for Adverse Events（CTCAE ver.3.0）に従って，グレード1：軽度，グレード2：中等度，グレード3：重度，グレード4：致死的，グレード5：死亡，と5段階に分けて分析した[15]。

身体的な晩期合併症のうち，少なくとも1つの軽度以上の障害（グレード1〜5）は62.3%，重度の障害（グレード3〜5）は27.5%の小児がん経験者でみられ，2つ以上複数の晩期合併症は37.6%でみられた。身体的晩期合併症の30年の累積発症率は，軽度以上の障害で73.4%，重度の障害では42.4%にも達した（Fig. 3A）。この点から，治療終了後数年あるいは5年たった時点で晩期合併症がない場合であっても，長期フォローは必須であることが裏付けられた。グレード3〜5の障害については，曲線の傾きはなだらかではあるものの，20〜30年たってから初めて出現することもあり，やはり長期フォローアップの重要性を示している[15]。

原疾患別にみると，Fig. 3Bに示したような3つのパターンがある。第1のパターンは，白血病のように診断後5年の時点で晩期合併症は20〜30%で比較的なだらかなカーブを描くタイプで，ウイルムス腫瘍や神経芽腫がそれにあたる。第2のタイプは，脳腫瘍のように診断5年後に既に60%近い症例がなんらかの晩期合併症を有しており，常に第1のタイプより晩期合併症率が高く持続するもので，脳腫瘍以外に骨腫瘍がこのタイプにあたる。3番目のタイプは，ホジキンリンパ腫のように診断後5年の時点で晩期合併症が約40%であり，第1のタイプと第2のタイプの中間に属するもので，軟部組織腫瘍や非ホジキンリンパ腫がこのタイプに近い[15]。

2. オランダからの報告（Fig. 4）

Geenenらは，オランダEmma小児病院で1962年から1996年の間に治療を受け，5年以上生存していた小児がん経験者1,362人を対象に，2004年の時点で晩期合併症の評価を行った[16]。対象症例はCCSSの報告よりかなり少ないが，CCSSが小児がん経験者本人のアンケート調査結果をもとに解析しているのに対して，本研究の最大の特徴は，すべて医療機関で評価を行っている点である。フォロー期間の中央値は17年（評価時の年齢は24.4歳）で，フォローアップ完遂率は94.3%であった。その結果，75%の経験者が，1つ以上の合併症をもっており，24.6%は5種類以上の合併症を抱えていた。また40%が重度か致死的な合併症を有していた。治療法別の分析では，放射線治療で55%，化学療法で15%，手術では25%が重度か致死的な合併症を有していた。以上の結果では，CCSSよりもやや晩期合併症率が高くなっているが，著者らはCCSSでは評価できなかった心理社会学的な問題（全体の頻度は7.9%）を含んでいるためであろうと推察している。Fig. 4に示したように重度の合併症は，骨腫瘍と脳腫瘍で高く，治療法としては放射線治療を行って

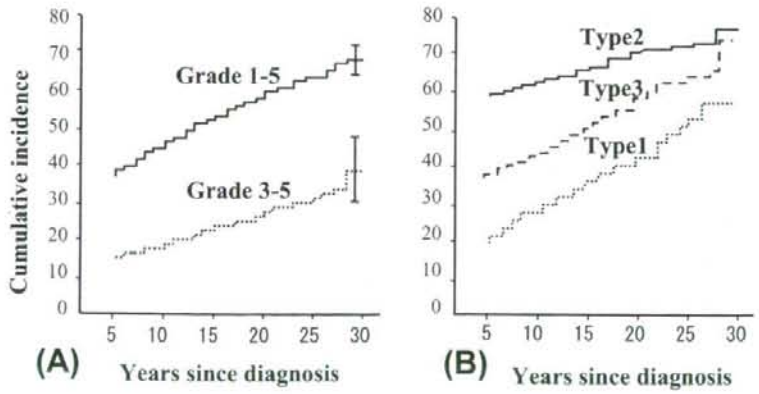

Fig. 3 Cumulative incidence of chronic health conditions among 5-year childhood cancer survivors[15]
The severity of subsequent health conditions was scored according to Common Terminology Criteria for Adverse Events (CTCAE ver.3.0) as either mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4) or fatal (grade 5). (A) All cancers. (B) The pattern of cumulative incidence according to the original cancer. Type 1: leukemia, Wilms' tumor and neuroblastoma, Type 2: brain tumor and bone tumor, Type 3: Hodgkin's lymphoma, non-Hodgkin's lymphoma and soft-tissue sarcoma.

いるものにとくに高い傾向がみられた[16]．

以上の2つの研究は，方法がまったく異なるにもかかわらずほとんど同様の結果を示しており，少なくとも1990年代までに治療を受けた小児がん経験者では約2/3以上の症例になんらかの晩期合併症を認めることが予想されるため，小児がん経験者の長期フォローアップの重要性が再確認された[17]．

IV. 二次がん（Fig. 5）

小児がん経験者の治療後20年間の二次がん累積リスクは3～10%で，これは一般集団に推定される値よりも3～20倍高くなっている[18]．小児がんが成人のがんと比べ二次がんのリスクが高くなる理由としては，遺伝的な要因があるものが一部存在すること（Li-Fraumeni症候群など），発育盛りの時期に発病・治療をすること，治療終了後の生命予後が長いため，長い潜伏期の後に明らかになる治療の影響が出やすいことなどが考えられる．Fig. 5に示した網膜芽腫を除外したCCSSの研究では，非黒色腫皮膚がんを除く二次がんの累積発症率は20年で3.2%，25年で4.7%であり，30年以降は統計学的に

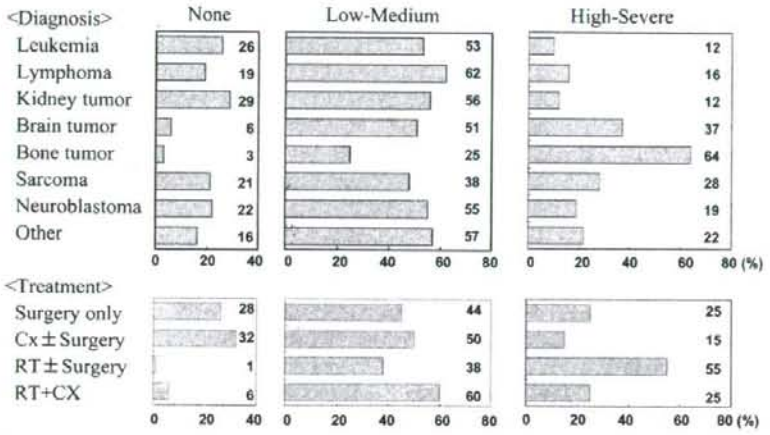

Fig. 4　Distribution of adverse events burden scores among 5-year survivors of childhood cancer[16]
(A) Primary childhood cancer: High and severe adverse events were common among the patients with brain tumor or bone tumor. (B) Treatment category: High and severe adverse events were common among the patients receiving radiotherapy.

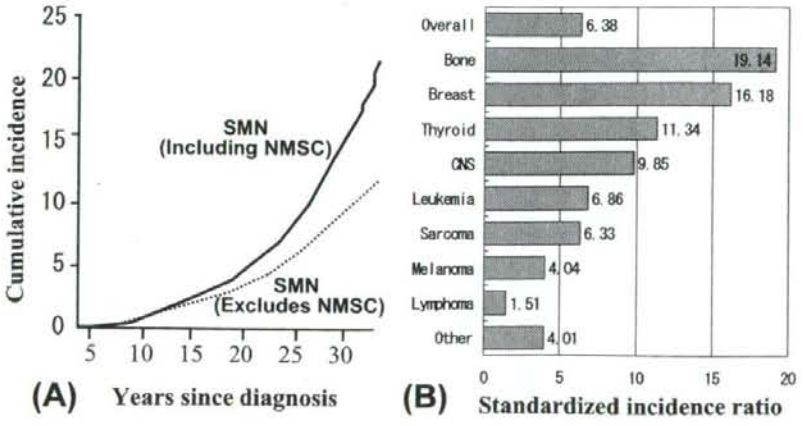

Fig. 5　Cumulative incidence of second malignant neoplasmas in the Childhood Cancer Survivor Study cohort (5-year survivors of childhood cancer)[20]
(A) All second neoplasmas with or without NMSC (nonmelanoma skin cancer). (B) Standardized Incidence Ratios according to subsequent cancers.

は約 10%の人に二次がんがみられる可能性が示された[17,20]．全体の二次がん危険率の標準化発生比（SIR）は全体では 6.38 であり，その中でも骨腫瘍（SIR＝19.1），乳がん（SIR＝16.2），甲状腺がん（SIR＝11.3）の SIR は 10 以上と非常に高い[19,20]．一方，イギリス[21]や北欧[22]の Population-based コホート研究でも，それぞれ SIR は 6.2 と 3.6，25 年累積発症率は 4.2%と 3.5%と，ほぼ同様の結果がみられている[23]．

二次がん発症までの中央値は白血病や脳腫瘍では 10 年以内と比較的短いが，乳がんや甲状腺がん，悪性リンパ腫では 10 年以上であり，その後の追跡調査でも二次がんは増加を続けており，生涯リスクは依然として不明である．それに関連して，最近 CCSS から統計学的に二次がんの発症数を予測する手法が報告されており，今後の検証結果が注目される[24,25]．

治療に関連した二次がん発症のリスク因子としては，放射線療法が固形腫瘍と白血病の両者の発症と関連し，アルキル化剤，白金製剤[26]，トポイソメラーゼ II 阻害剤[27,28]は，白血病の発症と関連している．放射線曝露を補正した多変量解析においては，女性であること，より年少での小児がん発症，ホジキンリンパ腫[29,30]または軟部組織肉腫の診断，およびアルキル化剤への曝露が独立因子として抽出された[19]．とくにホジキンリンパ腫の二次がんの統計学的累積頻度はきわめて高く，30 年後には約 40%にも及ぶ結果であった[20,29,30]．原疾患が急性白血病の場合，二次がん発症リスクは他の小児がんより低く，リンパ性（ALL）と骨髄性（AML）の差はみられなかった[20]．脳腫瘍[31]・軟部腫瘍も同様だが，ユーイング肉腫では骨肉腫に比べてやや高い傾向がみられ，この原因としては，ユーイング肉腫が放射線感受性がんであるために，照射症例が多くなることが関係していると考えられた[20,32]．

今後二次がんの病因解明が進むと考えられるが，環境曝露，食事の影響，ウイルスへの曝露，薬物代謝および DNA 修復酵素をコードする遺伝子における多型の研究を含めた遺伝子研究[33,34]により，遺伝子型-環境相互作用および個体間罹病性に関して，価値ある情報が提供されることが期待される．

V. 長期フォローアッププログラム（Fig. 6, 7）

1. アメリカ（Fig. 6A～D）

Aziz らは，24 のプログラムを分析して，理想的な小児がん経験者の長期ケアモデルを提案している[35]．プログラムのリーダーとしては，小児血液腫瘍医が最適であるが，小児がんの晩期合併症を熟知したプライマリケア医か内科医もその候補となる．コーディネーターとして，常勤の看護プラクティショナー，ソーシャルワーカー，心理学者（臨床心理士）が必要で，特殊な問題に関して

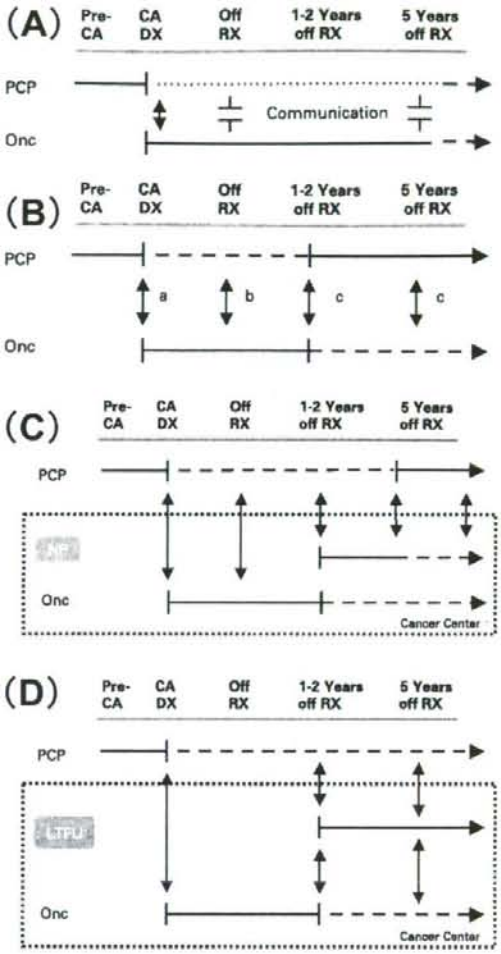

Fig. 6 Models for cancer survivors[35]
（A）Current practice.（B）Community-based shared practice. a: cancer diagnosis, stage and planned therapy, b: survivorship care plan（summary of cancer and cancer therapy, a list of potential late effects, up-to-date recommendations for monitoring for recurrence and late effects, contact information, c: continued update with changes in surveillance recommendations and new information regarding potential late effects.（C）Academically based survivor program models: Nurse practitioner-led shared care.（D）Academically based survivor program models: Multidisciplinary long-term follow-up program. CA: cancer, Dx: diagnosis, Off Rx: completion of cancer therapy, PCP: primary care physician, Onc: oncologist, NP: nurse practitioner, LTFU: long-term follow-up program.

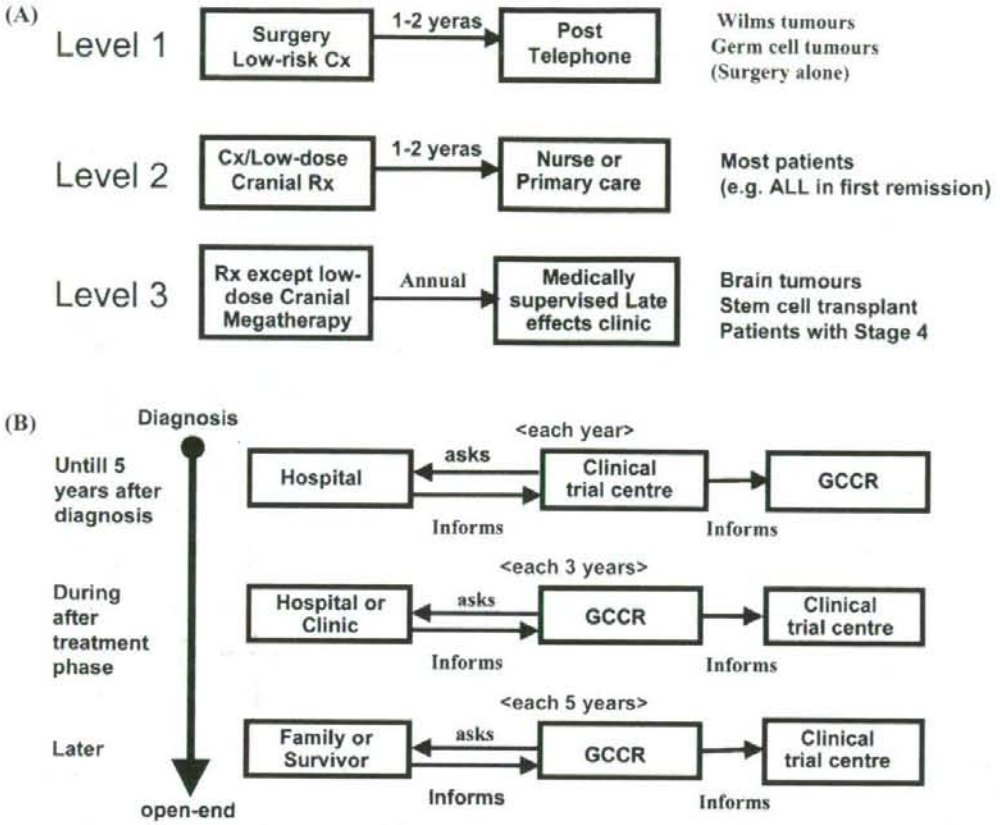

Fig. 7 Follow-up programs for childhood cancer survivors
(A) Proposed follow-up levels in the United Kingdom Children's Cancer Study Group (UKCCSG).
(B) Follow-up systems in the German Childhood Cancer Registry (GCCR).

は専門家のネットワークが不可欠である．治療終了2〜5年の間は，再発のサーベイと晩期合併症のスクリーニング開始，長期的な問題に関する小児がん経験者と家族の教育を行う．5年目以降は晩期合併症のスクリーニングに焦点をおき，健康増進や合併症のリスク減少に関する教育の比重を増やす．最低年1回の受診が必要だが，合併症のリスク次第では受診回数を増やす．小児期は小児病院か治療を受けたがんセンター（大学病院）の長期FU外来で，若年成人期以降は，小児長期FU外来か，若年成人のプログラムまたはコミュニケーションを継続したうえで地域の内科医によるフォローに移行する，というものである．

最近Oeffingerらは，成人のがんサバイバーのフォローアップケアについてのモデルを示した（Fig. 6）[36]．Fig. 6Aは，米国における現在の標準的なプログラムであり，がんと診断されたら，専門病院で腫瘍医が診療を行い，診断時の返事を除いて専門腫瘍医とプライマリケア医との情報交換はほとんど行われない．それに対して，Fig. 6Bは，地域密着型の共有プログラムであり，がんと診断された後も，治療は専門病院で腫瘍医が担当するが，地域プライマリケア医との情報交換を適宜行い，治療終了後1〜2年でプライマリケア医がフォローの中心となり，必要時に腫瘍医にコンサルトを行うというものである．

それに対して，学術的な基盤をもつプログラムも提唱されている．Fig. 6Cは看護プラクティショナー主導のもので，治療中から腫瘍医は看護プラクティショナーを介して，プライマリケア医と情報交換を行い，治療終了後1〜2年以降は看護プラクティショナーが主体となってフォローし，治療終了5年以降はプライマリケア医を主体にフォローするもの，Fig. 6Dは治療終了後1〜2年からは包括的な長期フォローアップ外来主導でフォローを行うというものである．

小児がん経験者では，これに加えて成人医療への移行の問題が重なる[37]ために，医療担当者の交代を考慮する必要があり，より複雑になる．この点はフォローアップ中の検査や受診費用の保険問題にも絡んで，米国でも大きな問題のようである[38]．

2. イギリス（Fig. 7A）

イギリスでは，Fig. 7A に示したように晩期合併症のリスク別に3つのレベルに分けてフォローアップが考えられている[39,40]．レベル1は，手術もしくは軽微な化学療法を行った症例（ウィルムス腫瘍や胚細胞腫瘍の1・2期，ランゲルハンス細胞組織腫瘍単一臓器型など）で，レベル2は多剤併用化学療法，または 24 Gy 未満の頭蓋照射を受けた症例，レベル3は 24 Gy 未満の頭蓋照射以外の放射線治療を受けた症例（ALL など多くの小児がん症例），または大量化学療法を受けた症例（脳腫瘍や造血幹細胞移植症例，病期4の進行症例など）である．レベル1は問題がなければ1〜2年に1度の郵便または電話でのフォロー，レベル2は問題がなければ1〜2年に1度の看護師またはプライマリケア医によるフォロー，レベル3では最低年に1回，晩期合併症の専門クリニックでフォローするというものである[39,40]．

3. ドイツ（Fig. 7B）

ドイツでは，マインツに本部を置く GCCR（German Childhood Cancer Registry）という小児がん登録センターが 1980 年以来の小児がん症例の登録を行っている[41,42]．2005 年までに 37,168 人の登録があり，ドイツ全体の 95 %以上を網羅していると考えられる．この GCCR は Fig. 7B に示したように，臨床研究と密接な関係をもち運営されている．診断後5年までは臨床研究センターを介して情報を得ているが，治療終了後長期フォローアップ時期になると，GCCR が病院またはクリニックと直接フォローアップ情報をやりとりし，若年成人期以降は家族または小児がん経験者自身と情報交換をしていくという形でのフォローが考えられている[42]．

4. イタリア（Fig. 8）

イタリアでは PPOA（Person Prevention Oriented Approach）というコンピュータシステムが構築されつつある[43]．これは，原疾患と治療内容によって晩期合併症リスクを判定し，自動的にフォローアップ計画を作成するというものであり，現在試作が進んでいる．Fig. 8 に示したように原疾患と医療内容によるリスク臓器を定義し，安全で効果的なコストベネフィットのあるフォロー計画をコンピュータによって自動作成した後，いくつかのルールと担当医の判断によりフォロー計画の改訂をするというものである．

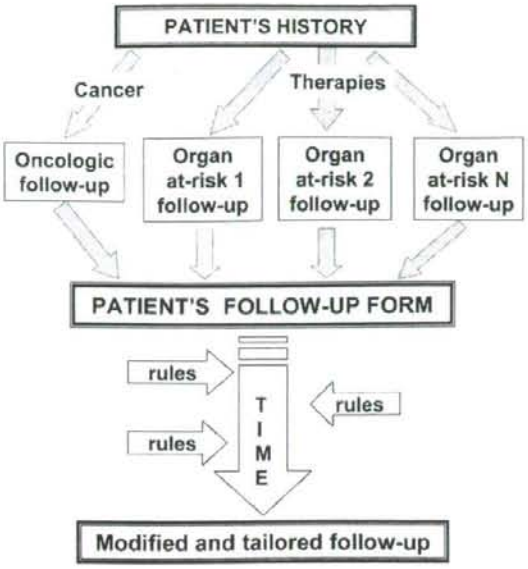

Fig. 8　Long-term follow-up programs by the Person Prevention Oriented Approach（PPOA）[40]

5. その他

第1回ヨーロッパ小児がん晩期合併症シンポジウム（2007 年 4 月 19〜20 日，スウェーデン，ルンドで開催）では，その他にオランダの LATER プロジェクト，デンマーク（コペンハーゲン）の Late effects Clinic を中心とするもの，米国サウスウエスタン大学の ACE（After the Cancer Experience）プログラムなどの報告があった．また Children's Oncology Group（COG）の秋季ミーティング（2007 年 10 月 16〜20 日，米国デンバーで開催）では，COG の長期 FU ガイドラインに基づいた治療サマリーと FU 計画作成をコンピュータで自動的に行う Passport for care などの報告があり，世界中で種々のプログラムが試行されている．

VI. 長期フォローアップケアモデルの紹介（Table 2）

COG のホームページ上[44]で，長期フォローアップケアモデルとしてあげられているものを比較して Table 2 にまとめて示した．それぞれに長所，短所があり，本邦の環境に合うものを採用していく必要がある．治療終了後5年くらいした後は，必要に応じて治療を担当した病院と長期 FU 拠点病院の長期 FU 外来と共同でフォローしていくことが望ましいと考えられるが，若年成人期以降については，今のところ本邦では良いモデルの確立が困難であり今後の大きな課題である．

Table 2 Models of long-term follow-up care[44]

MODEL	ADVANTAGES	DISADVANTAGES
CANCER CENTER: Primary Oncology Care LTFU occurs as continuation of on-therapy experience with treating oncologist in pediatric oncology clinic	• Comfortable for patients and family who have developed relationship with treating oncologist • Continuity of care • Oncologists don't feel they have to "give up" their patients to another provider	• Provider attention may be distracted by acuity of on-therapy patients • Illness (not wellness) focus • Potential lack of provider interest in or knowledge of late effects • Relapse-focused follow-up rather than risk-adapted screening and health promotion focus • Research may be difficult to coordinate
CANCER CENTER: Specialized LTFU Clinic LTFU handled by a designated late effects team in a separate clinic within or outside of the pediatric oncology clinic setting	• Providers with expertise in late effects • Emphasis on improving survivor knowledge of cancer treatment and risk • Comprehensive risk-based screening and follow-up care • Continued connection with cancer center provides "comfort zone" for survivor • Focus on modifiable risk factors • Health education • Opportunity to train healthcare professionals • Access to established network of sub-specialists with commitment to survivor care • Structure for research	• Cancer center may have negative connotations for survivors who want to "move on" • Survivors may not feel comfortable in pediatric setting as they get older • May not be geographically convenient • May discourage survivor use of primary care • Protects patient from having to negotiate their own healthcare in the community • Requires multiple hospital resources • Lack of familiarity and expertise of pediatric team with adult issues that arise as survivor enters adulthood
CANCER CENTER: Shared Care Care provided within a specialized cancer center program (e.g., Neuro-oncology; Leukemia/Lymphoma); LTFU clinician directs LTFU aspects of care	• Patient benefits from combined expertise of primary treatment team and late effects specialist • Structure promotes opportunities for research and training of healthcare professionals • Continued connection with treatment team and clinic setting provides "comfort zone" for survivor • Allows for continuity of care and ease of communications between oncologist and LTFU clinician • Provides smooth transition	• May discourage use of primary care provider (PCP) • Requires substantial hospital resources and dedicated clinicians as survivor population grows • Protects patient from having to negotiate their own healthcare
YOUNG ADULT TRANSITION: Formalized Transition Program Follow-up in a specialized clinic staffed by adult oncologist nurse practitioner or family practice physicians nurse practitioners with expertise in late effects of therapy; often in a partnership between treating pediatric institution and adult-focused academic setting	• Pediatric providers facilitate smooth transition to adult program • Collaborative approach to care • Established relationship with pediatric provider makes transition more comfortable for survivor • Multidisciplinary approach with access to adult-focused specialists as needed • Rich environment for ongoing research with young adults survivors as they age; ability to access ongoing studies at treating institution	• Not designed to provide primary care services • May not always be geographically convenient for survivors as they age and become more independent transient

Table 2 (continued)

MODEL	ADVANTAGES	DISADVANTAGES
[illegible] ADULT TRANSITION Adult Oncology-Oriented Care Adult oncologist in the cancer center or community provides LTFU care	• Specialized oncology-focused care • May be more convenient for patient (if in local community)	• Provider attention may be distracted by acuity of on-therapy patients • Illness (not wellness) focus • Potential lack of provider interest in or knowledge of late effects • Relapse-focused follow-up rather than risk-adapted screening and health promotion focus • Research may be difficult to coordinate
COMMUNITY-BASED CARE The pediatrician, family practice physician, advanced practice nurse, or internist within the community handles LTFU	• Promotes independence and reintegrates survivor into primary care • Wellness focus • Convenience for survivor	• Limited provider knowledge and training regarding late effects and risk-based screening (particularly relevant for survivors with more significant exposures) • Provider may lack time to devote to complex physical and psychosocial needs of survivors • Lack of sub-specialist resources with survivorship expertise • Requires survivor to know risks and advocate for their own needs • Difficult to coordinate research • Difficult to update survivors regarding new information as it becomes available
COMBINED APPROACH (Consultative Model) Initial follow-up in cancer center-based program with transition to community-based PCP; ongoing interaction with cancer center as needed or at request of PCP	• Allows for partnership between oncologist and primary care provider • Cancer center is always available as a resource • Access to cancer center network of specialists • Enhances local provider knowledge of late effects • Encourages PCP utilization of published screening guidelines for survivors	• PCP not an expert on childhood cancer late effects or issues • Difficult to keep PCPs up-to-date on new information as it becomes available • Initial transition may be difficult for survivor • May not be well-suited for survivors with more complex follow-up requirements • Potential loss of patient for research initiatives
NEED-BASED CARE Type and intensity ("level") of follow-up care determined by intensity of cancer treatment that survivor received	• Allows for more equitable distribution of healthcare resources (survivors with greatest need receive most intensive follow-up care) • May be more convenient for lower-risk survivors (follow-up for most survivors is by mail, phone, or with PCP in local community) • Encourages involvement of primary care providers in long-term follow-up • Promotes continued contact with patients, potentially enhancing research efforts	• PCP not an expert on childhood cancer late effects or issues • Difficult to keep PCPs up-to-date on new information as it becomes available • Survivors triaged to lower levels of care do not receive care from late effects expertise

VII. 本邦における問題点

本邦の現状では，小児がん経験者は十分な病名告知を受けていなかったり，診断/治療内容や晩期障害の危険性などの医療情報が不足していることが多く，親への過剰な依存から自己管理能力を欠くこともある．また患児の両親や家族は，治療を担当した主治医（小児科医または外科医）に対する信頼が強いことが多く，患児に対する過剰な保護や小児医療への精神的な依存から，将来のケアに関わる成人科医療者への不信感がみられることが多い．それに対して主治医自身も，何となく自分の患者・家族を手元から手放したくないような感覚をもち，小児がん経験者の自己管理能力を育成する視点に乏しいことが少なくない．一方，成人診療科は小児がん経験者の問題に関する知識や関心の欠如や，患児に対する共感が乏しく，また専門分化のため総合的視点をもちにくいなど，小児がん経験者をまるごと受け止めてくれないという不満が多く聴かれる．

しかし小児医療にも限界があり，小児がん経験者が思春期・若年成人から成人へと成長するにあたって適切な対応ができる長期FU移行プログラムが必要となる．大人になろうとしている彼らに必要な医療的ケアは，技術的に小児医療の枠を超えたものであることを当人や家族に明確に説明し，小児がん経験者として，スムースな次段階への移行が重要であることの理解を求め，移行の過程を無事，経過できるよう手助けすることが，小児がん経験者の自立心を生み出す結果につながると考えられる．

今後，小児科医は患者離れを上手に行いながらも，常にさまざまな問題の相談者として小児がん経験者を陰ながら支えるという姿勢が大切と思われる．そのためにも，主治医の交代や転勤によりフォローが中断したり，疾患や治療内容の情報が不明となりリスクの評価ができなくなることなどを避けることが必要であり[45]，小児がん長期FUプログラムやシステムの整備は急務である．今後小児がん専門家，コメディカル，小児がん経験者，その家族などと協議を重ねつつ，望ましい長期FUシステムについてコンセンサスを深めていく必要があると思われる．

本研究は，平成17・18・19年度厚生労働科学研究費補助金（がん臨床研究事業）「小児造血器腫瘍の標準的治療法の確立に関する研究」，平成18・19年度厚生労働省がん助成金「小児がん克服者のQOLと予後の把握及びその追跡システムの確立に関する研究」および平成19年度厚生労働科学研究費補助金（がん臨床研究事業）「小児がん治療患者の長期フォローアップとその体制整備に関する研究」の補助を受けた．

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