quality of life among survivors who have undergone therapy is the next challenge.

Central nervous system involvement among subjects with ALL has remarkably improved since the introduction of prophylactic cranial irradiation (CRI) therapy. Although CRI therapy has significantly improved the survival rate in children with ALL, late effects such as growth retardation, pituitary dysfunction, and secondary brain tumors resulting from CRI are factors that need to be addressed.[4-7]

Data regarding the adverse effects of therapy on the growth of children with leukemia are conflicting, and numerous factors other than CRI may affect patients who have undergone treatment for childhood leukemia. One matter of concern is how therapy may affect the final height of ALL survivors. In general, final height is evaluated by the height standard deviation score (HSDS), which is determined by comparing actual height with standard heights for the same age group and gender. However, in individual patients the expected final height is based on parental height (i.e., target height), which is determined by genetic predisposition.

The present study examined factors affecting final height and the ratio of final height to target height (RFT) by retrospectively examining growth records, therapeutic regimens, and the results of growth hormone (GH) provocation tests in patients with ALL who had undergone CRI and who survived to reach final height in adulthood.

II. Materials and Methods

We investigated the medical records of 51 patients (33 males, 18 females) who had undergone treatment for childhood ALL between July 1, 1978, and August 31, 1999, at our hospital and who had reached ≥ 5 years of event-free survival.

All survivors remained in first remission and none had received bone marrow transplantation. Fifty survivors had received CRI therapy with 12 to 24 Gy (mean, 20.5 Gy), and 1 survivor had received 30.5 Gy. None had received GH replacement therapy.

Before the 1980s, our institution treated ALL using vincristine, prednisolone L-asparaginase, and CRI as induction therapy, followed by intensive therapy with cyclophosphamide and methotrexate, as well as mercaptopurine and methotrexate for maintenance therapy. Since 1981, all patients have been treated in accordance with the protocols outlined by the Tokyo Children's Cancer Study Group.[1]

Growth records, radiation dosage, cumulative corticosteroid doses, duration of corticosteroid administration, results of a GH provocation test, parents' heights, and clinical details of each patient were obtained from medical records. The height of all survivors was measured every 6 or 12 months from diagnosis to final height. The age of 18 was considered appropriate for measuring final height because growth rates slow to <1 cm/year at this time, indicating that growth has reached a plateau. When investigating growth records, we considered four height values at the following time points: at diagnosis, at the end of intensive therapy, at the completion of all therapy, and final height (18 years).

HSDS were defined as the difference between the height of each patient and that of age-matched standard heights for Japanese children as of 1990.[8,9]

Target height was calculated in centimeters using the following formulae:

$$\text{Target height}_{\text{male}} = (\text{father's height} + \text{mother's height} + 13)/2$$

$$\text{Target height}_{\text{female}} = (\text{father's height} + \text{mother's height} - 13)/2$$

The RFT was also calculated to evaluate the influence of congenital factors. We classified patients into two groups: RFT <0.975 and RFT ≥ 0.975.

To evaluate the influence of corticosteroid therapy on final height, we examined cumulative doses of corticosteroid therapy from the clinical records of all patients. Each treatment consisted of either one or two types of corticosteroid therapy (prednisolone, dexamethasone, methylprednisolone, hydrocortisone, and betamethasone). When the comparison of total dosage was done, the dosage of corticosteroid was converted to prednisolone (mg/m^2) using the following conversion expression, as described by Shigel.[10]

Total dose of prednisolone (mg/m^2)
= prednisolone $\times 1$ + dexamethasone $\times 5/0.75$
+ methylprednisolone $\times 5/4$ + hydrocortisone
$\times 5/20$ + betamethasone $\times 5/0.6$

GH provocation tests were administered one to four times after the completion of all therapy. Provocation tests included propranolol and exercise stimulation,[11] growth hormone releasing hormone (GHRH) stimulation,[12] clonidine stimulation,[13] and sleep studies.[12] Subjects with peak GH levels ≥ 15 ng/ml on propranolol and exercise stimulation, ≥ 10 ng/ml on GHRH stimulation, and ≥ 10 ng/ml on clonidine stimulation provocation tests were considered to have normal GH secretion. For sleep studies, an average GH value ≥ 5 ng/ml was considered normal. Regardless of the number of trials, we considered GH to have been secreted if more than one result of a provocation test showed normal GH secretion.

Statistical analysis

The Student's t test was used to compare the HSDS and final height. The crude and adjusted effects on RFT of gender, age at diagnosis, dose of CRI, cumulative doses of corticosteroid therapy, and HSDS at diagnosis were estimated using logistic regression, and results were described as odds ratios and 95% confidence intervals. Relationships between RFT and results of GH provocation tests were evaluated using the Student's t test. A p value < 0.05 was considered statistically significant. All analyses were performed with SPSS, Advanced Statistics Release 6.0 (SPSS Inc., Chicago, IL, USA).

III. Results

The 51 survivors comprised 33 males and 18 females. Age at diagnosis, age at CRI, dose of CRI, cumulative dose of corticosteroid therapy, and duration of corticosteroid administration were not significantly different between males and females (Table 1). Mean cumulative corticosteroid dose for the 51 survivors was 7,828.3 mg/m^2 (range, 2,450 to 22,625 mg/m^2) prednisolone-equivalents. The mean duration of corticosteroid administration was 158.1 days (range, 73 to 334 days).

The final HSDS values were within the normal distribution in 46 of 51 patients, ranging between -2 and $+2$ standard deviations (SD). The mean final HSDS of all survivors was -0.543 (males, -0.291; females, -1.003). The final HSDS values of 17, 9, and 4 survivors were from 0 to -1, -1 to -2, and -2 to -3, respectively. Only one value was below -3 SD. Five survivors (9.8%; 1 male and 4 females) had values that were below -2 SD, indicating short stature.

The mean RFT was 0.989 in all survivors (males, 0.997; females, 0.975). The RFT of 3 male and 4 female survivors (13.7%) was below 0.95, and that of 6 male and 8 female survivors (27.5%) was below 0.975.

Table 2 shows that HSDS did not significantly differ between time of diagnosis and two other measurement points during treatment, but that values of final height and height at diagnosis differed significantly in all survivors ($p < 0.001$). This difference was signifi-

Table 1 Characteristics of survivors

	All ($n=51$)	Males ($n=33$)	Females ($n=18$)
Age at diagnosis			
Mean (yr)	6.02	6.85	4.48
Range (yr)	0.58–14.92	0.58–14.92	0.73–8.58
Age at CRI			
Mean (yr)	6.36	7.18	4.85
Range (yr)	1.67–15.67	2.42–15.67	1.67–10.17
Target dose of CRI			
Mean (Gy)	20.5	20.4	21.0
Range (Gy)	18–30.5	18–30.5	18–24
Cumulative PSL dose			
Mean (mg)	7,828.3	8166.0	7227.9
Range (mg)	2,450–22,625	3,530–22,625	2,450–8,050
Duration of PSL administration			
Mean (days)	158.1	165.9	154.0
Range (days)	73–334	73–334	84–188

yr: years old, CRI: cranial irradiation, PSL: prednisolone.

Table 2 HSDS at four points and RFT

	All ($n=51$)	Males ($n=33$)	Females ($n=18$)
HSDS at diagnosis	0.198	0.279	0.006
HSDS at end of intensive therapy	−0.223	−0.081	−0.484
HSDS at completion of all therapy	−0.212	−0.092	−0.431
HSDS at final height	−0.543*	−0.291**	−1.003*
RFT	0.989	0.997	0.975

HSDS: height standard deviation score, RFT: ratio of final height and target height, *: p-value between at diagnosis and final height was less than 0.001, **: p-value between at diagnosis and final height was 0.019.

cant for both males ($p=0.019$) and females ($p<0.001$).

We compared HSDS at four points between the two RFT groups (RFT <0.975 and RFT ≥ 0.975). Table 3 shows that HSDS of final height and RFT significantly differed between these two groups ($p<0.001$ for both comparisons). Age at diagnosis was 3.79 and 6.86 years in the two groups, respectively ($p=0.013$). Age at diagnosis of 14 survivors (6 males and 8 females) with RFT <0.975 was younger than 5 years. We also compared the HSDS at diagnosis and HSDS at the end of intensive therapy, HSDS at the end of intensive therapy and HSDS at completion of therapy, and HSDS at completion of therapy and final height in each group. In the group with a shorter final height (RFT <0.975), growth tended to be particularly slow during the interval from the completion of therapy to the attainment of final height ($p<0.001$).

In the multivariate model, the odds ratios of age at diagnosis and cumulative doses of prednisolone therapy was more than 1.0. Thus, RFT was positively associated with age at diagnosis, and cumulative doses of prednisolone therapy but negatively associated with gender and dose of CRI. The odds ratio of HSDS at diagnosis was 2.428 but this value was not statistically significant ($p=0.185$) (Table 4).

The GH provocation test was administered once to 24 survivors (15 males and 9 females), twice to 9 survivors (6 males and 3 females), three times to 8 survivors (5 males and 3 females), and four times to 1 survivor (1 male) after completion of all therapy. In total, the 42 survivors underwent 70 tests. The relationship between RFT and the results of the GH provocation tests did not differ significantly (Fig. 1). Only one female survivor of 12 survivors (6 males and 6 females) with an RFT <0.975 showed a low response to the GH provocation test. Eleven survivors with RFT <0.975 showed a normal response to the

Table 3 Comparison of HSDS and RFT for 2 groups (divided by RFT of 0.975)

	All ($n=51$)	RFT <0.975 ($n=14$)	RFT ≥ 0.975 ($n=37$)	p-value
Gender (male: female)	33:18	6:8	27:10	0.04
Age at diagnosis (yr)	6.02	3.79	6.86	0.013
Hegiht at diagnosis (cm)	111.8	95.3	118.0	0.01
HSDS at diagnosis	0.198	−0.221	0.3	0.016
HSDS at end of intensive therapy	−0.223	−0.708	−0.044	0.026
HSDS at completion of therapy	−0.212	−0.492	−0.112	0.272
HSDS at final height	−0.543	−1.531	−0.17	<0.001
RFT	0.989	0.948	1.005	<0.001

yr: years old, HSDS: height standard deviation score, RFT: ratio of final height and target height, p-value: the results of comparison between RFT <0.972 and RFT ≥ 0.975.

Table 4 Logistic regression anlysis of factors influencing RFT

	95%CI	Odds ratios	p-value
Gender	0.070–1.769	0.352	0.205
Age at diagnosis	1.026–1.886	1.391	0.034
Dose of CRI	0.749–1.199	0.948	0.655
Cumulative dose of PSL	1.000–1.001	1.001	0.022
HSDS at diagnosis	0.655–8.999	2.428	0.185

RFT: ratio of final height and target height, CRI: cranial irradiation, PSL: prednisolone, HSDS: height standard deviation score, CI: confidence interval.

Table 5 Results of GH provocation tests in 2 groups (those with RFT <0.975 and those with RFT ≥ 0.975)

	Stimulator	P & E ($n=24$)	GHRH ($n=31$)	Clonidine ($n=31$)	Sleep ($n=25$)
RFT <0.975	Normal response	4	7	6 (2)	8
	Low response	2	1	4	1
RFT ≥ 0.975	Normal response	12 (3)	19 (1)	10 (1)	10
	Low response	6	4	11	6

P & E: propranolol and exercise, GHRH: growth hormone releasing hormone. Numbers in parentheses refer to the number of survivors who showed different responses to the GH provocation tests each time.

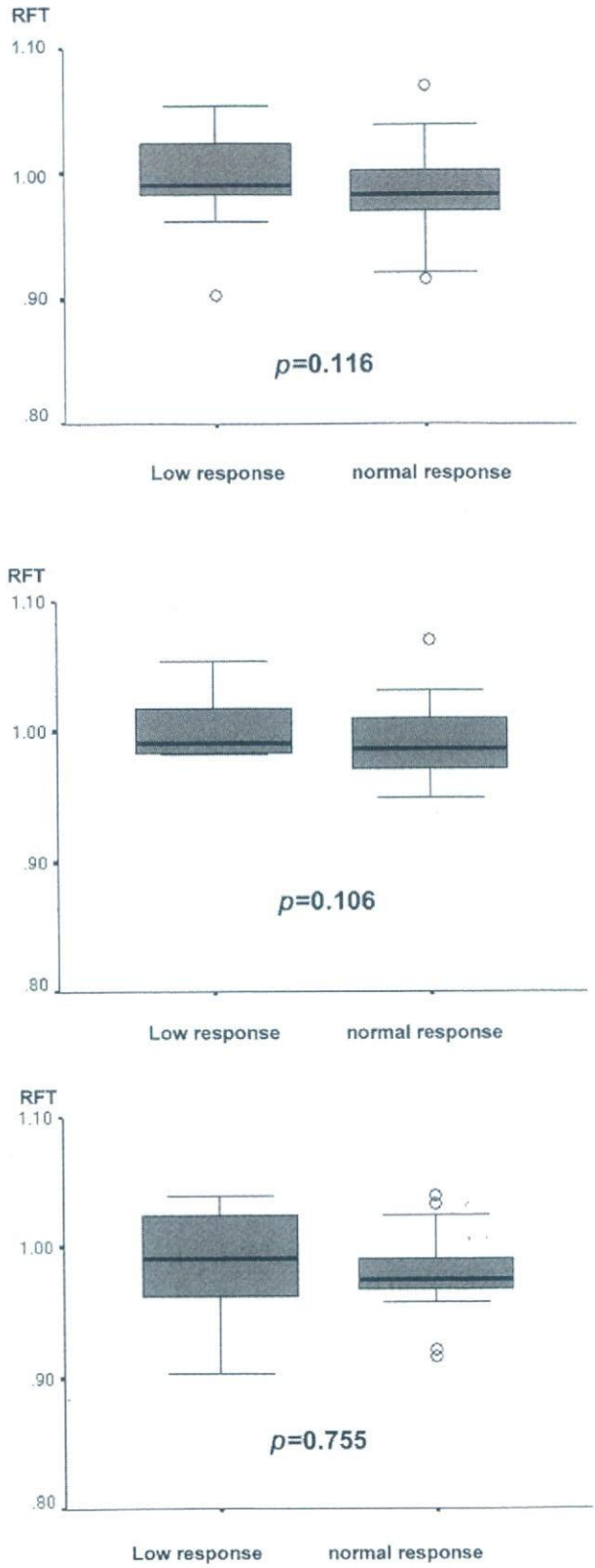

Fig. 1 The relationship between the ratio of final height to target height (RFT) and the results of provocation tests

Top: all survivors, middle: male survivors, bottom: female survivors. Box indicates 10th and 90th percentile, line in middle (bold) indicates median RFT.

GH provocation test. Seven (5 males and 2 females) of 30 survivors (21 males and 9 females) with RFT $\geqq 0.975$ showed a low response to GH provocation tests. Among 4 of these 7 survivors with RFT $\geqq 0.975$ who underwent two to four GH provocation tests, a low response was seen on all tests. Moreover, 3 (2 males and 1 female) of 17 survivors (13 males and 4 females) had a final height that exceeded the target height (RFT $\geqq 1.0$), although they showed a low response to GH provocation tests. Thus, there was no relationship between results of the GH provocation tests and final height.

Table 5 shows the results of GH provocation tests in survivors with RFT < 0.975 and those with RFT $\geqq 0.975$ based on positive or negative responses to different stimulators (i.e., propranolol with exercise stimulation, GHRH stimulation, clonidine stimulation, and sleep). There were no significant differences between survivors with RFT < 0.975 and those with RFT $\geqq 0.975$ despite responses to different stimulators. Eighteen survivors were administered GH provocation tests more than 2 times. Three survivors with propranolol and exercise stimulation, 1 survivor with GHRH stimulation, and 3 survivors with clonidine stimulation showed different responses to each provocation test.

IV. Discussion

The number of reports describing the late effects of leukemia treatment has increased along with improvements in patient prognosis.[14-16] Late effects include several disorders, among which, growth failure is one of the most significant. The reason for short final height in survivors with leukemia who undergo stem cell transplantation (SCT) is due to total body irradiation, using busulfan, or total cumulative doses of corticosteroid therapy. Among survivors who do not undergo SCT, impaired gains in height after treatment for leukemia are presumed to be associated with CRI, which is given to prevent central nervous involvement. However, in most cases, the reduction in final height is only moderate, and most survivors do not receive GH replacement therapy. Kirk et al. followed up patients with childhood leukemia for 6 years after onset and reported that their HSDS was 1.37 lower than the mean and that 71% of subjects were shorter than the standard height by 1 SD or more.[17] In addition, Clayton et al. reported that patients with ALL who were treated for 10 years were significantly shorter than the standard adult height.[18] We examined which factors affected final height in survivors of childhood ALL who underwent CRI but not SCT.

The final height was less than -2 SD in 5 (1 male

and 4 females) of the 51 survivors (9.8%) in the present study, which is approximately 4-fold that of the value reported in the Japanese statistics (2.3%; 2,275/100,000).[19] The final height evaluated by HSDS was −0.543 for survivors overall, −0.291 for males, and −1.003 for females. A comparison of HSDS at diagnosis and at the attainment of final height revealed decreases of −0.741, −0.54, and −1.009 among the overall, male, and female survivors, respectively. These results indicate that the therapy affected final height more in females than in males. Both male and female survivors grew slowly during intensive therapy, but the attenuation of growth during the interval between the end of treatment and the attainment of final height tended to be worse in females than in males. The influence of CRI for leukemia on height has been assessed from the viewpoint of total dose of CRI[20] and age at the start of treatment.[14] However, height is also inherited from parents. Thus we assessed final height using RFT and not HSDS, which is obtained from standard height values, to determine the degree to which final height corresponded to the estimated height based on the height of the parents.

Final height evaluated by RFT was 0.989 for survivors overall, 0.997 for males, and 0.975 for females. These results indicate that therapy did not obviously influence growth in males, but might affect the growth of females. However, the mean age at disease diagnosis was 4.48 and 6.85 years in females and males, respectively ($p=0.086$), indicating that the variance in the influence of treatment could be ascribed to differences in age at time of diagnosis between the two genders.

The age at diagnosis was lower in the group with RFT < 0.975. All survivors received CRI within 1 year of diagnosis, meaning that they were young when they received this treatment.

In the group with the shorter final height (RFT < 0.975), growth tended to be particularly slow during the interval from the end of treatment to the attainment of final height. Although the reason for this finding is unclear, it appears that the survivors who had a shorter final height could not catch up any lost growth in this interval.

Some investigators have maintained that reduced final height is mainly related to the total dose of CRI,[21] whereas others disagree.[22,23] Some reports describe reduced final height in patients with brain tumors exposed to high doses of CRI.[24-26] Our results indicate that age at diagnosis and cumulative doses of corticosteroids were related to final height, whereas the total dose of CRI was not.

Some reports have shown that a reduced final height is related to decreased GH secretion in treated survivors of childhood leukemia and that such decreased GH secretion, when recognized early and treated with GH replacement at the end of anti-leukemic therapy, results in favorable growth.[27] We retrospectively investigated results of GH provocation tests in survivors of childhood leukemia. According to the era in which the treatment was applied, one to four types of GH provocations tests, alone or in combination, were used. When the result of at least one test was positive, the GH provocation test was determined to be positive. Figure 1 shows that there were no significant associations between final height and the results of GH provocation tests.

The results of a comparison of GH provocation tests completed 1 month to 4.1 years after the completion of therapy did not reveal any significant relationship between test results and final height at any of the periods examined (data not shown). Similarly, we could not find significant stimulators to GH provocation tests to assess of GH insufficiency in survivors of childhood ALL who underwent cranial irradiation, as shown in Table 5.

Although GH secretion levels during intensive therapy have not been reported, growth is clearly delayed during this period. However, height later recovers and GH secretion is frequently recognized in GH provocation tests, even in patients whose final height is short. Although many survivors can receive GH replacement therapy, some survivors who received CRI and whose final height was short may not have received GH replacement therapy because of their normal response to GH provocation tests. It is possible that CRI and chemotherapy do not lead to a dysfunction in GH secretion, but rather to damage to GH receptors. Additional studies are needed on how to evaluate GH secretion among survivors who receive CRI.

V. Conclusion

We investigated final height after treatment and results of the GH provocation test in survivors of childhood ALL. Age at diagnosis and cumulative dose of corticosteroid therapy affected the final height in survivors with childhood ALL who received CRI. The results of GH provocations test did not correlate with the final height of the survivors. We conclude that the final height of childhood ALL survivors treated with CRI is difficult to predict based on results of GH provocation tests.

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—Review—

Late Effects of Childhood Cancer: Life-threatening Issues

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Abstract

Improvements in therapies for childhood cancers have increased the number of survivors. However, with this prolonged survival, the late effects of disease and anti-cancer therapy are becoming increasingly important. Approximately two-thirds of survivors of childhood cancer will have at least one late effect, and about one-third will have a late effect that is severe or life-threatening. A second neoplasm is one of the most severe late effects in survivors of childhood cancer. Compared with normal populations, persons with a history of childhood cancer have a 10- to 20-fold greater risk of a second malignant neoplasm. Patients who have undergone radiation therapy or been given specific chemotherapeutic agents and patients with a known genetic predisposition to malignancy have been shown to be at higher risk for a second malignant neoplasm. Cardiac problems are another serious late effect for survivors of childhood cancer. Anthracycline-induced cardiotoxicities are common in these patients. A cumulative dose of anthracycline greater than 300 mg/m^2 is associated with an 11-fold higher risk of clinical heart failure compared with a cumulative dose of less than 300 mg/m^2. Serial monitoring of cardiac functioning in children receiving anthracycline allows early identification of cardiac damage. One cardioprotectant (dexrazoxane) has proven effective in adult patients, but larger trials are needed to determine its efficacy in children. It is important to recognize that it may not be best to categorize surviving patients by primary diagnosis. Instead, strategies for surveillance of survivors should be based on the treatment each patient received.

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Key words: late effects, childhood cancer, survivors of childhood cancer, second neoplasm, cardiotoxicity

Introduction

Dramatic advances have been made in the treatment of childhood cancer in the last three decades. The survival rate for children with cancer is now about 80%[1], and more than 0.1% of young adults are survivors of childhood cancer. As the survival rates for childhood cancer have been improving, the late effects of cancer therapy have become a significant problem. To varying degrees, adverse outcomes, including second neoplasms, cardiac dysfunction, pulmonary dysfunction, neurocognitive dysfunction, impaired intellectual function, various endocrine problems, gonadal dysfunction, decreased fertility, and reduced growth (**Table 1**), have been shown to be more likely in long-term survivors. Late mortality in 5-year

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Table 1 Major physical late effects of childhood cancer

Category	Late effects
Second malignant neoplasm (SMN)	Second leukemia
	SMN in radiation field (brain, skin, bone, soft tissure, breast, thyroid)
Cardiac	Cardiomyopathy
	Valvular disease
	Pericardial complications
Pulmonary	Pulmonary fibrosis
Neuropathy	Neurocognitive deficit
	Leukoencephalopathy
Endocrine	Hypothyroidism
	Hyperthyroidism
	Growth hormone deficiency
	Adrenal insufficiency
Gonadal function	Gonadal failure
	Premature menopause
	Infertility
Growth	Short stature (Growth hormone deficiency. bone atrophy, etc)
Bone	Scoliosis
	Osteoporosis
	Avascular necrosis
Liver	Heepatitis B
	Heepatitis C
Ear	Hearing loss
Teeth	Deantal abnormalities

survivors of childhood cancer is 10.8 times higher than that in the general population[2]. Although the most common cause of death is relapse, late sequelae of treatment of the original disease also contribute to later mortality in survivors of childhood cancer.

Two life-threatening late effects of childhood cancer treatment are reviewed in this article: secondary neoplasm and cardiotoxicity.

Second Neoplasm

Second malignant neoplasm (SMN) is a severe late effect in survivors of childhood cancer. The Childhood Cancer Survivors Study (CCSS), a large cohort study of survivors of childhood cancer, has reported that the cumulative incidence of SMN 20 years after the original cancer diagnosis is 3.2% overall and varies by diagnostic subgroup: 7.6% in Hodgkin disease, 4.0% in soft-tissue sarcoma, 3.3% in bone sarcoma, 2.1% in leukemia, 2.1% in central nervous system cancer, 1.9% in neuroblastoma, and 1.6% in kidney tumor[3]. Compared with persons in the general population, persons with a history of childhood cancer have a 10- to 20-fold greater risk of a SMN[4]. Independent risk factors for SMN (adjusted for radiation exposure) include female sex, original cancer diagnosed at a younger age, original diagnosis of Hodgkin's lymphoma or soft tissue sarcoma, and exposure to alkylating agents[3]. The second adult-type carcinoma occurred at a median of 27 years (range, 10–44 years), and the median elapsed time between the development of the second carcinoma and primary therapy was 15 years (range, 6–28 years)[5].

Radiation therapy is a major cause of SMN[6]. Eighty to ninety percent of SMNs following radiation therapy occur within the radiation field. Breast cancer is the most frequent SMN in female survivors of Hodgkin's lymphoma. This represents a 57-fold risk compared with that in the general population. An increased risk of breast cancer is present in patients who have received more than 40 Gy to the chest, with a notable dose-response relationship. The risk of skin cancer also increases following radiation exposure. Basal cell carcinoma is the most commonly observed subsequent cancer. Forty-six percent of patients with secondary skin cancer have multiple occurrences: 90% have received radiation, and 90% of the cancers are within the radiation field[7]. Radiation therapy is associated with a 6.3-fold higher risk of skin cancer. Thyroid cancer may develop after irradiation of the head, neck, or chest. Papillary carcinoma accounts for 75% to 90% of all radiation-induced thyroid cancers. The incidence of thyroid cancer increases linearly with the dose of radiation but reaches a plateau with doses greater than 30 Gy[8]. This finding may be due to high-dose radiation inhibiting cellular proliferation and preventing the development of an expanded malignant clone. Bone and soft tissue sarcoma may occur after radiation therapy, and the risk is proportional to the dose and the concurrent use of alkylating agents. The British Childhood Survivor of Cancer Study has reported that the overall cumulative risk in a cohort of patients

treated from 1940 through 1983 was approximately 1% within a 20-year period following the original diagnosis[9].

Treatment-related leukemia and myelodysplastic syndrome may be caused by topoisomerase II inhibitors[10] and alkylating agents[11]. The cumulative risk for second leukemia after treatment with a topoisomerase II inhibitor is 0.5% to 18.4%, and the median latency period is 1 to 3 years (range, 0.5–4.5 years)[10]. There is usually rearrangement involving the *MLL* gene on chromosome band 11q23. Recently, Relling et al have reported that short-term use of granulocyte colony-stimulating factor after etoposide therapy might increase the risk of acute myeloid leukemia or myelodysplastic syndrome[12]. Secondary leukemias are also associated with alkylating agents. The cumulative risk for secondary leukemia after treatment with alkylating agents is 0.8% to 2.8%, and the median latency period is 4 to 6 years (range, 1–20 years)[11]. Alkylating-agent-related secondary leukemia is generally associated with abnormalities, usually deletions of chromosome 5 or 7[6].

Secondary brain tumors have been reported to occur with increased frequency in patients who have undergone cranial irradiation for brain tumors or acute lymphoblastic leukemia. A 10-fold or greater risk for brain tumors has been observed for survivors of cancers of the central nervous system (CNS) than for persons who have not had cancer. The CCSS has found that 116 subsequent CNS neoplasms in 14,361 5-year survivors of childhood cancer and glioma occurred at a median of 9 years after the original diagnosis and that meningioma occurred at a median of 17 years after the original diagnosis[13]. The cumulative risk of secondary CNS neoplasms is 0.5% to 2.0% at 20 years. Younger age at initial therapy is a risk factor for secondary CNS malignancies. Other potential risk factors for secondary CNS malignancies are an inherited genetic predisposition to cancer and genetic polymorphisms of metabolic enzymes. An example of a polymorphism that has been found to be predictive of the risk of second CNS tumors in childhood acute lymphoblastic leukemia is thiopurine S-methyl-transferase[14].

Stem cell transplantation (SCT) is another cause of second malignancies. The overall cumulative incidence of developing posttransplant malignancies is 6.9% at 20 years and increases by 2% with each successive 5-year follow-up period[15]. The CCSS has reported that patients who have undergone SCT had a 3-fold increased risk of posttransplant malignancies during 7-year periods[13]. Children younger than 10 years at the time of SCT have a greater risk than do older children[16].

Cardiotoxicity

Cardiologic problems are serious late effects in survivors of childhood cancer. Chief among these late adverse effects is the cardiotoxicity associated with anthracycline therapy. Valvular disease, pericardial disease, and arrhythmias have been reported as late cardiologic effects in cancer survivors. After anthracycline therapy, the risk of congestive heart failure is 0% to 16%, and that of subclinical cardiomyopathy is 0% to 57%. There are two kinds of anthracycline-induced cardiotoxicity: acute and chronic. In some cases, chronic cardiotoxicity is subdivided into two addition types: early and late (i.e., more than 1 year after completion of therapy). Most cases of acute cardiotoxicity are not severe. The incidence of anthracycline-induced chronic cardiomyopathy depends on the cumulative dose of anthracycline. A cumulative dose of anthracycline greater than 300 mg/m^2 is associated with an 11-fold higher risk of clinical heart failure than is a cumulative dose of less than 300 mg/m^2[17]. Steinherz et al have reported that 23% of 201 patients who have received a median cumulative dose of doxorubicin of 450 mg/m^2 have echocardiographic abnormalities at a median interval of 7 years after the completion of therapy[18]. An increased risk of cardiac abnormalities is associated with the cumulative dose of anthracycline, the length of follow-up, and mediastinal irradiation. Moreover, girls appear to be more likely than are boys to have cardiotoxic effects of anthracycline therapy[19]. Although the reason for this difference is not known, differences in sex-specific body fat percentages may be involved. In addition, patients younger than 4 years at the time of anthracycline

exposure are at a significantly greater risk for abnormal cardiac function than are older patients[20]. Recent studies have examined whether genetic factors affect anthracycline processing[21], but no conclusive findings have been obtained.

The precise mechanism underlying anthracycline-induced cardiotoxicity is not understood. Most evidence shows that anthracycline therapy generates free radicals through an enzymatic mechanism using the mitochondrial respiratory chain and through a nonenzymatic pathway incorporating iron. Both free radicals and iron can damage cells. Cardiac cells are more vulnerable to free radical damage. Furthermore, anthracycline has a high affinity for cardiolipin and a phospholipid in the inner mitochondrial membrane of cardiomyocytes, resulting in the accumulation of anthracycline inside cardiac cells[22]. The free radicals may continue to be generated after anthracycline treatment has been completed and could account for late cardiotoxic effects of this therapy. Once cardiomyocytes are damaged by anthracycline, the cells might not recover their function. Loss of cardiomyocytes leads to progressive left ventricular dilatation, left ventricular wall thinning, and decreased contractility.

Serial monitoring of cardiac function in children receiving anthracycline allows early identification of cardiac damage. There are many methods to monitor anthracycline-induced cardiotoxicity, including echocardiography, electrocardiography, and radionuclide ventriculography. Fractional shortening and ejection fraction are reliable echocardiographic measures of left ventricular systolic function. Some reports suggest that exercise testing is useful for detecting cardiac function abnormalities that were not significant at rest[23,24]. Signal-averaged echocardiography is another useful tool for early detection of anthracycline-induced cardiotoxicity[25]. Cardiac markers are an accurate and convenient means of monitoring the cardiac health of patients during and after cancer therapy. For example, brain natriuretic peptide and troponin T are markers of cardiomuscular function.

The best treatment for cardiotoxicity is prevention. Although early reports in adults have suggested a lower prevalence of cardiotoxicity with continuous infusion of anthracycline than with bolus administration, more recent reports in children show that the method of administration does not provide cardioprotection[26]. One recent approach to preventing or minimizing chemotherapy-induced cardiotoxicity is to add a cardioprotectant to the treatment regimen. Dexrazoxane (Ziecard; Phamacia & Upjohn, Peapack, NJ) is a cardioprotectant that has been proven to be effective in adult patients. Dexrazoxane was approved in 2002 by the United States Food and Drug for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who had received a cumulative doxorubicin dose of at 300 mg/m^2 and continued to receive anthracycline treatment to maintain tumor control[21]. Clinical trials with dexrazoxane in children have been encouraging. For example, children who received dexrazoxane before doxorubicin were significantly less likely to have cardiac injury during treatment as measured by elevated serum levels of cardiac troponin T[27]. An association between the use of dexrazoxane and the risk of SMN in children with Hodgkin's disease has also been reported[28]. However, a recent report found the absence of an association of secondary malignant neoplasm in children with acute lymphoblastic leukemia who had received dexrazoxane[29].

Conclusions

The number of long-term survivors of childhood cancer will continue to increase, and almost 75% will have a chronic health problem resulting from cancer therapy. More than 40% will have a severe, disabling, or life-threatening condition or will die of because of a chronic condition resulting from cancer therapy[30]. The most important method for preventing these problems is a follow-up survey of cancer survivors. It is important to recognize that patients are not necessarily best categorized by primary diagnosis in such a follow-up survey and that strategies for surveillance of survivors must be based on the treatment each patient received. Therefore, we are establishing a follow-up system

for survivors of childhood cancer that includes an individual treatment summary and follow-up notebook for patients.

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Ewing Sarcoma/Primitive Neuroectodermal Tumor of the Kidney in a Child

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A 6-year-old female was admitted with abdominal pain and a mass in the right abdomen. Her lactose dehydrogenase level was 1,200 IU/L, and neuron specific enolase was 120 ng/ml. Computed tomography scan confirmed a large right renal mass with necrosis. A right radical nephrectomy was performed. The tumor was completely encapsulated. Based on small round cell histology, strong MIC-2 (CD99) positive tumor cells, and EWS-FLI-1 fusion transcript, Ewing sarcoma/primitive neuroectodermal tumor of the kidney was diagnosed. Induction and follow-up with seven cycles of chemotherapy were given after surgery. She has had no evidence of recurrence 90 months from diagnosis. Pediatr Blood Cancer 2008;50:180–183. © 2006 Wiley-Liss, Inc.

Key words: electron microscopy; Ewing sarcoma/primitive neuroectodermal tumor; EWS-FLI-1; immunohistochemistry; kidney

INTRODUCTION

Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET) of the kidney is a rare and highly malignant neoplasm. It affects young adults, and only a few pediatric cases (younger than 15 years) have been reported [1–9]. ES/PNET arising in the kidney act aggressively and show poor response to therapy [1]. ES/PNET of the kidney needs to be differentiated from other small round cell tumors of the kidney, because each type of tumor is treated differently. The diagnosis of this neoplasm is currently based on a combination of light microscopy, immunohistochemistry, electron microscopy, chromosomal analyses, and specific chimeric transcripts. Our patient, who was diagnosed by histochemistry and molecular biology analysis of the resected kidney and treated with chemotherapy, has remained alive more than 90 months after diagnosis.

CASE

A 6-year-old female was admitted to our hospital with abdominal pain and an abdominal mass. On physical examination, a large and firm mass was evident in the right abdomen. Laboratory evaluation showed a lactate dehydrogenase level of 1,200 IU/L (normal 218–411 IU/L), a neuron specific enolase level of 120 ng/ml (normal <10 ng/ml), and ferritin level of 160 ng/ml (normal 15–89 ng/ml). Urine catecholamine levels were within normal limits. Abdominal computed tomography (CT) scan confirmed a large right renal mass with areas of necrosis and bleeding. There was no obvious lymphadenopathy and no intra-abdominal metastasis. Bone scintigraphy and CT scan of the thorax did not detect metastasis.

A right radical nephrectomy was performed. The tumor involved a large portion of the lower part of the kidney. The tumor was completely encapsulated and was 5.0 × 4.5 × 4.5 cm. Lymph nodes were negative for malignancy. Histologic examination revealed a small round cell tumor with massive necrosis, but no rosette formations. Periodic acid-Schiff (PAS) staining revealed diastase sensitive material in the tumor cell cytoplasm. Immunohistochemistry revealed that tumor cells were strongly positive for MIC-2 (CD99) as well as vimentin. The tumor cells were negative for chromogranin A, neurofilament, and synaptophysin. Electron microscopic examination showed a high nuclear-cytoplasm ratio and aggregated glycogen granules in the cytoplasm (Fig. 1A). A higher magnification of tumor cells showed neurosecretory-type granules, microtubules, and desmosome-like structures (Fig. 1B). The expression of EWS-FLI-1 fusion transcript was demonstrated by molecular biology (Fig. 2). A single 330 base pair cDNA product was detected by ethidium bromide staining, corresponding to the EWS-FLI-1 as previously reported by Sorensen et al. [10]. Direct DNA sequencing confirmed the presence of a fusion of EWS exon 7 to the FLI-1 exon 6. Unfortunately chromosomal findings failed because proliferation of the tumor cells was poor. According to results on small round cell histology and immunohistochemical profiles, electron microscopic findings, and EWS-FLI-1 fusion transcript, the tumor was diagnosed as an ES/PNET of the kidney. Therapy was initiated with 1.5 gm/m^2 vincristine on days 1, 8, 15, 22, 29, and 36; 500 mg/m^2 cyclophosphamide on days 2, 9, 30, and 37; and 0.45 mg/m^2 dactinomycin on days 16–20 for induction and then a total of seven cycles of 4-drug chemotherapy, consisting of 1.5 gm/m^2 vincristine on days 1, 15, 22, 29, 36, and 43; 0.45 mg/m^2 dactinomycin on days 1–5; 500 mg/m^2 cyclophosphamide on days 16, 23, 30, 37, and 44; and 60 mg/m^2 doxorubicin on day 44 after surgery. She had no serious adverse effects during chemotherapy. She had no evidence of recurrence after 90 months from diagnosis and no late effects have been noted.

DISCUSSION

Though the existence of renal PNET was reported in 1975 in a review of pediatric PNETs [11], only a small number of cases have been reported. Recently, Parham et al. [12] from National Wilms Tumor Study Group Pathology Center reported that 79 of 146 cases of primary malignant neuroepithelial tumors of the kidney in adults and children were considered to be ES/PNET. Follow-up information, however, was only provided for 14 of 146 cases, and it is unclear which, if any, of those were actually ES/PNET [8]. Pediatric cases (younger than 15 years old) of ES/PNET of the kidney are extremely rare, and only ten cases have been reported previously [1–9]. Clinical characteristics, pathologic features, treatments, and outcomes of those cases are summarized in Table I.

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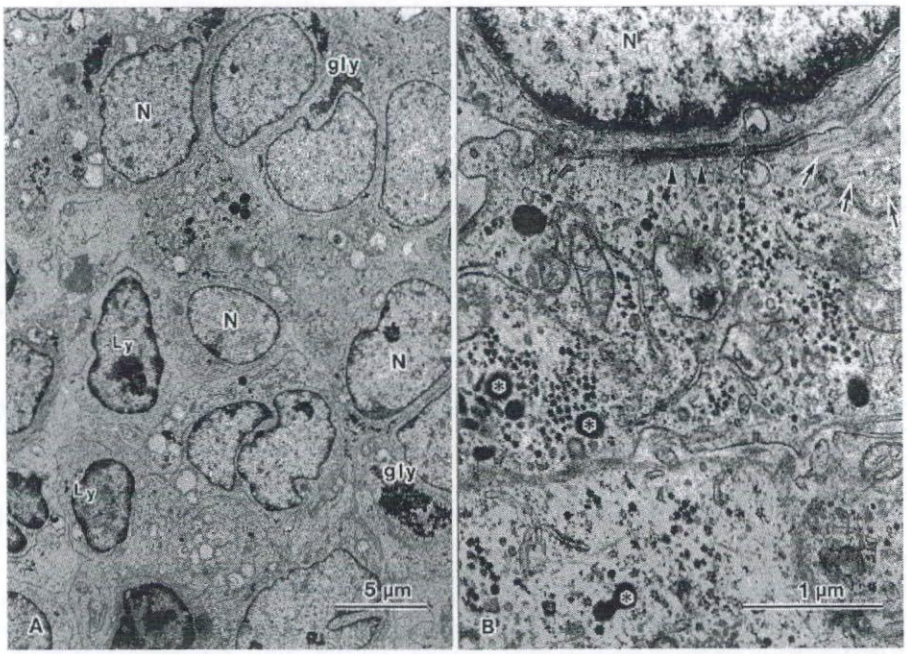

Fig. 1. Ultrastructural findings in the tumor cells. **A**: Tumor cells are oval and small (about 8–10 μm in a diameter). Nuclear-cytoplasm ratio is high. Nucleus has a few heterochromatin. Aggregated glycogen granules (gly) are observed in the cytoplasm. Ly, lymphocytes; N, nuclei. **B**: Neurosecretory granules (asterisks), microtubules (arrows), and desmosome-like structures (arrowheads) are observed in the tumor cells under higher magnification.

Several approaches can be used to arrive at a diagnosis of ES/PNET. The first approach is light microscopic examination of tumor tissue including immunohistochemistry. These tumors consist of primitive-appearing round cells with high nucleus to cytoplasmic ratios. The immunohistochemical features of ES/PNET are positive for CD99 (MIC2); however, expression of CD99 is by no means specific for ES/PNET among round cell tumors [13]. Although FLI-1 is a variable histochemical marker for ES/PNET, it is also positive in lymphoblastic lymphoma [14]. In contrast, WT-1 is a positive marker of Wilms tumor and desmoplastic round cell tumors, whereas it is a negative marker for ES/PNET, neuroblastoma and rhabdomyosarcoma. The second approach is electron microscopic examination of tumor tissue. Electron microscopic features include a specific high nuclear-cytoplasm ratio and aggregated glycogen granules in the cytoplasm. Neural differentiation appears on some cells with polar processes, which may contain microtubules or neurosecretory glands [15]. The third approach is chromosomal translocation, such as t(11;22) (q24;q12) which is positive in 88–95% of ES/PNET cases [16]. The final approach involves a molecular biologic examination. In 90–95% of cases of ES/PNET, the chimeric transcript is EWS-FLI-1; the remaining 5–10% are EWS-ERG. Other transcripts, including EWS-ETV1 and EWS-EIAF, have also been reported [16].

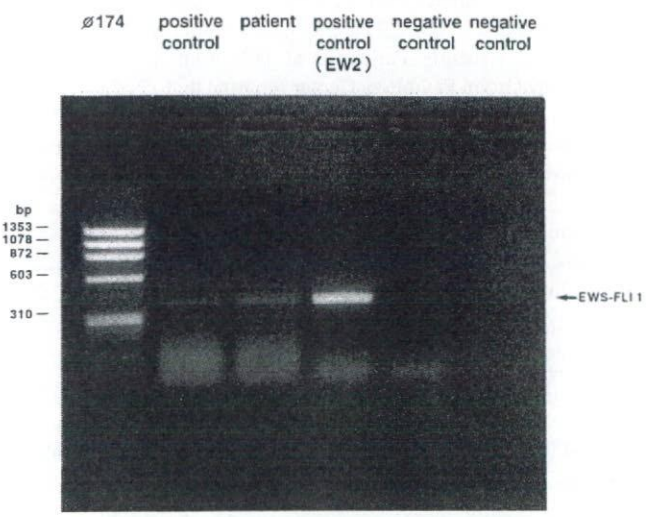

Fig. 2. A single 330 base pair transcript is detected in the patient sample following reserve transcriptase polymerase chain reactor (RT-PCR) performed on RNA extract from tumor tissue.

In terms of prognosis, the 5-year disease-free survival rate of ES/PNET is 45–55% [17], but the prognosis of ES/PNET of the kidney appears worse [1,18]. In pediatric cases (Table I), 5 of 8 patients were alive when the cases were reported; however, 1 patient (no. 6) was alive with disease, 2 patients (no. 3 and no. 5) were followed-up only for 6 and 8 months, and 1 patient was under treatment (no. 9). The follow-up duration was not described in this case. Only 2 patients (no. 8 and our case) were alive after 5 years. For 2 patients, it was not defined whether they were alive or not (Table I). Jimenez et al. [8] described that 3 of 11 patients were alive for 4–64 months, and 5 patients had local recurrence or distance metastasis then died of their disease, and 3 patients were lost to follow-up. Most of the recent therapeutic protocol for children with ES/PNET consists of vincristine, doxorubicin, cyclophsphamide, ifosphamide, and etoposide. Radiation and surgery have been used; some patients have been treated with myeloablative chemoradiotherapy followed by autologous bone marrow rescue. In spite of a lack of radiation therapy and our not using ifosphamide and etoposide for chemotherapy, our patient has survived for a relatively long period with no recurrence. Possible reasons for this good outcome might include the pathologic features of the tumor, the well-encapsulated nature of

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TABLE I. Clinical and Pathological Features of ES/PNET of the Kidney in Pediatric Cases

Case	Ref.	Age	Gender (yr)	Symptoms	Metastasis	Pathology (immunohistochemistries)	Chimeric transcript	Therapy	Outcome (follow-up [Mo])
1	1	4	F	Abdominal pain, fever	RPLN, liver	CD99(+),NSE(+),S-100(+), Ker(+),Act(−),Vim(−),Chro(−)	NS	IFO, CBP, VP-16 radiation	Died (1)
2	1	14	M	Bone pain, weight loss	Lung, bone, bone marrow	CD99(+),NSE(+),Vim(+),Synapto(+) (±)S-100(−),Ker(−),Act(−),Chro(−)	EWS/FLI-1(−) EWS/ERG(−)	CY, VCR, DOX,IFO,VP-16 auto BMT	Alive (under treatment)
3	2	13	NS	Abdominal pain, hematuria	No	MIC2(+),NSE(+),ker(−),Des(−), Act(−)	EWS/FLI-1(+)	Nephrectomy chemotherapy	NS
4	3	10	M	Abdominal mass	No	MIC2(+),NSE(+),Leu7(+), S-100(−),Ker(−), Des(−),Vim(−),Chro(−)	EWS/FLI-1(+)	Nephrectomy chemotherapy	Alive (6)
5	4	5	F	NS	IVC, right heart	NS	NS		NS
6	5	15	F	Abdominal pain, abdominal distention	No	MIC2(+),Vim(+),NSE(−), S-100(−)	NS	Nephrectomy CY, VCR, DOX,IFO,VP-16	Alive (8)
7	6	9	M	Abdominal pain, abdominal mass, weight loss	No	MIC2(+),NSE(−),Vim(−),Ker(−), LCA(−)	NS	Nephrectomy CY, VCR, DOX,IFO,VP-16	Alive (relapse+) (10)
8	7	9	F	Abdominal distention, abdominal mass	No	CD99(+),LCA(−),Ker(−),Act(−), NFM(−)	EWS/FLI-1(+)	Nephrectomy IFO,VP-16,CY,DOX,VCR auto BMT	Died (5)
9	8	11	M	Gross hematuria, abdominal mass	No	CD99(+)	NS	Nephrectomy VCR, DOX, VP-16, CY, DAC	Alive (64)
10	9	14	F	Abdominal pain, abdominal mass	IVC, right heart, liver	NS	NS	Chemotherapy	Died (24)
11	Present case	6	F	Abdominal pain, abdominal mass	No	MIC2(+),Vim(+)NFM(−),Chrom(−)	EWS/FLI-1(+)	Nephrectomy VCR, DAC, CY, DOX,	Alive (90)

RPLN, retroperitoneal lymphonode; IVS, inferior vena cava; NSE, neuron specific enolase; Ker, keratin; Act, actin; Vim, Vimentin; Chro, chromogrn A; MIC2, B microgloblin; Des, desmin; NFM, neurofibrofilament; Synapto, sinaptophilin; IFO, ifomide; CBD, carboplatinum; CY, cyclophosphamide; VCR, vincristine; DOX, doxrubicine; DAC, actinomycin D; BMT, bone marrow transplantation.

the tumor with no involvement beyond the capsule and the accurate diagnosis followed by prompt treatment with chemotherapy. Several approaches including cytogenetical methods are important for early, accurate diagnosis of ES/PNET.

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ランチョンセミナー

小児がん経験者のQOL

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Ⅰ．はじめに

近年小児がんの治療成績は著しく向上し，現在では70～80％が治癒すると考えられている。現在，本邦における15歳以下の１年間あたりの小児がんの発生率は，１万人に約１人といわれている。治癒率を70％と仮定すると日本では若年成人の930人に１人が小児がん経験者であるということになる。またアメリカ合衆国では，現在20～39歳の640人に１人が小児がん経験者であり，そう遠くない将来に約450人に１人になると予想されている[1)]。

しかし，治療が終了した後に小児がんの治療に起因する合併症，あるいは小児がんの疾患自体の侵襲による後遺症を呈する者が少なくない。このことは小児がん経験者のQOLが必ずしも良好でないことを意味する。彼らが直面している問題は，身体的な事項だけでなく，心理的な問題，さらに社会的な問題と多岐にわたる。これらを小児がんにおける晩期合併症（late effects）といっており，この晩期合併症が彼らのQOLに大きく影響しているといってよい。

Ⅱ．小児がん経験者とQOL

小児がん経験者におけるQOLは，図１に示すように，身体機能，心理状態，社会生活機能などと密接に関係する。年齢，性別，家庭環境，経済状態，教育環境などの本人の特性や，病気の発症年齢，原発部位，治療内容によっても大きく左右される。疾患によりQOLが異なると

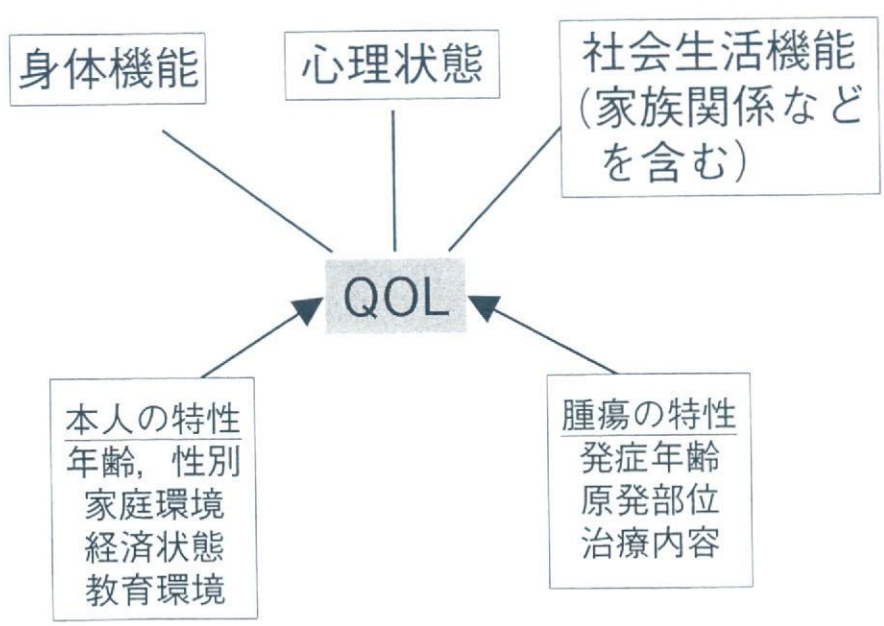

図１　小児がん経験者のQOL

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いう研究もある[2]。

そもそもQOLとは，個人の主観的な満足度を示すものであり，一人ひとりその評価は異なる。以前，小児がんのほとんどが治癒しなかった時代では，小児がんのQOLは，残された時間をいかに本人にとって幸せに過ごすかということから評価されていたが，現在，小児がんのQOLは，小児がんを経験し，それを克服した人たちが，成長，発達し成人になっていく過程，および成人になってからの生活がいかに満足のいくものであるかという観点から，評価されることがほとんどである。

しかし，小児がんのQOLの調査は非常に困難である。対象者が小児の場合，QOL調査に本人が回答できないため，両親が回答することが少なくない。また病名の告知の有無により，回答は大幅に異なる。本人にはそのような調査が行われていることを隠していることさえある。また欧米では小児がんに対するQOL評価表の整備が進んでいる[3~6]が，日本では最近ようやく小児用のQOL評価表ができたところであり，まだ一般的に使用されているわけではない。

Ⅲ．晩期合併症とQOL

以上述べてきたように，現在，小児がん経験者のQOLを規定するもののほとんどが晩期合併症といっても過言ではない。晩期合併症には，治療終了時には認められず，治療終了後年月を経て問題になってくる事項もある。診断5年後では約30%が晩期合併症を抱えているが，20~30年後には約70%になるとの報告もある。最近オランダから報告された研究では，1966~1996年に小児がんの治療を受けた1,362名の約75%に一つ以上の有害事象が発生しており，40%に重度，あるいは生命にかかわる機能障害をともなう有害事象が1つ以上あった。治療との関係では放射線療法のみでは55%，化学療法のみでは15%，外科手術のみでは25%であった。さらに疾患別では骨腫瘍の経験者の64%に高度の有害事象が認められ，白血病およびウイルムス腫瘍の経験者における有害事象は12%と最も頻度が低かったとの結果であった[7]。

表1に小児がんの晩期合併症の項目について示した。

Ⅳ．身体的晩期合併症

晩期合併症は身体のあらゆる部位に起こり，さまざまな身体機能に関係する。疾患の種類や治療法あるいは治療を受けた年齢，性別などによって，起こりやすい症状や身体の部位などが異なる。表2に晩期合併症と治療との因果関係のうち，現在明確にされているものを示した。

頭蓋放射線照射は，脳腫瘍の治療や白血病・リンパ腫の中枢神経浸潤予防のために行われる治療である。照射野の中には，視床下部や下垂体など内分泌と大きくかかわる臓器が含まれるため，成長ホルモンをはじめとするいくつかのホルモンの分泌に障害が出てくることがある。われわれが，東京小児がん研究グループのプロトコールで治療された急性リンパ性白血病（ALL）の経験者287名（全例頭蓋放射線照射を受けている）の最終身長を調べた結果では，男子161名中8名（5.0%），女子126名中6名（4.8%）が−2SD以下の低身長であった。また小児がんの治療後にはさまざまな神経障害の報告があるが，頭蓋放射線照射との関連が強く示唆される障害も少なくない。たとえばわれ

表1　小児がんの晩期合併症

1）成長・発達への影響
低身長，肥満，やせ，骨格・筋・軟部組織の異常，知能低下，認知力低下，心理的，社会的成熟に関する問題，性的成熟の異常

2）生殖能力への影響
妊孕力低下，子孫への影響

3）免疫機能低下

4）臓器機能への影響
心毒性，呼吸器障害，肝機能障害，腎機能障害，消化管障害，骨・筋の異常，内分泌機能異常，視力・視野異常，聴力障害，皮膚障害，神経障害

5）二次性腫瘍
良性腫瘍，
悪性腫瘍（二次性白血病，脳腫瘍など）

表2 晩期合併症と治療との関係

成長ホルモン欠乏	頭蓋放射線照射
肥満	頭蓋放射線照射
神経・認知障害	頭蓋放射線照射，MTX/Ara C 髄注
心毒性・うっ血性心不全	アントラサイクリン
思春期早発	頭蓋放射線照射
甲状腺機能低下	甲状腺・頭蓋・脊椎放射線照射
不妊	アルキル化剤，全身放射線照射，腹部・睾丸放射線照射
骨粗鬆症	副腎皮質ホルモン，性腺放射線照射，頭蓋・脊椎放射線照射，MTX
大腿骨頭壊死	副腎皮質ホルモン
白内障	頭蓋放射線照射，副腎皮質ホルモン
HCV 関連肝障害	1992年2月以前の輸血
歯芽異常	頭蓋放射線照射，幼少時の抗がん剤使用
二次性脳腫瘍	頭蓋放射線照射
二次性白血病	トポイソメラーゼII阻害薬，アルカリ化剤
皮膚癌	放射線照射

われの調査では，ALL 治療後にもやもや病を発症した6例は全例頭蓋放射線照射を受けていた[8]。さらに二次性の脳腫瘍などの発症原因ともなることが指摘されている[9]。

抗がん剤と晩期合併症との関係についてもいくつか明らかになっていることがある。たとえば，アントラサイクリン系の抗がん剤には心毒性があり，とくに慢性蓄積性の心毒性は拡張型心筋症，さらにはうっ血性心不全を起こすことがあり，晩期合併症の中でも重大な問題である[10,11]。また，トポイソメラーゼII阻害剤や代謝拮抗剤による二次性白血病の発症も生命にかかわる重大な晩期合併症である[12]。

近年，小児がんの治療成績向上に大きな役割を果たした造血幹細胞移植（SCT）に関する晩期合併症も，最近多くの報告がある。その内容は移植後の GVHD と関連したもの，全身放射線照射による不妊やさまざまな内分泌学的な問題，二次性腫瘍など多種多様であり，化学療法のみの治療より重大でかつ頻度が高いとされている。しかし最近でも，SCT 治療を選択する際に疾病の治癒が最優先され，治療後の QOL を重要視するという意識は患者側には低いというアンケート結果が報告されている。この論文では QOL について医師が利用できるデータが少ないため，患者への説明が困難なことに原因があり，医師と患者が共有できる QOL についての情報の蓄積が必要であると結論されている[13]。

V．その他の晩期合併症

小児がん経験者の15～30％に心的外傷後ストレス症候群（PTSD：Post Traumatic Stress Disorder），うつ状態，情緒不安定などの心理的な問題があるといわれている。生命の危機，治療にともなう苦痛だけでなく身体的晩期障害である成長障害や不妊，四肢の切断などは PTSD の原因となり，小児がん経験者の約20％が PTSD の診断基準を満たすとの報告がある[14]。また教育（学校），就職，結婚，保険への加入など小児がんに罹患したことがその後の人生に大きなマイナスの影響を及ぼすことがある。これらも広い意味で晩期合併症の範疇となり，QOL と多大な関係があるものである。

VI．小児がん経験者が良好な QOL を保つために

治療が成功した後，小児がんの経験者が良好な QOL を保った健常な生活を一生送れるようにするために，どのような支援をすべきかということを医療者は考えなければならない。その中で，小児がんを患った方たちを長期にわたりきちんとフォローアップし，必要に応じ援助できるような体制を用意すべきではないかという考えが広まりつつあり，最近その準備が始まっている。日本小児白血病リンパ腫研究グループ（JPLSG）長期フォローアップ委員会では，この活動の一環として，本邦での現状を把握し，今後のあり方を提言するためにアンケート調査を行い報告した。その結果，多様な晩期合併症

に対し各施設が限られた体制の中で対処している現状が浮き彫りになった[15]。2006年には厚生労働省がん助成，2007年には厚生労働省科学研究費補助金による研究班が成立し，今後国のレベルで小児がん経験者に対する対策がたてていける可能性が出てきたことは喜ばしいことである。

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Case Report

A CASE SERIES OF CHILDREN WITH HIGH-RISK METASTATIC NEUROBLASTOMA TREATED WITH A NOVEL TREATMENT STRATEGY CONSISTING OF POSTPONED PRIMARY SURGERY UNTIL THE END OF SYSTEMIC CHEMOTHERAPY INCLUDING HIGH-DOSE CHEMOTHERAPY

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□ *The aim of this study was to clarify the feasibility of a novel treatment strategy consisting of postponed primary surgery till the end of systemic chemotherapy including HDC without interruption by local therapy for neuroblastoma patients at a high risk for relapse. After induction chemotherapy, patients received double conditioning HDC consisting of thiotepa and melphalan. Radical surgery was applied to local lesions. Irradiation was not applied to any lesions. Eleven consecutive pediatric neuroblastoma patients were treated according to this strategy. Seven of 11 patients remained in complete remission for 21(171 months. This treatment strategy seems feasible and a further study is warranted.*

Keywords delayed primary surgery, high-dose chemotherapy, high-risk neuroblastoma, melphalan, thiotepa

Advanced neuroblastoma is a systemic disease that spreads to the whole body, including the bone marrow, liver, lymph nodes, and bones. Morphologic or radiologic methods only detect metastases larger than a certain size. This indicates that high-risk neuroblastoma should be considered as a

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