Table 2 Summary of efficacy

	Rasburicase dose		Total
	0.15 mg/kg	0.20 mg/kg	
Number of evaluable patients	15	14	29
Responders, *n* (%) [95% CI]	14 (93.3) [68.1–99.8%]	14 (100) [76.8–100%]	28 (96.6) [82.2–99.9%]
Hyperuricemic			
Evaluable patients, *n*	8	5	13
Responders, *n* (%)	7 (87.5)	5 (100)	12 (92.3)
Nonhyperuricemic			
Evaluable patients, *n*	7	9	16
Responders, *n* (%)	7 (100)	9 (100)	16 (100)
Inhibitory rate (%)[a]			
Evaluable patients, *n*	15	14	29
Mean [95% CI]	84.8 [76.7–92.9]	92.9 [88.7–97.0]	88.7 [84.1–93.3]

CI confidence interval

[a] Measured on day 1, 4 h after administration of rasburicase. The rate of uric acid inhibition (%) was calculated as follows: (plasma uric acid concentration at baseline – plasma uric acid concentration at each timepoint) divided by (plasma uric acid concentration at baseline) multiplied by 100

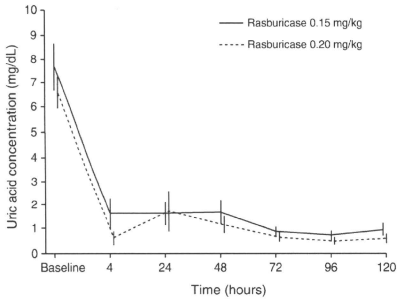

Fig. 1 Mean plasma uric acid concentration by dose over time. Patients aged <18 years with newly diagnosed hematologic malignancies with hyperuricemia, or newly diagnosed hematologic malignancies presenting with a high tumor burden regardless of uric acid level, were randomly allocated (based on stratification by weight [<10 or ≥10 kg]) to receive rasburicase (SR29142) administered at either 0.15 or 0.20 mg/kg/day for 5 days, followed by chemotherapy starting from 4 to 24 h after the first infusion of rasburicase

(70.0%). All of these AEs occurred with a similar frequency in both dose groups, with the exception of neutropenia (rasburicase 0.15 mg/kg, 93.3%; rasburicase 0.20 mg/kg, 73.3%). The majority of AEs reported during the study period were judged by the investigators to be related to the underlying malignancies and/or chemotherapy. There was no difference in the safety profiles of rasburicase 0.15 mg/kg/day for 5 days and rasburicase 0.20 mg/kg/day for 5 days.

The three grade 4 AEs (cerebral hemorrhage, brain edema, and brain herniation) experienced by one patient in the rasburicase 0.15 mg/kg group who withdrew from the study on day 8, were judged by the investigators to be unrelated to rasburicase treatment. The patient died after withdrawal from the study. No other deaths were reported during the study.

Drug-related AEs occurred in six patients ($n = 4$ in the rasburicase 0.15 mg/kg group; $n = 2$ in the 0.20 mg/kg group). One patient in the rasburicase 0.20 mg/kg group experienced grade 3/4 hemolysis; the patient did not have G6PD deficiency. The risk of rasburicase-induced hemolysis, possibly leading to hemolytic anemia and methemoglobinemia, is greater in patients with G6PD deficiency because of the accumulation of hydrogen peroxide [13]. However, rare cases of rasburicase-induced methemoglobinemia have been reported in patients without G6PD deficiency [12, 16]. Two rasburicase-related AEs occurred after the administration of rasburicase but before the start of chemotherapy (grade 1/2 hypersensitivity in the rasburicase 0.15 mg/kg group and grade 3/4 anemia in the rasburicase 0.15 mg/kg group).

Hypersensitivity reactions (all grades) were reported in 8 patients (53.3%) in the 0.15 mg/kg group and 12 patients (80.0%) in the 0.20 mg/kg group. Grade 3/4 events were only reported in two patients in the 0.15 mg/kg group: one patient completely recovered from the hypersensitivity reaction by day 6, although the other patient experienced persistent drug hypersensitivity until day 32. However, these grade 3/4 hypersensitivity reactions were judged to be unrelated to rasburicase. Only two AEs (hypersensitivity [grade 1/2] and hemoglobin decreased [grade 1/2]), observed before chemotherapy, were considered to be related to rasburicase. Anti-rasburicase antibodies or anti-SCP antibodies were not observed in any patients with hypersensitivity reactions.

A slight decrease in serum creatinine levels from baseline was observed. The mean values (±standard deviation) of serum creatinine were 52.3 μmol (±22.6) at baseline, 43.6 μmol (±16.3) on day 3, and 33.5 μmol (±11.5) on

day 36 for the 0.15 mg/kg rasburicase group; and 44.4 μmol (±19.1) at baseline, 36.7 μmol (±11.8) on day 3, and 27.1 μmol (±7.1) on day 36 for the 0.20 mg/kg group. No clinically significant changes were observed for the other renal function parameters (potassium, phosphorous, and calcium) during the study period.

3.5 Antibodies

Anti-SCP antibodies were detected in one patient before administration of rasburicase 0.20 mg/kg. Anti-rasburicase antibodies were detected in another patient in this group on day 29 and the patient tested negative for antibodies 6 months after the first administration. Neither patient experienced a hypersensitivity reaction during the study.

3.6 Pharmacokinetics

Blood samples to determine plasma concentrations of rasburicase were collected from 20 patients, 10 in each dose group. One patient in the 0.20 mg/kg dose group was excluded due to only two samples having been collected on day 1 of the study. Therefore, 19 patients were evaluable for AUC_{0-24} on day 1 and C_{min}, C_{eoi}, AUC_{0-24}, and $t_{1/2z}$ on day 5.

The pharmacokinetic profile of rasburicase is summarized in Table 3. Increase in exposure to rasburicase over days 1–5, as measured by AUC_{0-24} and C_{eoi}, was dose proportional. For the 1.33-fold increase in dose from 0.15 to 0.20 mg/kg, AUC_{0-24} increased 1.13-fold and 1.30-fold on days 1 and 5, respectively, while C_{eoi} increased 1.21-fold and 1.23-fold on days 1 and 5, respectively.

Rasburicase accumulated slightly on day 5, as assessed by AUC_{0-24} and C_{eoi}. The accumulation ratios of AUC_{0-24} and C_{eoi} (defined as the ratio of day 5 to day 1 for AUC_{0-24} and C_{eoi}) were 1.13 (95% CI 1.02–1.25) and 1.17 (95% CI 1.09–1.27), respectively, indicating slight accumulation. Mean $t_{1/2z}$ was comparable for both dose groups.

4 Discussion

The data from this study show that administration of rasburicase 0.15 or 0.20 mg/kg before the start of chemotherapy is well tolerated in Japanese pediatric patients with acute leukemia or non-Hodgkin's lymphoma. A rapid reduction in plasma uric acid levels to ≤7.5 mg/dL in patients ≥13 years or ≤6.5 mg/dL in patients <13 years within 48 h after the start of the first rasburicase administration occurred and lasted until 24 h after the last rasburicase administration on day 5 in 28 of 29 patients (96.6%). Moreover, 12 of 13 patients with hyperuricemia at baseline responded to treatment. A high overall RR of 96.6% was observed, indicating the efficacy of rasburicase for both the prophylaxis and treatment of hyperuricemia in pediatric patients receiving chemotherapy.

Notably, all evaluable patients in the rasburicase 0.20 mg/kg group achieved a response and only one evaluable patient in the 0.15 mg/kg group did not respond. In addition, there was a greater reduction in plasma uric acid concentrations from baseline at 4 h with the higher dose of rasburicase (92.9 vs. 84.8%), further demonstrating the greater efficacy of the rasburicase 0.20 mg/kg dose.

These findings add further credence to the results of the randomized US study conducted by Goldman et al. [12],

Table 3 Pharmacokinetic parameters after once-daily intravenous administration of rasburicase over 30 min (5-day treatment)

Rasburicase dose group (mg/kg)	Day 1		Day 5			
	AUC_{0-24} (ng h/mL)	C_{eoi} (ng/mL)	AUC_{0-24} (ng h/mL)	C_{eoi} (ng/mL)	$t_{½z}$ (h)	C_{min} (ng/mL)
0.15						
n	10	10	10	10	10	10
Mean (SD)	28,200 (7,270)	2,160 (512)	29,700 (6,460)	2,490 (373)	11.6 (5.0)	536 (218)
CV (%)	26	24	22	15	43	41
0.20[a]						
n	9[a]	10	9[a]	9[a]	9[a]	9[a]
Mean (SD)	31,500 (4,540)	2,580 (432)	38,100 (5,640)	3,050 (383)	11.2 (3.1)	780 (335)
CV (%)	14	17	15	13	27	43

[a] One patient in the rasburicase 0.20 mg/kg dose group had only two pharmacokinetic samples taken on day 1 because the patient withdrew from the study due to a low white blood cell count on day 1 after the first administration of rasburicase

AUC_{0-24} area under the rasburicase plasma concentration–time curve from 0 to 24 h, C_{eoi} plasma concentration of rasburicase at the end of infusion, C_{min} minimum rasburicase plasma concentration, *CV* coefficients of variation, *GM* geometric mean, *SD* standard deviation, $t_{1/2z}$, terminal half-life

which demonstrated more rapid control of uric acid and a lower plasma uric acid concentration during the first 96 h of therapy with rasburicase 0.20 mg/kg/day compared with 5–7 days of treatment with allopurinol in pediatric patients with high risk for TLS. In addition, several single-arm studies conducted in Europe, North America, Australia, and Asia have evaluated the 0.20 mg/kg dose of rasburicase for up to 7 days in pediatric and adult patients with high risk for TLS [17–21]. In line with our findings and those of Goldman et al. [12], these studies also reported numerically greater response rates (based on normalization of uric acid concentration) of 97–100% with rasburicase 0.20 mg/kg.

This is the first report to comprehensively assess rasburicase-related AEs occurring before the start of chemotherapy in pediatric patients. The majority of AEs reported during the treatment period were judged to be related to the underlying malignancies or chemotherapy by the investigators, with a low incidence of rasburicase-related AEs. Only two rasburicase-related AEs, including one hypersensitivity reaction, were observed before the start of chemotherapy in the rasburicase 0.15 mg/kg group. Most rasburicase-related AEs observed after the start of chemotherapy had a similar profile to those related to the underlying malignancies or chemotherapy. Patients who receive chemotherapy for hematologic malignancies are often exposed to risk of renal dysfunction. In the present study, renal parameters such as serum creatinine were not aggravated until completion of chemotherapy, suggesting that rasburicase might preserve renal function during induction chemotherapy.

Interestingly, new guidelines regarding the management of patients at risk of developing TLS and its prevention have recently been published [22]. Prevention strategies, including hydration and prophylactic rasburicase in high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and close monitoring for low-risk patients, are advised [22]. In addition, the guidelines advise aggressive hydration and diuresis plus allopurinol or rasburicase for hyperuricemia as primary management of established TLS.

An observational study has shown that treatment with rasburicase according to this new guideline is effective in preventing and controlling hyperuricemia and TLS in children with hematologic malignancies [23]. The study reported that the duration of rasburicase treatment should be tailored to the duration and intensity of tumor cell lysis in the patient by closely monitoring clinical chemistry. The superiority of rasburicase in comparison with allopurinol for the prophylaxis and treatment of hyperuricemia in children with leukemia and lymphoma has been demonstrated [24]. Rasburicase, administered at a dose of 0.20 mg/kg for 5 consecutive days, resulted in a rapid and significant decrease in uric acid levels after 4 h [24], in line with the findings reported in the current study. Rasburicase was also a more potent and more rapid uricolytic agent than allopurinol.

As rasburicase is a recombinant protein, antibodies can be produced against this agent. However, the clinical implication of such anti-rasburicase antibodies is unknown. In this trial, anti-rasburicase antibody production was reported in one patient on day 29, however, this patient did not experience a hypersensitivity reaction during the study. None of the patients had any anti-rasburicase antibodies on day 8. In previous studies in which rasburicase was administered to patients with cancer, although a small number of patients were shown to have anti-rasburicase antibodies, production of the antibody was not associated with the clinical status of the patients or the occurrence of AEs, including hypersensitivity reactions [25]. Goldman et al. [12] reported no cases of rasburicase antibody production in the US pediatric study using rasburicase 0.20 mg/kg, whereas Pui et al. [26] reported antibody production in 17 of 121 children and young adults treated with rasburicase 0.15 or 0.20 mg/kg. Other studies evaluating rasburicase did not assess rasburicase antibody production [18–21]. The production of anti-SCP antibody was also reported in one patient before the first administration of rasburicase. In this patient, a hypersensitivity reaction was not experienced during this study. This suggests that there was no correlation between the presence of anti-rasburicase or anti-SCP antibodies and the occurrence of hypersensitivity reactions in this study. However, because of the limited number of patients with antibody production in the current study, further studies are required in order to confirm this finding.

The pharmacokinetic data obtained in this study support the premise of dose proportionality of rasburicase, with only slight drug accumulation during 5 days of treatment. These data are consistent with the known pharmacokinetic profile of rasburicase in Western populations [26], suggesting that there is no ethnic variation in terms of the pharmacokinetic profile of rasburicase. Based on the results presented here, a daily rasburicase dose of 0.20 mg/kg might be recommended, particularly for patients who are more seriously ill and at high risk of developing TLS. However, as only a small sample size was studied in the present study and no comparator or placebo arm was included for comparison, further studies are needed to confirm the optimal dose of rasburicase for patients in different risk categories.

In conclusion, this study provides further evidence that rasburicase is highly effective in the control of hyperuricemia, a component of TLS, in pediatric patients undergoing chemotherapy for non-Hodgkin's lymphoma or acute leukemia. The study also demonstrates that rasburicase is safe and well tolerated when administered before the start of chemotherapy in this group of patients.

Acknowledgments We thank the following additional investigators: Shoichi Koizumi, M.D., Ph.D. (Department of Pediatrics, Kanazawa University Hospital); Akira Ohara, M.D. (Department of Blood Transfusion, Toho University Omori Medical Center); Yoshihiro Komada, M.D., Ph.D. (Institute of Molecular and Experimental Medicine, Mie University Hospital); Takashi Kaneko, M.D. (Department of Hematology/Oncology, Tokyo Metropolitan Kiyose Children's Hospital). Members of the Efficacy and Safety Evaluation Committee: Fumio Bessho, M.D. (Kyorin University Hospital); Shuki Mizutani, M.D. (Tokyo Medical and Dental University Hospital); Hideo Mugishima, M.D. (Nihon University Itabashi Hospital). Other participating institutions: Nippon Medical School Hospital; National Center for Child Health and Development; Tohoku University Hospital, Saga Medical School Hospital; Shizuoka Children's Hospital; National Hospital Organization Hokkaido Cancer Center; Hiroshima University Hospital. Editorial support provided by sanofi-aventis.

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Pediatr Surg Int
DOI 10.1007/s00383-009-2449-0

ORIGINAL ARTICLE

Outcome of pediatric renal tumor treated using the Japan Wilms Tumor Study-1 (JWiTS-1) protocol: a report from the JWiTS Group

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Abstract

Purpose In 1996, the Japan Wilms Tumor Study (JWiTS) group was founded to elucidate the efficacy and safety of the regimen established by the National Wilms Tumor Study (NWTS) group in the USA, and a multicenter cooperative study (JWiTS-1) was started in Japan. This report reviews the results of JWiTS-1.

Methods A total of 307 patients with malignant renal tumor were enrolled in the JWiTS-1 study between 1996 and 2005. Central pathological diagnosis and follow-up data were available in 210 cases. The protocol regimens were similar to the NWTS-5 regimens. Clinical stage was classified according to the Japanese Staging System.

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Published online: 23 August 2009

Results Five-year overall survival (OS) rate was 91.1% for nephroblastoma, 72.9% for clear cell sarcoma of the kidney (CCSK), and 22.2% for rhabdoid tumor of the kidney (RTK). In the nephroblastoma patients, 5-year OS was 90.5% for stage I disease, 92.2% for stage II, 90.9% for stage III, 86.7% for stage IV, and 78.7% for stage V.
Conclusions The OS of patients in the JWiTS-1 study were comparable with the results of other multicenter studies in the USA and Europe. The outcome for patients with nephroblastoma and CCSK was fair. In contrast, the cure rate for those with RTK was not satisfactory. New treatment strategies are needed for patients with RTK.

Keywords Clinical trials · Group study · Japan · Survival · Wilms tumor

Introduction

Wilms tumor (WT), or nephroblastoma, is the most common malignant renal tumor in childhood. The survival of patients with WT has improved dramatically from 30% just a few decades ago to almost 90% in the modern era [1]. The improvements in survival have occurred as the result of advances in multimodality treatments including surgical management, irradiation, and chemotherapy, established in trials and studies conducted by many national and international cooperative groups. In the USA and Canada, the National Wilms Tumor Study (NWTS) group, now part of the Children's Oncology Group (COG), has studied the therapy and outcomes of children with WT since 1969 [2]. In Europe, international cooperative studies have been conducted predominantly by the International Society of Paediatric Oncology (SIOP) since 1971 [3].

The goals of these groups are to increase cure rates while minimizing morbidity. In NWTS studies primary surgical resection of the tumor was the initial treatment of most children, whereas in SIOP studies chemotherapy was the initial treatment. Both approaches have distinct advantages and disadvantages. The benefit of the NWTS approach is that it enables accurate assessment of histology, extent, and molecular biology of the untreated tumor. However, the resection of large tumors sometimes results in intraoperative tumor spillage, which increases the risk of local abdominal relapse and subsequent poor outcome [4]. On the other hand, the benefit of the SIOP approach is that preoperative chemotherapy usually reduces tumor volume, thereby decreasing the likelihood of spillage and downstaging the tumor [5]. Moreover, clinical and histological responses to the chemotherapy may provide valuable prognostic information [6]. Most patients treated on SIOP WT studies do not undergo tumor biopsy before starting chemotherapy. Therefore, patients who are not subsequently diagnosed as having WT may have received unnecessary therapy. In the SIOP 93-01 trial approximately 5% of lesions in patients treated with chemotherapy were ultimately shown not to be WT and 1.8% were benign [7]. Moreover, the true extent of disease may be masked by pretreatment.

Before 1996, Japanese children with renal tumor were treated individually at local institutions or by doctors using protocols developed by the NWTS. However, exact incidence and prognosis were unclear, and the survival rates of patients with stages III and IV WT were 10–15% worse than those in Western countries. The 5-year survival rate of children with WT registered with the Japanese Society of Pediatric Surgeons between 1991 and 1995 was 81.8% in stage III and 57.1% in stage IV disease, whereas the 4-year survival rate of patients registered to the NWTS-4 trial (1986–1994) was 90.9% in cases of stage III disease and 80.9% in stage IV [8, 9]. To improve the outcome of children with renal tumor the Japan Wilms Tumor Study (JWiTS) group was founded in 1996, and a nationwide multicenter cooperative study (JWiTS-1) was started. At that time, the Japanese Staging System defined by the Japanese Society of Pediatric Surgeons was broadly used in Japan. The patients enrolled into JWiTS-1 study were classified using the Japanese Staging System to compare the prognosis between the patients treated before and after the introduction of JWiTS-1 study.

The objectives of the JWiTS were (1) to elucidate the efficacy and safety for Japanese patients of the regimen established by the NWTS group; (2) to start the multicenter cooperative study in Japan; (3) to establish a central system of pathological diagnosis; (4) to create a database of children with renal tumors; (5) to create a tissue bank for basic research to study the biology of renal tumors in childhood; and, finally, to improve the prognosis and quality of life of Japanese children with renal tumors. Here, we report the results of the JWiTS-1 study for pediatric renal tumor.

Materials and methods

Registration

JWiTS-1 was a multiinstitutional cooperative study for patients aged under 16 at diagnosis with primary untreated renal neoplasms. The study was approved by the ethics board of each local hospital, and informed consent was obtained from the parents before registration. Between 1996 and 2005, 307 patients with renal tumor were registered from 116 pediatric institutions. Among them, histological slides were submitted for central pathology in 269 cases (87.6%), and follow-up data were submitted in 229 cases (74.6%). Both follow-up data and central pathological

diagnosis were available in 210 cases (68.4%). Survival data were calculated in these cases.

Pathological diagnosis and clinical staging

Microscope slides, institutional pathology reports, and JWiTS pathology forms were sent and reviewed by JWiTS pathologists (J. Hata, H. Horie). The histology of each tumor was categorized as favorable or anaplastic WT, clear cell sarcoma of the kidney (CCSK), rhabdoid tumor of the kidney (RTK), or other tumor type, and a written report of the central review was sent to the patient's physician at the relevant institution.

Clinical stage was classified according to the Japanese Staging System defined by the Japanese Society of Pediatric Surgeons as follows: stage I, tumor limited to kidney, capsule is intact; stage II, tumor extends around the kidney (capsule, attached lymph nodes, renal vein, or pelvis); stage III, tumor extends to the surrounding organs such as aortic lymph nodes, ureter, or bladder; stage IV, hematogenous metastases are present; and stage V, bilateral renal tumor.

Treatments

The therapeutic strategy was similar to that of the NWTS-5 protocol. As a basic principle, all patients underwent an initial nephrectomy. Preoperative chemotherapy was performed only when the tumor seemed unresectable. The surgical procedure was performed via a transabdominal incision. Biopsies were performed on any lesion suspected of being WT. Both histological slides and snap-frozen tumor specimens were sent to the Central Pathologists and Tissue Preservation Center, respectively.

Patients received postoperative chemotherapy with or without radiation therapy according to pathological diagnosis and clinical stage defined by the Japanese Staging System as shown in Table 1. Chemotherapy regimens are listed in Table 2. The NWTS Group permitted to use these regimens. Patients with one or more pulmonary nodules identified on plain chest radiographs received 12 Gy to both lungs and the mediastinum. Patients under 2 years with stage I favorable WT, and whose tumor weighted <550 g, received no postoperative chemotherapy. However, shortly

Table 1 Treatment strategies used in the JWiTS-1 trial

Stage, histology	Radiation (cGy)	Chemotherapy regimen	Duration (weeks)
Stages I or II FH	None	EE-4A[a]	18
Stage I focal or diffuse anaplasia	None	EE-4A	18
Stages III or IV FH or stages II–IV focal anaplasia	1,080	DD-4A	24
Stages II–IV diffuse anaplasia, or CCSK	1,080	I	24
Stages I or II RTK	None	RTK	24
Stages III or IV RTK	1,080	RTK	24

CCSK clear cell sarcoma of the kidney, *FH* nephroblastoma with favorable histology, *RTK* rhabdoid tumor of the kidney

[a] Patients under 2 years with stage I favorable WT, and whose tumor weighed less than 550 g, received no postoperative chemotherapy until January 2003

Table 2 Treatment regimens used in the JWiTS-1 study

Regimen	Weeks																							
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
EE-4A	A			A			A			A			A			A			A						
		V	V	V	V	V	V	V	V	V	V		V*			V*			V*						
DD-4A	A			D			A			D			A			D*			A			D*			A
		V	V	V	V	V	V	V	V	V	V		V*			V*			V*			V*			V*
I	D			C			D			C			D			C			D			C			D
		V	V	E	V	V	V	V	V	E	V	V	V*	V*		E			V*			E			V*
							C*						C*						C*						C*
RTK	P			P			C			P			P			C			P			P			C
	E*			E*						E*			E*						E*			E*			

These regimens are same as the regimens used in NWTS-5. NWTS Group permitted to use these regimens

A actinomycin D (0.045 mg/kg, max 2.3 mg), *C* cyclophosphamide (14.7 mg/kg/day × 5), *C** cyclophosphamide (14.7 mg/kg/day × 3), *D* doxorubicin (1.5 mg/kg), *D** doxorubicin (1.0 mg/kg), *E* etoposide (3.3 mg/kg/day × 5), *E** etoposide (100 mg/m^2/day × 3), *P* carboplatinum (16.7 mg/kg/day × 2), *V* vincristine (0.05 mg/kg, max 2 mg), *V** vincristine (0.067 mg/kg, max 2 mg)

after the initiation of the JWiTS-1 trial recurrence was reported in these patients. These observations demonstrated that the postoperative chemotherapy is necessary even in patients with localized tumor. Therefore, in January 2003, the protocol was changed and postoperative chemotherapy was performed in all patients.

Statistical analysis

Survival time was defined as the time from diagnosis until death or last contact. Death regardless of cause and relapse were considered as an event. Overall survival (OS) and relapse-free survival (RFS) rates were calculated by the Kaplan–Meier method. Comparisons of the prognostic impact of each factor were performed using the log-rank test.

Results

Pathological diagnosis

Pathological review was completed for 87.6% (269 out of 307) of patients enrolled. According to the central pathological reports, 172 (75.1%) of the cases were nephroblastoma, 21 (9.2%) were RTK, 16 (7.0%) were CCSK, and 20 (8.7%) were other tumors such as congenital mesoblastic nephroma, renal sarcoma, and renal cell carcinoma. Anaplasia was observed in six out of 172 (3.5%) cases with nephroblastoma. Institutional and central pathological diagnoses were obtained in 197 cases, and the institutional diagnosis matched the central one in 161 (81.7%) of those cases. Table 3 shows some examples of the mismatching of institutional and central pathological diagnoses. Most cases were a misdiagnosis between favorable and unfavorable histology.

Table 3 Examples of the mismatching of institutional and central pathological diagnoses

Local diagnosis	Central diagnosis	Case no.
Nephroblastoma	CCSK	5
Nephroblastoma	RTK	1
Nephroblastoma	Nephroblastoma with anaplasia	3
Nephroblastoma with anaplasia	RTK	1
Nephroblastoma with anaplasia	Nephroblastoma, no anaplasia	7
CCSK	CMN	2
CCSK	Nephroblastoma	1
CCSK	Sarcoma	1
CCSK	RTK	1

CMN congenital mesoblastic nephroma

Outcome ($n = 210$)

One hundred and seventy-seven (84.3%) of the patients with WT for whom survival data were calculated in this study are alive and 33 (15.7%) have died. Of these, 23 died from the tumor and 7 died as a result of their treatment. Figure 1 shows the OS and RFS curves for patients with WT, CCSK, and RTK. The 5-year OS and RFS rates were 91.1 and 82.0% for WT ($n = 155$), 74.5 and 72.9% for CCSK ($n = 15$), and 22.2 and 16.7% for RTK ($n = 18$), respectively. The prognosis of patients with RTK was significantly worse than that of patients with WT or CCSK.

Figure 2 shows the OS and RFS curves for 132 patients with WT according to the clinical stage defined by the Japanese Staging System. Five-year OS and RFS rates were 90.5 and 86.8% for stage I ($n = 54$), 92.2 and 72.1% for stage II ($n = 43$), 90.9 and 66.4% for stage III ($n = 11$), 86.7 and 58.4% for stage IV ($n = 15$), and 78.7 and 78.7% for stage V ($n = 12$), respectively. RFS rates

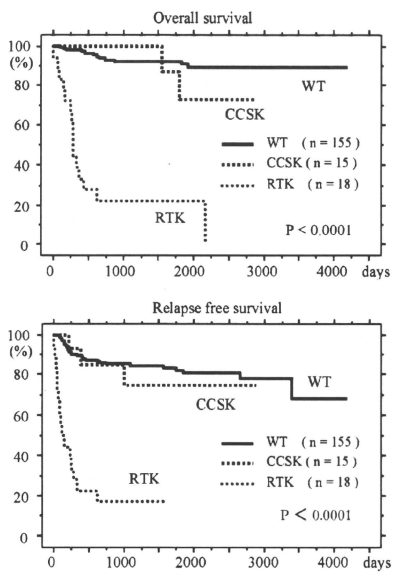

Fig. 1 Overall survival (*upper*) and relapse-free survival (*lower*) curves for patients with Wilms tumor (WT), clear cell sarcoma of the kidney (CCSK), and rhabdoid tumor of the kidney (RTK)

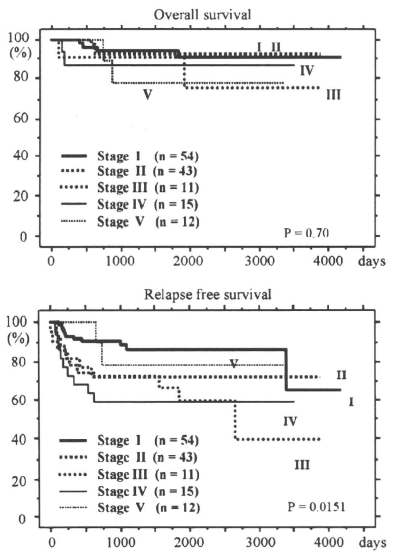

Fig. 2 Overall survival (*upper*) and relapse-free survival (*lower*) curves for patients with Wilms tumor according to the clinical stage classified according to the Japanese Staging System defined by the Japanese Society of Pediatric Surgeons

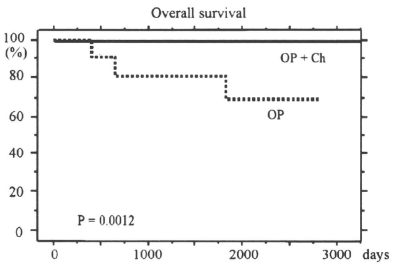

Fig. 3 Overall survival curves for patients with stage I Wilms tumor treated with surgery only and treated with surgery and postoperative chemotherapy using protocol EE-4A. The prognosis of the cases treated with surgery only was significantly worse than those treated with surgery and postoperative chemotherapy

were significantly lower in advanced cases; however, the differences in OS rates were not significant. Table 4 lists the six patients with WT who showed anaplastic histology; they are all alive without disease. Twenty-five out of 155 patients with WT relapsed, and of these 16 re-entered complete remission following salvage treatment.

Between 1996 and 2003 patients under 2 years of age with stage I, favorable histology nephroblastoma, and whose tumor weighed <550 g, received no postoperative chemotherapy. However, 4 cases out of 11 had recurrent disease. The prognosis of cases with stage I WT treated with surgery only was significantly worse than for those treated with surgery and postoperative chemotherapy (protocol EE-4A) (Fig. 3). Therefore from January 2003, the protocol was changed so that postoperative chemotherapy was performed in all cases.

Japan Wilms Tumor Study recommendations for the management of bilateral WT include initial biopsy or tumor resection and local staging followed by chemotherapy according to abdominal stage and histologic features, and second-look surgery at week 5. The surgeon should attempt to preserve renal function without compromising cancer control; 10 of the 12 patients with bilateral WT in this trial are alive. Concerning renal preservation, nephrectomy and partial resection of the opposite site was performed in seven cases and bilateral nephrectomy was performed in one case. Finally, two patients experienced renal failure and required dialysis or renal transplantation.

Table 4 Nephroblastoma with anaplasia

Case	Age, sex	Stage	Type	Treatment	Relapse	Prognosis
1	2 years, F	?	Diffuse	?	–	Alive, 3 years
2	6 years, F	I	Diffuse	EE-4A	–	Alive, 8 years
3	5 months, F	I	Focal	Operation only	–	Alive, 5 years
4	3 years, M	III	Diffuse	DD-4A + RT	–	Alive, 6 years
5	3 years, M	II	Focal	DD-4A + RT	+	Alive, 2 years
6	3 years, F	IV	Focal	?	–	Alive, 2 years

F female, *M* male, *RT* radiation therapy

Discussion

The main objective of the JWiTS-1 study was to elucidate the efficacy of the regimen established by the NWTS group for Japanese patients, and to improve the prognosis and quality of life for Japanese children with renal tumors. Prior to the JWiTS survival rates for stages III and IV WT were 81.8 and 57.1%, respectively, 10–15% worse than in Western countries. The staging system used in JWiTS-1 study was similar to the staging system used in the NWTS studies. Therefore, most of the patients were classified into the same stage in both staging systems. In the JWiTS-1 study, 5-year OS rates for stages III and IV WT have been improved to 90.9 and 86.7%. These results were not worse than those from the NWTS-4 or SIOP 93-01 regimens [9, 10]. Therefore, the JWiTS-1 study has successfully achieved its objectives. However, there are some remaining problems to solve.

Histologic characteristics are the most powerful prognostic indicators for renal tumor in children. Previous studies have proven that the prognosis of anaplastic WT, CCSK, and RTK is worse, resulting in their categorization as having "unfavorable histology" [11]. However, the histological diagnosis of WT with focal or diffuse anaplasia, CCSK, or RTK can be difficult. In the present study, around 5% of the children with "unfavorable histology" had an initial institutional diagnosis of favorable WT (Table 3). These distinctions are critical, because they result in the administration of different chemotherapy regimens. Thus, prompt central pathological review is essential to ensure that all children have an accurate diagnosis and receive appropriate treatment in all cases. Therefore, central diagnosis is considered to be important in improving outcomes for children with renal tumor.

A retrospective study of pathology samples from the NWTS-1 trial showed that anaplasia (irregular mitotic figures, large nuclear size, and hyperchromasia) is associated with worse prognosis [11]. The results from NWTS studies have shown that anaplasia is present in about 5% of WT cases, and that it is rare in patients younger than 2 years and increases to 13% in those over 5 years old. In the present Japanese study, anaplasia was present in 6 of 172 patients with WT (3.5%), and all of them are alive. Our results suggest that the incidence of anaplastic histology is a little lower and that the biology is more favorable in Japanese patients with WT than in Western populations. However, the number of cases in this trial is too small to draw further meaningful conclusions.

Cell sarcoma of the kidney and RTK initially believed to belong to the WT family, are now considered distinct tumor types. In the present study, 5-year OS rates were 91.1% for WT, 72.9% for CCSK, and 22.2% for RTK. Therefore, the prognosis was extremely worse in RTK those in WT and CCSK. There results were compatible with the recent studies conducted by the NWTS [12–15]. In the NWTS-4 study, the 4-year OS rate was only 23.3% in patients with RTK despite aggressive postoperative chemotherapy. Therefore, the development of more effective protocols for RTK is an urgent issue for the future program of the JWiTS.

Retrospective review of NWTS-4 found that a quite favorable outcome occurred in patients younger than 2 years, with tumors of <550 g, and with stage I favorable histology [16]. Therefore, from the outset the JWiTS-1 protocol included no adjuvant treatment after nephrectomy for these patients. However, the protocol was changed in 2003 because of the high-relapse rate. Figure 3 compares the survival of patients with stage I WT treated with surgery only and surgery followed by chemotherapy regimen EE-4A. The prognosis for patients who received postoperative chemotherapy was significantly better than for patients treated by surgery only. The result demonstrated that postoperative chemotherapy could effectively eradicate undetected residual disease in patients with stage I WT, and therefore, we changed the protocol so that every patient now receives postoperative chemotherapy.

Our recommendations for the management of bilateral WT include initial tumor resection or biopsy followed by chemotherapy and second-look surgery at week 5. Long-term survival rates for patients with synchronous bilateral WTs are reported to be 70–80% [17–19]. These results are compatible with ours, in which the 5-year OS rate for patients with bilateral WT was 78.7%. Bilateral WT poses the challenge of establishing local tumor control while preserving renal function.

With regard to renal preservation, among the 15 cases with bilateral WT hemilateral nephrectomy was performed in seven cases and bilateral nephrectomy was performed in one. Finally, two patients had renal failure and needed dialysis or renal transplantation. These results were not satisfactory, and in response to this the protocol for the treatment of bilateral tumor will be changed in the near future, so that preoperative chemotherapy will be performed to shrink tumors without biopsy confirmation. Preoperative chemotherapy often results in a significant reduction in tumor size, thereby facilitating subsequent renal salvage.

To avoid acute and long-term toxicities, therapy should be reduced for children with low-risk tumors. For this reason, reliable biological prognostic markers are needed to distinguish between favorable and unfavorable tumors. There are few prognostic factors for pediatric renal tumor, but several biological factors have been identified recently. One such factor is loss of heterozygosity (LOH) on chromosomes 1p and 16q [20]. The NWTS-5 study has shown that LOH on the 16q and 1p chromosomal arms is associated with an adverse prognosis regardless of tumor

stage and histology. The study also showed positive links between telomerase RNA expression and relapse rates, although there was no association with overall survival [21]. During the JWiTS study, we created a tissue bank to help elucidate molecular biological mechanisms operating in pediatric renal tumor. Using these materials, several lines of basic research have been pursued on the biological markers associated with WT and the roles of the *IGF2* and *WT1* genes in the tumorigenesis of WT have been clarified [22–24].

In conclusion, the JWiTS-1 treatment protocol has provided a reasonable standard of care for patients with WT and CCSK. However, the prognosis for patients with RTK and bilateral and relapsed WT is not satisfactory. We have to seek more effective therapy for patients with these high-risk tumors in the future programs of the JWiTS.

Acknowledgments We thank the investigators of the JWiTS and the many pathologists, surgeons, pediatricians, and radiation oncologists who managed the children enrolled on the JWiTS. This work was supported by a Grant-in-Aid for scientific research (no. 20390452) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

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ウイルムス腫瘍

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要旨

ウイルムス腫瘍は小児腎腫瘍の90%以上を占める．本腫瘍は無虹彩症や生殖泌尿器系の奇形を伴うことが多く，*WT1* 遺伝子のクローニングに繋がった．その後11p15領域にある一連のインプリンティング遺伝子の発現と腫瘍発生との関連が明らかになり，臓器発生とepigeneticな遺伝子発現に興味深い示唆を与えた．本稿ではこれらの遺伝子の腫瘍発生と器官形成の意義について概説した．

Key words：ウイルムス腫瘍，Denys-Drash症候群，*WT1*，imprinting gene，H19

はじめに

神経芽腫，ウイルムス腫瘍，肝芽腫，胚細胞腫瘍に代表される胎児性腫瘍は，主に乳幼児期に発生する特有な腫瘍群である．これら胎児性腫瘍は器官形成途上の母細胞から発生し，腫瘍細胞が発生母地の有する分化・成熟能を潜在的に有している．一方，腫瘍発生機構においては遺伝子異常が重要な要因であり同時に，それは環境の付加的要因により修飾されることが明らかになっている．本腫瘍の発生は疫学的にもきわめて興味深い．すなわち白人種に多く，日本人を含めて「有色人種」に少ない．ちなみに，米国の統計では16歳以下の10,000人に1人の割合で発生し，年間460名内外の患者が発生し，小児がんの6%を占めている．さらに白人種だけに3倍の頻度であるという．

本腫瘍の発生母地や腫瘍発生機序に関しては，最近，多くの分子遺伝学的研究の集積がみられる．ウイルムス腫瘍は組織像の類似性から腎発生途上に生じる後腎芽細胞に由来するという見解が一般的である．すなわちウイルムス腫瘍は後腎組織由来の腫瘍で，同組織を構成する後腎芽細胞が胎生30週以前に尿管芽に誘導されて，糸球体や尿細管に分化する途上の細胞が腫瘍化したものと考えられている．腫瘍性の後腎芽細胞は多分化能を有しており，糸球体様ならびに尿細管上皮に分化した上皮様細胞と同時に横紋筋，平滑筋，軟骨，脂肪などの間葉細胞にも分化し，腫瘍構成成分の一部となる．本腫瘍の特異性は，家族内発生が多いこと，患児の胚細胞系列に染色体異常や奇形をしばしば伴うことにある．ウイルムス腫瘍と染色体異常，奇形の合併は古くから知られていた．本稿ではこのようなウイルムス腫瘍の遺伝子異常の特徴について概説する．

Ⅰ　11p13に存在するWT1遺伝子（*WT1*）の構造・機能および発現

先に述べたように，ウイルムス腫瘍を発生する患児に形成異常（奇形）を伴うことが古くから知られていた．このような奇形は染色体異常のパターンと密接に関連している．11p13領域の欠失を伴う奇形として無虹彩症，尿道下裂，WAGR症候群，Drash症候群があり，同領域にウイルムス腫瘍の発生と器官形成にかかわる遺伝子の存在が想定されてきた．1990年にほぼ同時に2つのグループより，11p13領域からウイルムス腫瘍の発生に関連する *WT1* と命名された遺伝子が単離された．[1)2)]

WT1 は全長約50 kbで10個のエクソンからなり，mRNAの大きさは3.5 kbである．エクソン5全体とエクソン9のエクソンイントロ

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1. 4個のzinc finger構造をもつ転写因子をコード
2. 2カ所のalternative splice sitesが存在
　エクソン5：全体
　エクソン9：3′側　9塩基［lysine, threonine, serine(KTS)］
3. 胎児期の腎・性腺に発現し，泌尿生殖器形成に関与
4. Pax，PDGFなどの結合して転写調節を行う

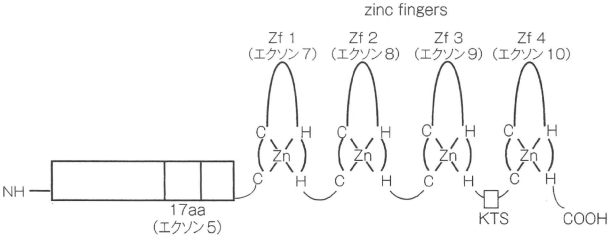

図1　*WT1*の構造
エクソン7～10はzinc finger domeinをコードしている．

ン接合部付近の2カ所にalternative spliceの部位があり，4種のsplicing variantsが存在する．*WT1*のNH側はglutamine-proline-glycine rich部位で，またCOOH側の4個のエクソンはそれぞれ（Cys）2-(His) 2 zinc finger構造をもつ（**図1**）．同部はDNAの特定の配列(-GCGGGGGCG-)に結合することが証明され，転写調節因子であることが判明した．実際にEGR-1，IGF2，IGF2 receptor，PDGF，Pax-2などの発現を転写レベルで調節し，分化を促進させる機能をもつことが明らかにされている[3]．一方，WT1蛋白は胎児期では腎糸球体の原基であるpodocyteおよび後腎芽細胞に発現している．また，精巣，卵巣の間質細胞の原基である生殖隆起，中皮細胞，脾臓，中枢神経などにも時期特異的に発現している．成人では糸球体上皮，精巣のSertoli細胞および卵巣の濾胞細胞に発現している[4]．

Keridbergらによって行われた*WT1*のターゲッティングによって，同遺伝子が欠失した胎仔は後腎芽細胞にアポトーシスが生じ，その結果腎組織は形成されなかった．また，生殖器の分化に重要なSertoli細胞や卵巣の濾胞細胞の原基である生殖隆起の萎縮が生じていたという[5]．このような実験結果から，*WT1*が腎形成のほか，男性生殖器，すなわち生殖隆起を起源とする間質細胞が惹起するY染色体上にある性決定遺伝子*SRY*の活性化，および男性生殖器の形成に重要な機能を有することが判明した．

1．*WT1*異常とウイルムス腫瘍発生のメカニズム

散発性ウイルムス腫瘍での*WT1*変異の頻度は15%程度といわれている．われわれは97例の散発性ウイルムス腫瘍の解析の結果，サザンブロッド法で5例，PCR産物の塩基配列決定で15例に異常を認めた．微小変異の範囲はほとんどすべてのエクソンにわたっているが，多くはzinc fingerドメインの変異であり，エクソン8，9のミスセンス変異を伴った点突然変異や数十塩基対の重複や欠失例の報告を含めて，後述する奇形症候群を伴うものよりも多彩であった．変異を有する症例の組織像は胎児性横紋筋腫様腎芽腫（fetal rhabdomyomatous nephroblastoma：FRN）を含めた古典的ウイルムス腫瘍で15例中9例に葉内腎芽腫症を伴っ

ていた．しかしながら，散発性ウイルムス腫瘍における *WT1* 変異と腫瘍発生機序の詳細はいまだ明確にされていない．同遺伝子の変異がウイルムス腫瘍の発生に必ずしも十分条件でない可能性も指摘されている[6]．

2．*WT1* 異常とウイルムス腫瘍の組織像

WT1 が腎発生→成熟に重要な機能を有することが判明し，その異常がウイルムス腫瘍の発生に関連していることが明らかになっているが，*WT1* の機能消失が組織型にどのように反映しているのかについては不明な点が多い．Schumacher ら[7]，Miyagawa ら[8]は *WT1* の機能喪失によって，ウイルムス腫瘍において，間葉成分の優位性，とくに筋成分の増多が認められるとしている．

われわれはウイルムス腫瘍のうち，腫瘍組織に横紋筋細胞を多く含む FRN，または腫瘍の間葉成分として横紋筋成分が腫瘍の約 1/4 を占める組織型を示した 5 例の腫瘍組織で，*WT1* 変異を検索した結果，いずれもエクソン 9 における ^{1168}C→T の変異となり，結果として ^{390}Arg が stop codon になるナンセンス変異を認めた．しかもこれらは 1 例を除いて，両側性の腫瘍であった．また，このような患者では germline で，腫瘍に認められた変異と同一の変異を認めた．

これら 4 例の身体的特徴を詳細に検索すると，4 例中 3 例が男児で，停留精巣および尿道下裂を伴い，1 例の女児でも卵巣低形成などの生殖泌尿器系小奇形を合併していた．*WT1* の特定部位の germline 変異（^{1168}C→T）は同遺伝子の機能喪失を招来し，生殖泌尿器系の小奇形とともに，きわめて特異的な組織像も示すウイルムス腫瘍を発生せしめる可能性が示唆される[9]．

3．ウイルムス腫瘍・奇形症候群における *WT1* 異常

散発性ウイルムス腫瘍と異なり，Drash 症候群では *WT1* が責任遺伝子であることが明らかにされた．本症候群はウイルムス腫瘍の発生と乳児期に発症し，進行性に経過する diffuse mesangial sclerosis による腎不全および 46XY の核型を示しながら女性外性器を伴う，いわゆる XY gonadal dysgenesis から構成される[10]．外性器の異常は生殖隆起の間質細胞に発現する *WT1* の機能不全によると考えられている．Drash 症候群では *WT1* の zinc finger ドメインの点突然変異が体細胞レベルで，一方の対立遺伝子に生じるとドミナントネガティブ効果で腎障害・性分化の異常を，さらに腎で両方の対立遺伝子に生じるとウイルムス腫瘍を発生し，同症候群を惹き起こすという仮説が Pelletier によって提唱された[11]．Drash 症候群では報告例も含めほぼ 100%，zinc finger 領域に異常が認められる．

一方，興味深いのは同症候群に類似した Frasier 症候群（晩発性の腎障害，精巣性女性化症候群，ウイルムス腫瘍発生なし）[12]では，イントロン 9 の splicing donor sites に点突然変異を示すことが明らかにされた．エクソン 9 は *WT1* の alternative splicing site にあたり，splicing isoform として 9 塩基対で構成される 3 つのアミノ酸 lysine，threonin，serine（KTS と略）が存在する isoform（＋KTS）とそれらを含まない isoform（－KTS）が構成される．splicing donor sites に異常をきたすと＋KTS isoform が形成されない．その結果，正常のアレルからは＋KTS/－KTS が正常に構成されるのに対して，異常をもつ対立遺伝子からは－KTS しか生じない．そのため，＋KTS/－KTS の不均衡が生じることになる．すなわち，Frasier 症候群が *WT1* isoform の均衡の異常が原因である可能性が示唆される[13]．すなわちエクソン 7～10 における質の異なる遺伝子異常によって，近似はしているが異なった症候群が生じることが判明した（genotype-phenotype correlation）（**図 2**）．このような *WT1* 変異の同定は難治性腎障害の予後や，Drash 症候群で

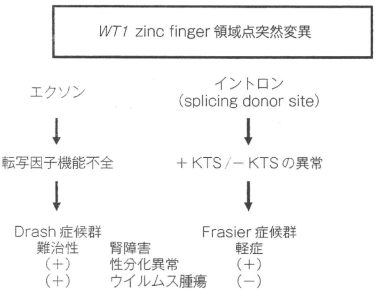

図2 Drash/Frasier 症候群の遺伝子型と表現型の対比

は，6歳以上になると80%以上の確率でウイルムス腫瘍が発生するといわれているので，腫瘍発生の予測診断としても有用である．

II 11p15 のインプリンティングを受ける遺伝子群

1．Beckwith-Wiedemann 症候群に伴う腎芽腫

腎芽腫は，WAGR 症候群や Denys-Drash 症候群とともに，Beckwith-Wiedemann 症候群に伴うことが知られている．本症候群は，片側肥大（hemihypertrophy），内臓肥大（visceromegaly），巨舌（macroglossia），臍帯ヘルニア（omphalocele）を特徴としており，染色体11p15 領域の異常が原因と考えられている．Beckwith-Wiedemann 症候群では，胎児性腫瘍，とくに腎芽腫を発生するリスクが高いことが知られており，本症候群の原因とされる11p15 領域が WT2 ともよばれ，また腎芽腫の原因遺伝子として腫瘍発生との関連が解析されてきた．

2．11p15 にクラスタリングするインプリンティング遺伝子群

11p15 領域には，インプリンティングを受ける遺伝子，すなわち，片親から受け継いだアレルのみを発現する遺伝子がクラスターをなして存在することが知られている．また，腎芽腫では母親由来のアレルが欠失しやすいことが報告されており，腎芽腫の発生にインプリンティング異常が関与することが想定されてきた．この領域は，2つのドメインから構成され，それぞれインプリンティングセンター（differentially methylated region，父親由来アレルと母親由来アレルで DNA メチル化の状態が異なる）によってコントロールされている（**図3**）．

1つ目の領域は IGF2/H19 ドメインあるいはインプリンティングドメイン1とよばれ，IGF2 と H19 からなる．IGF2 は父親由来のアレルのみが発現する胎児性の成長因子である．H19 は母親由来アレルのみが発現するが，蛋白をコードしていないと考えられている．この領域のインプリンティングは H19-DMR（H19 differentially methylated region，imprinting center 1：IC1）において，父親由来のアレルがメチル化を受けることによって制御されている．H19-DMR は非メチル化状態では，CTCF が結合しインスレーターとして作用することにより下流にあるエンハンサーがブロックされ，IGF2 のプロモーターに作用できない．したがって母親由来アレルの IGF2 は発現せず，H19 が発現する．一方，父親由来の H19-DMR はメチル化されているため CTCF が結合できず，下流のエンハンサーが作用し IGF2 は発現する．

2つ目の領域は CDKN1C（p57Kip2），KCNQ10T1（LIT1）から構成されており，KIP2/LIT1 ドメインあるいはインプリンティングドメイン2とよばれる．インプリンティングセンターである LIT1 DMR（imprinting center 2：IC2，KvDMR1）によって，IGF2/H19 ドメインとは独立して制御されている．p57Kip2 は，サイクリン/CDK 複合体を阻害する細胞増殖の負の制御因子であり，LIT1 は KvLQT1 のアンチ

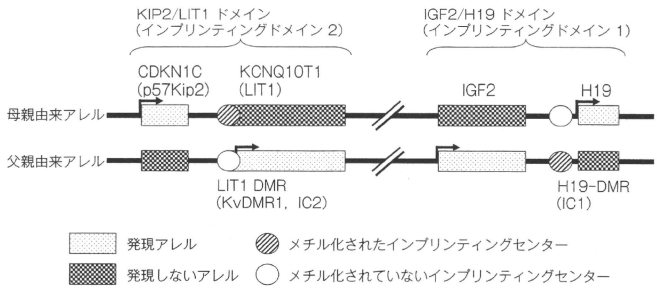

図3　11p15 領域に認められるインプリンティング遺伝子群とその機能

センス転写産物である．

3．Beckwith-Wiedemann 症候群と 11p15 領域の異常

Beckwith-Wiedemann 症候群では，11p15 領域に遺伝的な，あるいはエピジェネッティックな異常が同定されている．本症候群における 11p15 の異常としては，IGF2/H19 ドメイン，KIP2/LIT1 ドメインどちらか，あるいは両者を含む異常が同定されている．KIP2/LIT1 ドメインの異常としては，インプリンティングセンターである LIT1 DMR の低メチル化，あるいは p57Kip2 の遺伝子変異がある．IGF2/H19 ドメインの異常としては H19-DMR の高メチル化と IGF2 のインプリンティング喪失（loss of imprinting：LOI），IC1 の microdeletion などが報告されている．また，両方のドメインを含む異常としては，11 番染色体の父性片親性ダイソミー（uniparental disomy：UPD）や 11 番染色体の重複や転座などがある．なお 1/3〜1/4 程度の症例では，11p15 に異常が同定されない．

Beckwith-Wiedemann 症候群における腫瘍発生のリスクは，父性 UPD を伴う症例や IGF2/H19 ドメインの異常を有する例に高い．一方，KIP2/LIT1 ドメインの異常のみを伴う症例では，腫瘍発生のリスクが低いと考えられており，腫瘍，とくに腎芽腫発症には IGF2/H19 ドメインが関与していると想定されている．一方で，Beckwith-Wiedemann 症候群の父性 UPD 症例の 5 歳時の腫瘍発生リスクは 24%と報告されており，11p15 領域の異常のみでは腫瘍発生に不十分と考えられる[14]．

4．腎芽腫と 11p15 領域の異常

腎芽腫では，IGF2 のヘテロ接合性消失（LOH）が 30〜40%に報告されており，IGF2 の LOI は 30〜70%に報告されている．IGF2 の LOI の多くは H19-DMR の高メチル化を伴っている．インプリンティングの喪失により，本来は父親由来のアレルのみから発現する IGF2 が両アレルから発現することにより過剰となることが腫瘍発症に関与すると考えられる．

本邦においては，Satoh らが 35 例の腎芽腫における 11p15 の遺伝的あるいはエピジェネティックな異常を解析し，29%で 11p15 の LOH を，40%で IGF2 の LOI（H19-DMR の過剰なメチル化を含む）を認めると報告した[15]．また，Haruta らは，WT1 異常を伴う腎芽腫 36 例で IGF2/H19 ドメインの異常を解析したところ半数の 18 例に異常，すなわち 13 例に 11p13-15 の父性 UPD，3 例に 11p15 に限局する UPD，2 例に IGF2 の LOI を同定した[16]．これらの結果より，腎芽腫における 11p15 の異常は，当初考えられていたよりも頻度が高く，WT1 異常

の有無にかかわらず，IGF2/H19 ドメインの異常が腫瘍発生にかかわっていると考えられはじめている．一方で，アジア人では IGF2 の LOI はまれとする報告もあり[17]，本邦の腎芽腫における IGF2/H19 ドメインの関与はさらなる検証が必要である．

近年，奇形を伴わない散発性腎芽腫の中にも，胚細胞系列での 11p15 の異常を示す症例があることが報告された．Scott らは，437 例の散発性ウイルムス腫瘍患者の 11p15 領域の IGF2/H19 ドメイン，KIP2/LIT1 ドメインを解析し，3%に何らかの異常を同定した[18]．とくに両側腎芽腫では 12%に異常が同定され，その中には一家系の家族性腎芽腫が含まれていた．その異常には，H19-DMR の高メチル化，11p15 の UPD，H19-DMR の micro deletion/insertion が含まれていたが，KIP2/LIT1 ドメインに限局する異常は認められなかった．このことも 11p15，とくに IGF2/H19 ドメインの異常が腎芽腫発生の原因の一つであることを支持している．

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PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Metastatic Wilms' tumor in an adolescent successfully treated with multimodal pediatric therapy

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Key words adolescents and adults, stem cell transplantation, toxicity, wide-field irradiation, Wilms' tumor.

Adult Wilms' tumor (WT) is a rare disease entity occurring in adolescents, and very rarely in adults with adults reportedly comprising only about 3% of all cases of WT.[1] The prognosis of WT in adults appears to be worse than that of WT in small children, because of the higher frequency of advanced stage, a higher incidence of recurrence, a poorer response to treatment, and the absence of any established optimal treatment guidelines. However, the prognosis of adult WT improves when patients are treated based on pediatric protocols.[1-3]

We herein report an adolescent patient who was diagnosed with a WT that metastasized to the bone marrow, lungs, and liver despite favorable histological findings. The patient remained in a progression-free status for 5 years after the termination of the treatment, which included preoperative chemotherapy, a surgical resection of the tumor of the left kidney, wide-field radiation covering the primary lesion and all metastatic lesions, followed by autologous peripheral blood stem cell (PBSC) rescue.

Case Report

A 16-year-old Japanese girl, with a 2-month history of pain of the lower back, was transferred to the National Cancer Center Hospital. The patient's medical history and family history were unremarkable. A physical examination revealed a large palpable mass in the left lower quadrant of the abdomen, while neither organomegaly nor lymph node swelling was noted. The laboratory data were within the normal limits, except for a slightly elevated creatinine level (0.9 mg/dL) and a high level of neuron-specific enolase (NSE, 115.2 ng/mL). A computed tomography (CT) scan showed a large mass, which was barely distinguishable from the left kidney, in the left abdominal space. The tumor measured 110 mm × 130 mm × 250 mm in size according to 3-D measurements. Multiple liver metastases and multiple bilateral lung metastases were also detected (Fig. 1a,b). The pathology of the primary tumor was consistent with the blastemal type of WT without anaplasia, thus indicating a favorable histology (Fig. 1c). Bone marrow aspiration smears showed the massive infiltration of malignant cells (Fig. 1d).

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Received 9 July 2008; revised 23 September 2009; accepted 10 November 2009.
doi: 10.1111/j.1442-200X.2010.03210.x

The disease was not indicated for surgery as the primary treatment due to the size of the tumor. The patient underwent chemotherapy according to the National Wilms' Tumor Study (NWTS)-V. At the beginning of two courses, the patient received the revised DD4A regimen including vincristine (VCR), doxorubicin (DOX), actinomycin D (ACD) and cyclophosphamide (CPA). After treatment, the primary and metastatic tumors decreased in size, while the malignant cells in the bone marrow also disappeared. A left-sided radical nephrectomy was thereafter performed with a total tumor resection after a total of four courses of chemotherapy. The pathological findings of the resected tumor showed 95% necrosis of the whole tumor tissue.

The patient received a total of nine courses of chemotherapy according to the DD4A regimen. A course of VCR+DOX (VD) and a course of VCR+ACD (VA) were alternatively repeated at 3-weekly intervals. At the bone marrow recovery phases during the 7th and 8th courses of chemotherapy, PBSC was collected and cryopreserved. After the last course of chemotherapy, X-ray irradiation with a total of 1050 cGy in seven fractions was administered to cover the whole lung and abdomen with a shield placed around the right kidney region (Fig. 2a,b). Thereafter, the patient underwent PBSC rescue with a total number of 1.03×10^6/kg of $CD34^+$ cells. Grade 3 neutropenia and grade 2 thrombocytopenia were observed after irradiation.

The hematological toxicity caused by chemotherapy worsened to grade 4 and then it became further aggravated as its courses progressed. The interval between each chemotherapy course was therefore prolonged to 4 weeks. Neuropathy, which was probably secondary to the use of vincristine, was evaluated as Grade 3 after the second course of chemotherapy and it later resolved within 6 months after the completion of the treatment.

At the end of the treatment protocol, all metastatic lesions disappeared except for one small nodule, which measured 5 mm in diameter, in the right lower lung. An excisional biopsy of the nodule was deferred because of the patient's and her parent's refusal. Five years after the termination of treatment, there are no signs of any recurrent disease based on physical examinations, as well as the findings of CT scans and positron emission tomography scans.

Discussion

Currently, in excess of 80% of children with WT can be expected to achieve long-term survival.[4,5] On the other hand, the prognosis of adult WT is normally inferior to that of children. Byrd *et al.*

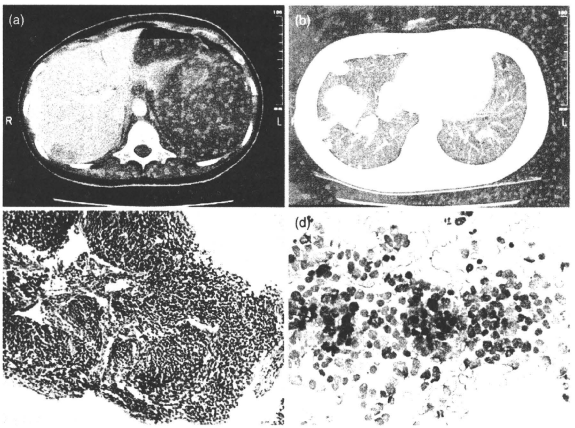

Fig. 1 Computed tomography (CT) scan showing the pathological features of the left renal tumor obtained by a needle biopsy and the bone marrow aspiration at the time of diagnosis. (a) CT scan of the abdomen showed a renal mass, which measured 110 mm × 130 mm × 250 mm, and multiple liver metastases. (b) CT scan of the chest showed multiple lung metastases. (c) The pathological findings were consistent with the blastemal type of Wilms' tumor. (d) Infiltration of the bone marrow (magnification: ×400; May–Giemsa stain).

reported the 3-year survival rate for adult WT to be 24%, in comparison to 74% for children between the 1960s and 70s.[6]

Using multimodal therapy similar to that performed for children, the prognosis of adult patients has recently improved. In NWTS studies, the 5-year relapse-free survival (RFS) and the overall survival (OS) rate of adult patients with WT have been reported to improve to 77.3% and 82.6%, respectively.[2] The International Society of Pediatric Oncology 93-01/Society for Pediatric Oncology and Hematology (GPOH) showed the RFS and OS (with a median observation time of 4 years) to be 57%

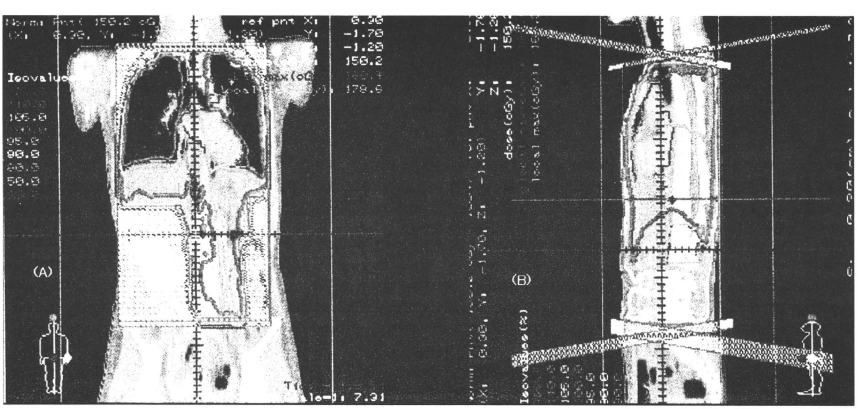

Fig. 2 The radiation field was planned to cover the whole lung and abdomen with a shield surrounding the right kidney region. (a) Frontal view. (b) Lateral view.

and 83%, respectively.[1] However, patients presenting with an advanced stage of adult WT still show a poor outcome. In a recent NWTS retrospective report, OS (with a mean observation time of 54 months) was only 20% for stage IV adult WT.[7]

The present patient initially presented with highly extensive disease, which was cured with multimodal therapy based on pediatric strategy. Because the patient's hematological toxicities were always serious, the interval between chemotherapy was thus prolonged. In addition, we also decided to use the minimum required radiation dosage and PBSC rescue. Furthermore, the patient's neurotoxicity secondary to vincristine was also serious, thus requiring the use of special equipment.

This case demonstrated that WT observed in the adolescent and adult population, even when identified at an advanced stage, appears to be curable if multimodal treatment according to the established pediatric strategy is effectively performed. However, toxicity such as hematological toxicity and neuropathy may develop at a higher incidence and at a more severe grade.[1,2] In this case the PBSC rescue may not have been needed, however this method should nevertheless be considered in patients presenting with severe hematological toxicity. Kalapurakal *et al.* pointed out the risk of veno-occlusive disease associated with an overdosage of ACD in adult patients.[2] Therefore, such toxicities should be closely monitored in adult patients with WT. Moreover, prospective trials in both adolescent and adult patients with WT are warranted in order to establish the appropriate dosages and optimal schedule of chemotherapy, as well as to determine the ideal sequence and effective design of local treatments and supportive care.

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Vaccine-associated paralytic poliomyelitis in a non-immunocompromised infant

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Key words oral poliovirus vaccine, poliomyelitis, primary immunodeficiencies, tissue injury, vaccine-associated paralytic poliomyelitis.

Oral poliovirus vaccine (OPV) was introduced in Japan in 1961 and it has become a routine immunization for infants since 1964. During the 1960s, the widespread use of OPV led to a dramatic decrease in the number of patients contracting poliomyelitis. Since 1981, no poliomyelitis cases caused by wild poliovirus have been reported in Japan.[1] Live virus vaccination, however, is associated with the serious consequence of vaccine-associated paralytic poliomyelitis (VAPP). In 2002, the World Health Organization estimated that between 250 and 500 cases of VAPP occur every year due to the use of OPV in routine childhood immunization programs around the world.[2] Although VAPP can occur in healthy recipients or their close contacts, persons with primary immunodeficiencies have a much higher risk of the disease.[3,4]

In Japan, the overall risk for recipient and contact VAPP has been reported as one case in every 2 million doses given, while the risk of recipient VAPP and recipient VAPP following the first OPV dose is one in every 3.7 million doses and one in every 2.3 million doses given, respectively.[5]

In this study, we report a case of VAPP in an infant who did not have any obvious immunodeficiency.

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Received 23 May 2009; revised 8 January 2010; accepted 29 January 2010.
doi: 10.1111/j.1442-200X.2010.03132.x

Case report

A 7-month-old male infant of healthy parents was presented with a high fever of 39°C and a perianal abscess, 15 days after his first