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References

1. Ronco C, Inguaggiato P, Bordonia V, De Cal M, Bonello M, Andrikos E, et al. Rasburicase therapy in acute hyperuricemia and renal dysfunction. Contrib Nephrol. 2005;147:115–23.
2. Jones DP, Stapleton FB, Kalwinsky D, McKay CP, Kellie SJ, Pui CH. Renal dysfunction and hyperuricemia at presentation and relapse of acute lymphoblastic leukemia. Med Pediatr Oncol. 1990;18:283–6.
3. Arrambide K, Toto RD. Tumor lysis syndrome. Semin Nephrol. 1993;13:273–80.
4. Davidson MB, Thakkar S, Hix JK, Bhandarkar ND, Wong A, Schreiber MJ. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. Am J Med. 2004;116:546–54.
5. Cohen LF, Balow JE, Magrath IT, Poplack DG, Ziegler JL. Acute tumor lysis syndrome. A review of 37 patients with Burkitt's lymphoma. Am J Med. 1980;68:486–91.
6. Stapleton FB, Strother DR, Roy S, Wyatt RJ, McKay CP, Murphy SB. Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic lymphoma. Pediatrics. 1988;82:863–9.
7. Bowman WP, Shuster JJ, Cook B, Griffin T, Behm F, Pullen J, et al. Improved survival for children with B-cell acute lymphoblastic leukemia and stage IV small noncleaved-cell lymphoma: a pediatric oncology group study. J Clin Oncol. 1996;14:1252–61.
8. Cheson BD, Dutcher BS. Managing malignancy-associated hyperuricemia with rasburicase. J Support Oncol. 2005;3:117–24.
9. Sood AR, Burry LD, Cheng DK. Clarifying the role of rasburicase in tumor lysis syndrome. Pharmacotherapy. 2007;27:111–21.
10. Legoux R, Delpech B, Dumont X, Guillemot J-C, Ramond P, Shire D, et al. Cloning and expression in *Escherichia coli* of the gene encoding *Aspergillus flavus* urate oxidase. J Biol Chem. 1992;267:8565–70.
11. Oldfield V, Perry CM. Spotlight on rasburicase in anticancer therapy-induced hyperuricemia. BioDrugs. 2006;20:197–9.
12. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood. 2001;97:2998–3003.
13. Bessmertny O, Robitaille LM, Cairo MS. Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome. Curr Pharm Des. 2005;11:4177–85.
14. Ishizawa K, Ogura M, Hamaguchi M, Hotta T, Ohnishi K, Sasaki T, et al. Safety and efficacy of rasburicase (SR29142) in a Japanese phase II study. Cancer Sci. 2008 Dec 14. [Epub ahead of print].
15. Graybill FA, Wang C. Confidence intervals on nonnegative linear combinations of variances. J Am Stat Assoc. 1980;75:869–73.
16. Kizer N, Martinez E, Powell M. Report of two cases of rasburicase-induced methemoglobinemia. Leuk Lymphoma. 2006;47:2648–50.
17. Pui CH, Jeha S, Irwin D, Camitta B. Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. Leukemia. 2001;15:1505–9.
18. Bosly A, Sonet A, Pinkerton CR, McCowage G, Bron D, Sanz MA, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer. 2003;98:1048–54.
19. Jeha S, Kantarjian H, Irwin D, Shen V, Shenoy S, Blaney S, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek™), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. Leukemia. 2005;19:34–8.
20. Shin HY, Kang HJ, Park ES, Choi HS, Ahn HS, Kim SY, et al. Recombinant urate oxidase (rasburicase) for the treatment of hyperuricemia in pediatric patients with hematologic malignancies: results of a compassionate prospective multicenter study in Korea. Pediatr Blood Cancer. 2006;46:439–45.
21. Wang L-Y, Shih LY, Chang H, Jou ST, Lin KH, Yeh TC, et al. Recombinant urate oxidase (rasburicase) for the prevention and treatment of tumor lysis syndrome in patients with hematologic malignancies. Acta Haematol. 2006;115:35–8.
22. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26:2767–78.
23. Bertrand Y, Mechinaud F, Brethon B, Mialou V, Auvrignon A, Nelken B, et al. for SFCE (Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent) recommendations for the management of tumor lysis syndrome (TLS) with rasburicase: an observational survey. J Pediatr Hematol Oncol. 2008;30:267–71.
24. Rényi I, Bárdi E, Udvardi E, Kovács G, Bartyik K, Kajtár P, et al. Prevention and treatment of hyperuricemia with rasburicase in children with leukemia and non-Hodgkin's lymphoma. Pathol Oncol Res. 2007;13:57–62.
25. Pui CH. Rasburicase: a potent uricolytic agent. Expert Opin Pharmacother. 2002;3:433–42.
26. Pui CH, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. J Clin Oncol. 2001;19:697–704.

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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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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

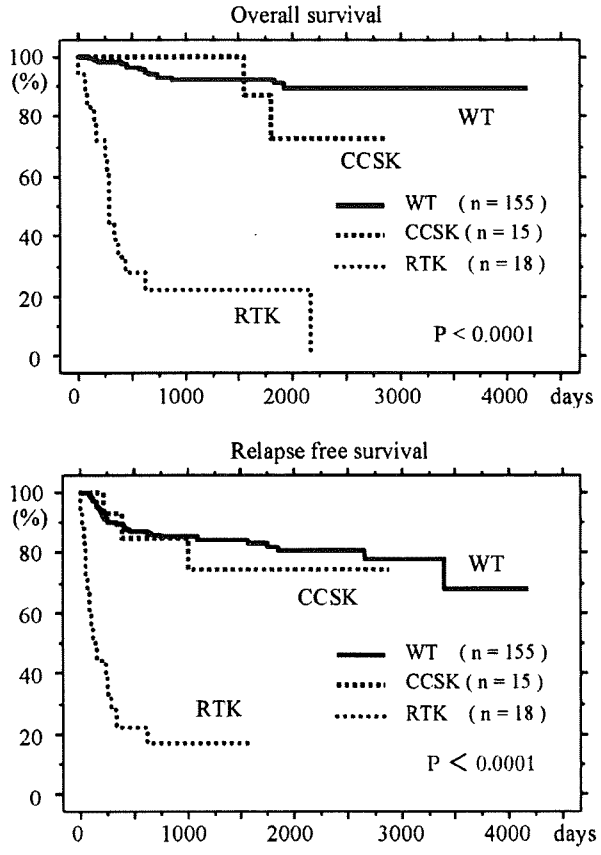

Fig. 1 Overall survival (*upper*) and relapse-free survival (*lower*) curves for patients with Wilms tumor (WT), clear cell sarcoma of the kidney (CCSK), and rhabdoid tumor of the kidney (RTK)

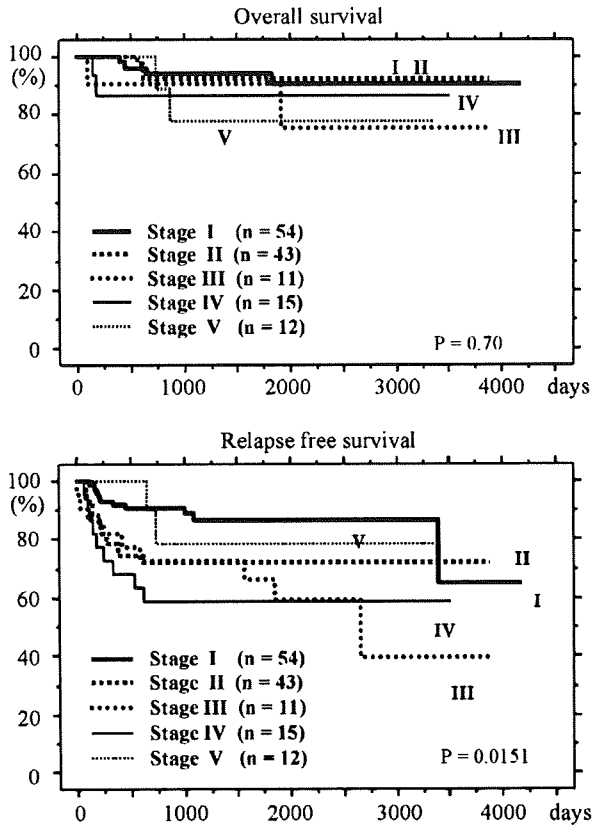

Fig. 2 Overall survival (*upper*) and relapse-free survival (*lower*) curves for patients with Wilms tumor according to the clinical stage classified according to the Japanese Staging System defined by the Japanese Society of Pediatric Surgeons

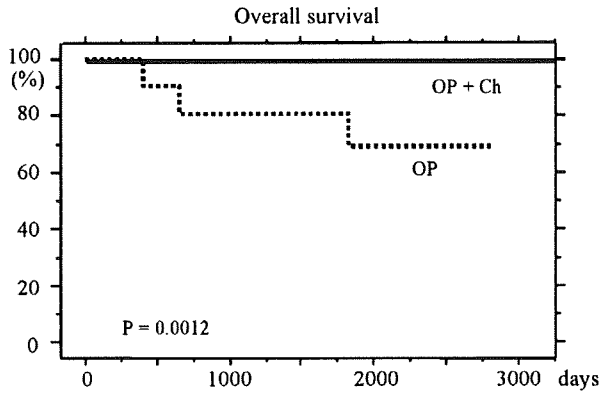

Fig. 3 Overall survival curves for patients with stage I Wilms tumor treated with surgery only and treated with surgery and postoperative chemotherapy using protocol EE-4A. The prognosis of the cases treated with surgery only was significantly worse than those treated with surgery and postoperative chemotherapy

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.

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References

1. D'Angio GJ (2007) The National Wilms' Tumor Study: a 40 year perspective. Lifetime Data Anal 13:463–470
2. D'Angio GJ, Evans AE, Breslow N et al (1976) The treatment of Wilms' tumor: results of the national Wilms' tumor study. Cancer 38:633–646
3. Grundy P, Perlman E, Rosen NS et al (2005) Current issues in Wilms tumor management. Curr Probl Cancer 29:221–260
4. Shamberger RC, Guthrie KA, Ritchey ML et al (1999) Surgery-related factors and local recurrence of Wilms' tumor in National Wilms' Tumor Study 4. Ann Surg 229:292–297
5. Mitchell C, Jones KP, Shannon R et al (2006) Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3) by the UK children's cancer study group. Eur J Cancer 42:2554–2562
6. Weirich A, Leuschner I, Harms D et al (2001) Clinical impact of histologic subtypes in localized non-anaplastic nephroblastoma treated according to the trial and study SIOP-9/GPOH. Ann Oncol 12:311–319
7. de Kraker J, Graf N, van Tinteren H et al (2004) Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93–01 trial): a randomised controlled trial. Lancet 364:1229–1235
8. Malignant Tumor Committee of the Japanese Society of Pediatric Surgeons (2003) The follow up data of the Pediatric solid malignancies registered from 1991 to 1995. J Jpn Soc Pediatr Surg 39:677–706
9. Pizzo PA et al (eds) (2001) Principles and practice of pediatric oncology, 5th edn. Chapter 30 renal tumors. Lippincott Williams & Wilkins, Philadelphia, pp 905–932
10. Jereb B, Burgers JM, Tournade MF et al (1994) Radiotherapy in the SIOP (International Society of Pediatric Oncology) Nephroblastoma studies: a review. Med Pediatr Oncol 22:221–227
11. Beckwith JB, Palmer NF (1978) Histopathology and prognosis of Wilms' tumours: results from the first national Wilms' tumour study. Cancer 41:1937–1948
12. Green DM, Breslow NE, Beckwith JB et al (1994) Treatment of children with clear-cell sarcoma of the kidney: a report from the National Wilms' Tumor Study Group. J Clin Oncol 12:2132–2137
13. Haas JE, Palmer NF, Weinberg AG et al (1981) Ultrastructure of malignant rhabdoid tumor of the kidney: a distinctive renal tumor of children. Hum Pathol 12:646–657
14. Haas JE, Bonadio JF, Beckwith JB (1984) Clear cell sarcoma of the kidney with emphasis on ultrastructural studies. Cancer 54:2978–2987
15. Weeks DA, Beckwith JB, Mierau GW et al (1989) Rhabdoid tumor of kidney: a report of 111 cases from the National Wilms' Tumor Study Pathology Center. Am J Surg Pathol 13:439–458
16. Green DM, Breslow NE, Beckwith JB et al (2001) Treatment with nephrectomy only for small, stage I/favourable histology Wilms' tumour: a report from the national Wilms' tumour study group. J Clin Oncol 19:3719–3724
17. Montgomery BT, Kelalis PP, Blute ML et al (1991) Extended follow-up of bilateral Wilms' tumor: results of the National Wilms' tumor study. J Urol 146:514–518
18. Bishop HC, Tefft M, Evans AE et al (1977) Survival in bilateral Wilms' tumor–review of 30 National Wilms' Tumor Study cases. J Pediatr Surg 12:631–638
19. Blute ML, Kelalis PP, Offord KP et al (1987) Bilateral Wilms' tumor. J Urol 138:968–973
20. Grundy PE, Breslow N, Li S et al (2005) Loss of Heterozygosity for Chromosomes 1p and 16q is an adverse prognostic factor in favorable histology Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 23:7312–7321
21. Dome JS, Bockhold CA, Li SM et al (2005) High telomerase RNA expression level is an adverse prognostic factor for favorable-histology Wilms' tumour. J Clin Oncol 23:9138–9145
22. Watanabe N, Nakadate H, Haruta M et al (2006) Association of 11q loss, trisomy 12 and possible 16q loss with loss of imprinting of insulin-like growth factor-II in Wilms tumor. Genes Chromosomes Cancer 45:592–601
23. Haruta M, Arai Y, Sugawara W et al (2008) Duplication of paternal IGF2 or loss of maternal IGF2 imprinting occurs in half of Wilms tumors with various structural WT1 abnormalities. Genes Chromosomes Cancer 47:712–727
24. Haruta M, Matsumoto Y, Izumi H et al (2008) Combined BubR1 protein down-regulation and RASSF1A hypermethylation in Wilms tumors with diverse cytogenetic changes. Mol Carcinog 47:660–666

各論 Ⅲ. 話題の疾患遺伝子

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

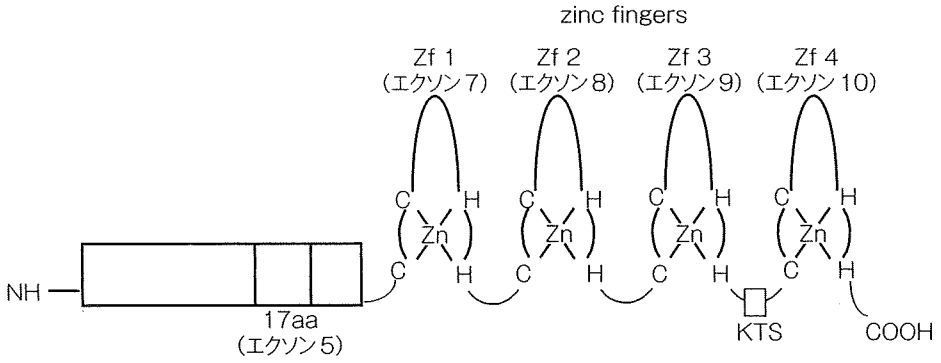

図1　*WT1*の構造
エクソン7～10はzinc finger domeinをコードしている．

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

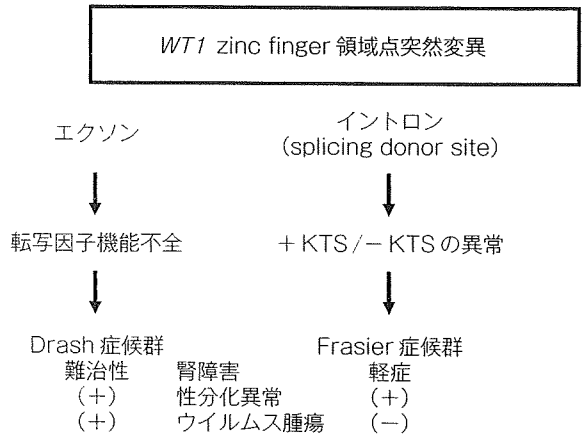

図2 Drash/Frasier 症候群の遺伝子型と表現型の対比

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

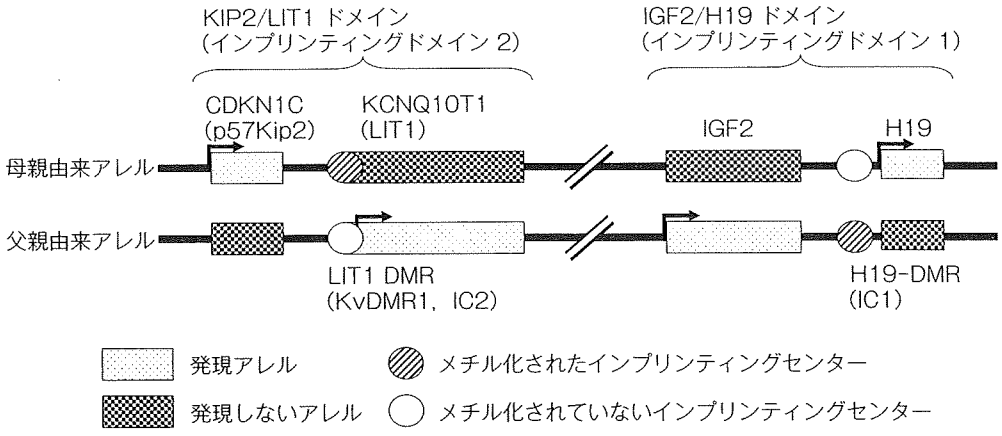

図3　11p15 領域に認められるインプリンティング遺伝子群とその機能

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．

文献

1) Call KM et al：Isolation and characterization of a zinc finger polypeptide gene at the human chromosome 11 Wilms' tumor locus. Cell 1990；60：509
2) Gessler M et al：Homozygous deletion of Wilms' tumors of a zinc finger gene identified by chromosome jumping. Nature 1990；343：774
3) Drummond, IA et al：Repression of the insulin-like growth factor II gene are associated by the Wilms' tumor supressor WT1. Science 1992；257：674
4) Pritchard-Jones K et al：The candidate Wilms' tumor gene is involved in genitourinary development. Nature 1990；346：194
5) Keridberg JA et al：WT1 required for early kidney development. Cell 1993；74：679
6) Kikuchi H et al：A critical mutation in both WT1 alleles is not sufficient to cause Wilms' tumor. FEBS Lett 1995；360：16-28
7) Schumacher V et al：Correlation of germline mutations and two-hit inactivation of the WT1 gene with Wilms tumors of stromal-predominant histology. Proc Natl Acad Sci USA 1997；94：3972-3977
8) Miyagawa K et al：Loss of WT1 function leads to ectopic myogenesis in Wilms' tumour. Nat Genet 1998；18：15-17
9) Shibata R et al：Correlation between a specific Wilms tumour suppressor gene (*WT1*) mutation and the histological findings in Wilms tumour (WT). J Med Genet 2002；39：E83-85
10) Drash A et al：A syndrome of peudohermaphroditism, nephritis, Wilms' tumor, hypertension and degenerative renal disease. J Pediatr 1970；76：585
11) Pelletier J et al：Germ line mutations in the Wilms' tumor suppresor genes are associated with abnormal irogenital development in Dynes-Drash syndrome. Cell 1991；67：437
12) Moorthy AV et al：Chronic renalfailure and XY gonadal dysgenesis："Frasier syndrome"-a commentary on reported cases. Am J Med Genet 1987；3 (Suppl)：297-302
13) Kikuchi H, Takata A, Hata J：Do intronic mutations affecting splicing of WT1 exson 9 cause Frasier syndrome?. J Med Genet 1998；35：45-48
14) Cooper WN et al：Molecular subtypes and phenotypic expression of Beckwith-Wiedemann syndrome. Eur J Hum Genet 2005；13：1025-1032
15) Satoh Y et al：Genetic and epigenetic alterations on the short arm of chromosome 11 are involved in a majority of sporadic Wilms' tumours. Br J Cancer 2006；95：541-547
16) Haruta M et al：Duplication of paternal IGF2 or loss of maternal IGF2 imprinting occurs in half of Wilms tumors with various structural WT1 abnormalities. Genes Chromosomes Cancer 2008；47：712-727
17) Fukuzawa R et al：Epigenetic differences between Wilms' tumours in white and east-Asian children. Lancet 2004；363：446-451
18) Scott RH et al：Constitutional 11p15 abnormalities, including heritable imprinting center mutations, cause nonsyndromic Wilms tumor. Nat Genet 2008；40：1329-1334