Chapter 7

Neoadjuvant Transcatheter Arterial Chemoembolization and Systemic Chemotherapy for the Treatment of Wilms Tumor

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Abstract

From 2003 to 2013, 55 patients (median age 3.3 years; 29 males, 26 females) with unresectable, metastatic, or diffuse anaplastic histology (AH) Wilms tumor were treated with neoadjuvant transcatheter arterial chemoembolization (TACE) and systemic chemotherapy. Characteristics

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of patients were maximal tumor diameter greater than 10 cm, involvement of periaortic lymph nodes, tumor thrombus in inferior vena cava/right atrium, distal metastasis, or diffuse AH. The chemoembolic emulsion for TACE consisted of pirarubicin, vindesine, and iodized oil. For the tumor with distal metastasis or diffuse AH, cisplatin was added in the chemoembolic emulsion. Intravenous chemotherapy with vindesine and actinomycin D was administered 2–3 weeks after TACE. For the patients with distal metastasis or diffuse AH Wilms tumor, intravenous chemotherapy consisted of ifosfamide and etoposide. Nephrectomy was performed 2–3 weeks after preoperative combination therapy. Surgical stage was assigned according to local operative findings in terms of the National Wilms Tumor Study (NWTS) Group combined with the pretherapeutic imaging to define metastatic disease. Postoperative treatment was based on tumor histology and surgical stage. All patients were followed up for 17–141 months (median: 82 months). No cardiotoxicity, renal insufficiency, and hepatic dysfunction after neoadjuvant TACE and systemic chemotherapy were found. Oral mucositis developed in 5 patients, grade I–II marrow suppression developed in 12 patients, and 19 patients became moderately febrile. In terms of response evaluation criteria in solid tumors, partial response (PR) in 34 (61.8%), stable disease (SD) in 19 (34.5%), and progressive disease (PD) in 2 (3.6%) patients were observed. Four of five patients had complete regression of inferior vena cava tumor thrombus. Atrial tumor thrombus retreated to inferior vena cava in one of two patients. Distant metastasis disappeared in four of six cases. Fifty patients (90.1%) underwent complete tumor resection. Tumor spillage occurred in 3 patients (5.5%). Two patients (3.6%) had microscopic residual disease. Surgical stages were stage II in 25, stage III in 24, and stage IV in 6 patients. On pathologic examination, tumor necrosis was >90% in 14 (25.5%), 50%–90% in 23 (41.8%), and <50% in 18 cases (32.7%). The 5-year event-free survival was 92.7%, and the overall survival was 94.5%. These preliminary results suggest that the use of neoadjuvant TACE and systemic chemotherapy may provide a promising choice in the treatment of unresectable, metastatic, or diffuse AH Wilms tumor in children. Further investigations are necessary.

Key words: Neoadjuvant therapy; Systemic chemotherapy; Transcatheter arterial chemoembolization; Wilms tumor

Introduction

Wilms tumor accounts for about 6% of all malignant tumors in children, and it is the most common malignant renal tumor of childhood. The outcome for patients with Wilms tumor has improved remarkably during the past decades owing to the use of adjuvant chemotherapy and neoadjuvant chemotherapy (1). However, the treatment of children with unresectable, metastatic, or diffuse anaplastic histology (AH) Wilms tumor remains a challenge (2–4). The unresectable criteria most commonly utilized are the tumor diameter greater than or equal to 10 cm, involvement of adjacent vital structures, and intracaval/atrial tumor extension. These

factors significantly increase the risk of surgical morbidity (4). Novel treatment strategies are needed to maximize survival and minimize long-term morbidity for these patients.

Preoperative embolization of the renal artery as a coadjuvant treatment in high-risk renal neoplasia has benefits for the subsequent nephrectomy (5–20). In an attempt to improve the outcome of patients with unresectable, metastatic, or diffuse AH Wilms tumor, we have performed preoperative transcatheter arterial chemoembolization (TACE) since 1995 (21–24). In previous studies, we found preoperative TACE combined with systemic chemotherapy could induce more massive necrosis of the tumor, further improving the complete resection rate of the tumor (25). In this phase II study, we examined the efficacy and safety of combined-modality neoadjuvant therapy using TACE and systemic chemotherapy as a first-line treatment for unresectable, metastatic, or diffuse AH Wilms tumor.

Patients and methods

From January 2003 to December 2013, 55 patients with unilateral unresectable, metastatic, or diffuse AH Wilms tumor were treated using preoperative TACE combined with systemic chemotherapy at our hospital.

All patients underwent abdominal computed tomography (CT), magnetic resonance imaging, ultrasound scan, and chest CT examination at admission. When metastasis in liver or lung was visible on CT, the patient was classified as stage IV disease. A core-needle biopsy for histologic diagnosis was performed before the treatment. Histology results were classified as unfavorable if diffuse anaplastic (AH) features were present and favorable (FH) if absent. This study was approved by the institutional ethics committee, and informed consent was obtained from the children's parents before enrollment. Characteristics of the patients were as follows: maximal tumor diameter greater than 10 cm, involvement of periaortic lymph nodes, tumor thrombus in inferior vena cava (IVC)/right atrium, distal metastasis based on the imaging studies, or tumor with diffuse AH according to the biopsy report (Table 1). Eligible patients were between 5 months and 11 years of age (median: 3.3 years), 29 boys and 26 girls. The right kidney was treated in 33 patients and the left in 22 patients. Patients with bilateral renal tumors, congenital mesoblastic nephroma, clear cell sarcoma of kidney, rhabdoid tumor of kidney, and renal cell carcinoma were excluded from this study.

The preoperative treatment consisted of alternating TACE and intravenous chemotherapy. Patients underwent TACE under intravenous and caudal epidural anesthesia. The femoral artery was catheterized using the Seldinger technique. A 5-F Pigtail catheter (Cook Vascular Incorporated, Pennsylvania) was introduced into the abdominal aorta to perform aortography and to define the tumor blood supply for the purpose of planning the chemoembolization (Figure 1A and B). The selective renal arterial catheterization and angiography of the

Table 1. Demographics and tumor characteristics of 55 patients with unresectable, metastatic, or diffuse AH Wilms tumor

Median age, y (range)	3.3 (0.5–11)
Sex, M:F ratio	29:26
Tumor side, right/left	33/22
Tumor characteristics on admission	
Greatest dimension >10 cm	29 (52.7%)
Involvement of periaortic lymph nodes	9 (16.4%)
Tumor thrombus in inferior vena cava/right atrium	7 (12.7%)
Distal metastasis	6 (10.9%)
Diffuse anaplastic histology	4 (7.3%)

involved kidney were performed using a 4-F or 5-F Cobra catheter (Cook Vascular Incorporated) (Figure 1C). The chemoembolic emulsion consisted of pirarubicin (Main Luck Pharmaceuticals Inc, Shenzhen, China) 40 mg/m^2; vindesine (Minsheng Pharmaceuticals Inc, Hangzhou, China) 3 mg/m^2; and iodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) 0.5 mL per tumor maximal diameter (in centimeters). The drugs were mixed, diluted in 120 mL of normal saline, and infused into the renal artery over 60 minutes. For the tumor with distal metastasis or diffuse AH, cisplatin 80 mg/m^2 was added in the chemoembolic emulsion. The catheter was removed after treatment. Intravenous hydration and alkalization were administered before, during, and after TACE. Postprocedure nausea and vomiting were treated with antiemetics.

Intravenous chemotherapy was administered 2–3 weeks after TACE. It consisted of vindesine 3 mg/m^2 (maximum 4 mg) weekly and actinomycin D 3 days × 15 μg/kg/d (maximum 500 μg) weeks 1 and 3. For the patients with distal metastasis or diffuse AH Wilms tumor, the intravenous chemotherapy consisted of ifosfamide 1,200 mg/m^2 and etoposide 100 mg/m^2 on days 2–4. For the patients younger than 1 year or with a body weight of <12 kg, the dosages of drugs for TACE and intravenous chemotherapy were reduced to two thirds.

Pirarubicin is a new anthracycline antibiotic with an antitumor efficacy similar to that of doxorubicin but less cardiotoxic because of its different pharmacodynamic properties (26). To minimize the side effects of anthracycline, we used pirarubicin instead of doxorubicin hydrochloride in this study. Vindesine is an analogue of the vinca alkaloids. Its spectrum of antitumor activity is similar to that of vincristine, but with milder neurotoxicity (27).

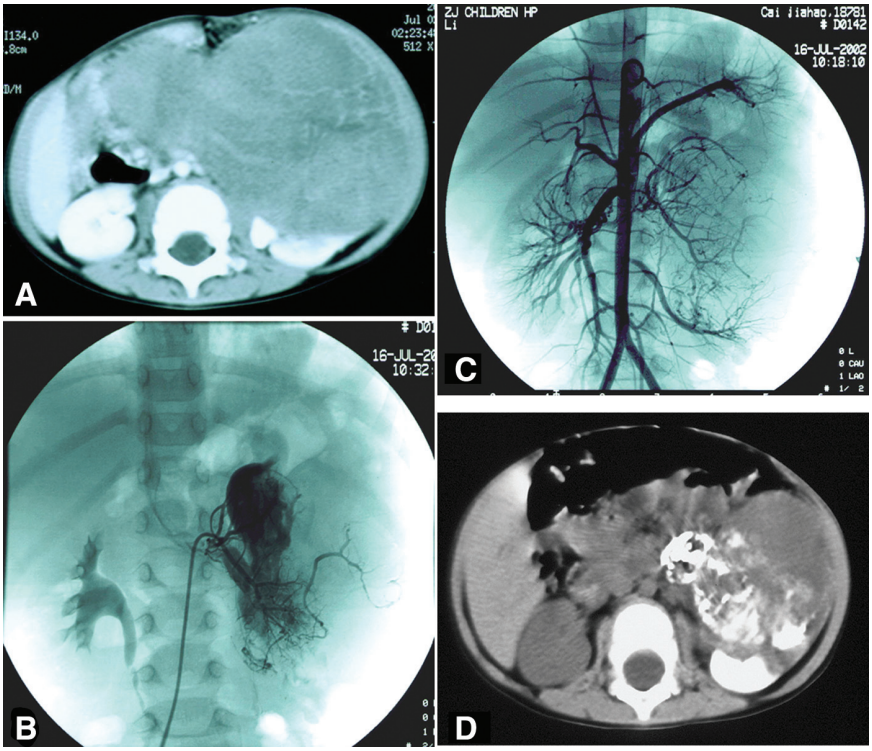

Figure 1. Preoperative TACE in a 2-year-old boy with left renal Wilms tumor. (A) Computed tomography (CT) finding left retroperitoneal huge tumor, invasion to the right side. (B) Aortography showing a large hypervascular lesion in the left kidney with abundant neovascularity. (C) Selective renal arterial catheterization and the chemoembolic emulsion infusing into the left renal artery. (D) Tumor volume is significantly reduced after alternating TACE and intravenous chemotherapy. Iodized oil deposits still visible within the tumor in the repeated CT scan before operation.

Nephrectomy was performed 2–3 weeks after preoperative TACE combined with systemic chemotherapy. Four patients underwent repeated preoperative combined treatment due to pulmonary metastasis. Tumor volumes were measured on ultrasound scans using the ellipsoid formula (length × thickness × depth × 0.523). The measurement was performed before preoperative therapy and repeated before surgery. Tumor volume reduction in comparison with the initial volume was calculated. Tumor response to treatment was defined according to the new response evaluation criteria in solid tumors [Response Evaluation Criteria In Solid Tumors (RECIST) 1.1] (28). Toxicity was scored according to the Children's Cancer Group toxicity grading system (29). After tumor resection, surgical specimens were microscopically examined for features of tumor, such as the surgical margin and necrosis, which was defined as complete if no viable cells were found in the tumor and nodules. Histopathologic

classification and surgical stage were assigned according to the National Wilms Tumor Study (NWTS) Group (30). Postoperative treatment using systemic chemotherapy and radiotherapy was based on tumor histology and its surgical stage. The treatment protocol was worked out according to the NWTS protocol modified by the Beijing Children's Hospital (31). Fifteen patients received radiotherapy after operation due to stage III or diffuse AH Wilms tumor. Postoperative follow-up was performed at the first month and then every 3–6 months after surgery, including physical, imaging (abdominal sonography and CT, chest x-ray, and electrocardiogram), and laboratory screening (blood and urine analysis, and liver and renal function tests). All patients were followed up until December 31, 2014.

Statistical methods

Standard methods were used for the analysis of censored and noncensored data. Event-free survival (EFS) time was defined as the time from the date of diagnosis to the first occurrence of progression, relapse, or death. Overall survival (OS) time was measured from the date of diagnosis to death or the patients being still alive on December 31, 2014. The Kaplan–Meier method was used to calculate EFS and OS rates, and the rates are presented as the rate ± SE. All analyses were carried out using the SPSS 16.0 statistical software system.

Response to treatment

No patients experienced death while preoperative treatment. No preoperative tumor rupture, drug-induced cardiotoxicity, renal insufficiency, or hepatic dysfunction were found in all of the patients. Oral mucositis developed in 5 (9.1%) patients, grade I–II marrow suppression developed in 12 (21.8%) patients, and 19 (34.5%) patients became moderately febrile after chemoembolization; this was controlled with symptomatic treatment (Table 2). Tumor volumes were significantly reduced after preoperative TACE and systemic chemotherapy. Iodized oil deposits were still visible within the tumor in the repeated CT scan before operation (Figure 1D). Color Doppler ultrasonography showed the abundant blood flow decreased significantly in the tumor after preoperative treatment (Figure 2A and B). Tumor volume was 488 mL (median) at diagnosis and 198 mL (median) before operation. In terms of new response evaluation criteria in solid tumors (RECIST 1.1) (28), partial response (PR) was observed in 34 (61.8%), stable disease (SD) in 19 (34.5%), and progressive disease (PD) in 2 (3.6%) patients after preoperative therapy (Table 2). Five patients had tumor invading the IVC. Four of them had complete regression of the IVC tumor thrombus before operation. One patient underwent vena caval thrombectomy during nephrectomy. Two cases additionally had extensive venothrombotic invasion to the right atrium at admission. The atrial tumor thrombus retreated to IVC in one patient who underwent radical nephrectomy and vena caval thrombectomy. The atrial tumor thrombus reduced obviously but not completely disappeared in another patient who underwent thrombectomy under cardiopulmonary bypass with deep

Table 2. Complications, tumor response, and outcome of 55 patients treated with preoperative TACE and systemic chemotherapy

Complications during preoperative treatment	
Death while treatment	0 (0.0%)
Cardiotoxicity	0 (0.0%)
Renal insufficiency	0 (0.0%)
Hepatic dysfunction	0 (0.0%)
Oral mucositis	5 (9.1%)
Grade I–II marrow suppression	12 (21.8%)
Moderate febrile	19 (34.5%)
Tumor volume, mL	
On admission	488 (292–804)
Before operation	198 (126–324)
Tumor response	
PR	34 (61.8%)
SD	19 (34.5%)
PD	2 (3.6%)
Inferior vena and atrial tumor thrombus disappeared	4/7 (57.1%)
Distal metastasis disappeared	4/6 (66.7%)
Complete tumor resection	50/55 (90.9%)
Rapture during operation	3/55 (5.5%)
Microscopic residual	2/55 (3.6%)
Tumor necrosis	
>90% tumor necrosis	14/55 (25.5%)
50–90% tumor necrosis	23/55 (41.8%)
<50% tumor necrosis	18/55 (32.7%)
Postoperative stage	
I	0 (0.0%)
II	25 (45.5%)
III	24 (43.6%)
IV	6 (10.9%)

(*Continued*)

Table 2. Continued

Histology	
FH	51 (92.7%)
AH	4 (7.3%)
Outcome	
EFS	92.7% (95% CI: 85.8–99.6%)
OS	94.5% (95% CI: 88.5–100%)

PR, partial response; SD, stable disease; PD, progressive disease; FH, favorable histology; AH, anaplastic histology; EFS, event-free survival; OS, overall survival.

hypothermia and circulatory arrest during nephrectomy. Histopathologic examination of the resected atrial thrombus showed epithelial and mesenchymal components. Six patients had distant metastasis on admission, including one case of liver metastasis and five cases of pulmonary metastasis. Distal metastasis disappeared in front of the renal tumor resection in four cases (Figure 3A–C) and during postoperative chemotherapy in two patients. Fifty patients (90.1%) underwent complete tumor resection after preoperative therapy. Tumor spillage occurred in 3 patients (5.5%). Two patients (3.6%) had microscopic residual disease. The overall distribution of patients in the series according to surgical staging was stage II in 25 (45.5%), stage III in 24 (43.6%), and stage IV in 6 (10.9%) patients (Table 2).

Histopathologic findings

Postoperative histopathology revealed FH Wilms tumor in 51 patients (92.7%) and diffuse AH in 4 patients (7.3%) (Table 2). Pathologic examination of the specimen found massive necrosis in the tumor and increased thickness of the fibrous envelope around the tumor (Figure 4A and B). Tumor necrosis was >90% in 14 (25.5%), 50%–90% in 23 (41.8%), and <50% in 18 cases (32.7%) (Table 2). Necrosis was visible not only in the main tumor but also in the metastases of periaortic lymph nodes (25). Iodized oil deposition in the para-aortic lymph nodes was observed in six cases. Postoperative histologic examination of these marked lymph nodes confirmed lymph node metastases with necrosis. This finding implies that the chemo-embolization agent flowed directly into the para-aortic lymph node metastases.

Outcomes

All patients were followed up until December 31, 2014. The median length of follow-up was 82 months (range: 17–141 months). Thirty-one patients had been followed up for more than 5 years. The 5-year EFS was 92.7% [95% confidence interval (CI): 85.8%–99.6%] and OS was 94.5% (95% CI: 88.5%–100%) (Table 2) (Figure 5A and B). Four patients relapsed.

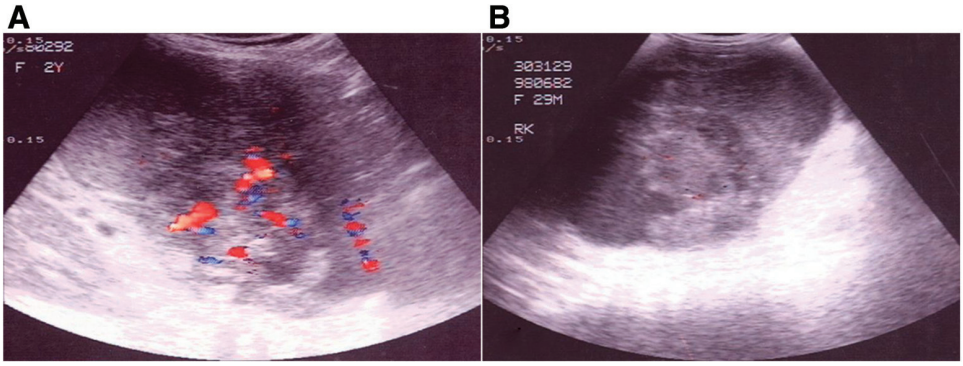

Figure 2. Color Doppler ultrasonography appearances of the left renal Wilms tumor in a 3-year-old boy. (A) Diffusely increased blood flow in the tumor before treatment. (B) Blood flow deceased significantly within the tumor after preoperative TACE and systemic chemotherapy.

One of them relapsed with pulmonary metastases 8 months after operation and was cured by chemotherapy. Three of them died. The first patient was a 6.5-year-old boy with a stage III FH Wilms tumor. He had a relapse involving the proximal tibia 1 year after operation that was unresponsive to treatment, and he died 20 months after presentation. The second patient, a 7-year-old boy with a stage II FH tumor, died 18 months after operation from liver metastatic disease. The third was an 8-year-old girl with a surgical stage III AH tumor and IVC thrombus invasion to the right atrium at admission. The tumor thrombus retreated to suprahepatic IVC after preoperative therapy, and nephrectomy with thrombus removal was performed. She relapsed with pulmonary and liver metastases 6 months after operation and subsequently died. Late effects of therapy were evaluated in the survivors. One patient had scoliosis caused by radiotherapy after operation. No case(s) of anthracycline cardiotoxicity, liver disease, hypertension, and renal dysfunction were documented in survivors. Puberty and growth disturbances were not observed in all patients. No new late cancers were detected on follow-up.

Discussion

Although the FH Wilms tumors showed excellent outcome, the survival rate for unresectable, metastatic, or diffuse AH Wilms tumor cases remains to be improved. Patients with unresectable or metastatic Wilms tumor fare worse than patients with localized and resectable tumors (32). The unresectable criteria commonly utilized are huge size of the tumor, involvement of adjacent vital structures, and intracaval/atrial tumor extension. These factors significantly increase the risk of surgical morbidity, principally hemorrhage, and tumor spillage during initial nephrectomy (4). Larger tumors are at higher risk of intraoperative

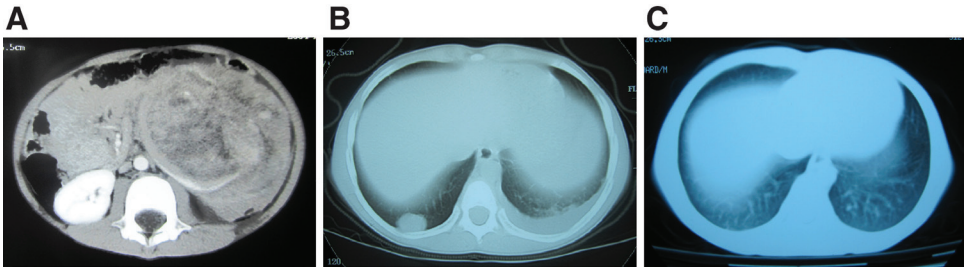

Figure 3. A 7-year-old boy had left Wilms tumor with pulmonary metastases. (A) Enhanced CT of the abdomen showing a huge mass in the left renal fossa. (B) Chest CT examination demonstrated right lung metastasis and left pleural effusion. (C) Pulmonary metastases disappeared after preoperative TACE and systemic chemotherapy.

tumor spillage (33). Primary nephrectomy for Wilms tumor diameter greater than or equal to 10 cm was also associated with an increased risk of surgical complications (4). The patients with stage III disease, diffuse AH, and tumor spillage during surgery also observed the relative risks of local recurrence and poor survival (34). Patients with diffuse anaplastic Wilms tumor, particularly stages III and IV, continue to have poor outcomes and may benefit from new treatment strategies (3, 30, 35).

The SIOP studies largely focus on the issue of preoperative chemotherapy to facilitate surgery of a shrunken tumor and to treat metastasis as early as possible. The duration of conventional preoperative chemotherapy is 4 or 8 weeks (2, 36–38). Preoperative chemotherapy is also used for the treatment of "inoperable" or "unresectable" Wilms tumor by NWTS and

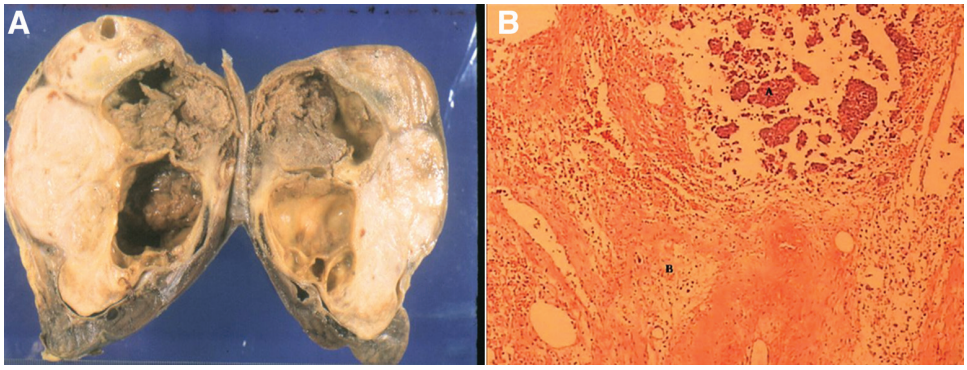

Figure 4. Pathologic examination of the surgical specimen. (A) Macroscopic examination of the specimen found massive necrosis and thickening of the tumor fibrous capsule. (B) Microscopically, extensive and homogenous necrosis was found in the tumor (hematoxylin and eosin stain, ×40).

United Kingdom Children's Cancer Study group in recent years (39, 40). However, some patients did not respond to conventional preoperative chemotherapy and died before the excision of the primary tumor. Ritchey et al. (4) reviewed 131 children in NWTS-3 who had received preoperative chemotherapy for unresectable tumors or were judged inoperable by imaging. Thirteen of them did not respond to chemotherapy, but the disease progressed. Eight children died before the removal of the primary tumor. Ora et al. (41) reported tumor progression during preoperative chemotherapy in 57 of 1,090 patients (5%) with localized Wilms tumors. Patients whose tumors do increase in size have poorer EFS and OS rates independently of stage distribution and histopathologic risk group.

Actinomycin D, vincristine, doxorubicin, ifosfamide, etoposide, and carboplatin are the commonly used drugs for more advanced and recalcitrant Wilms tumor (42). Actinomycin D and vincristine were used by the SIOP studies for patients with unilateral localized Wilms tumor and stage II or III with low-risk (LR) or intermediate-risk (IR) histology (43). Doxorubicin, cyclophosphamide, etoposide, and carboplatin are now the standard part of the treatment protocols for more advanced and recalcitrant cases (42, 44). NWTS-5 regimen for patients with stages II to IV diffuse AH Wilms tumor was treated with vincristine, doxorubicin, cyclophosphamide, and etoposide (3). Children's Cancer Group used ifosfamide, carboplatin, and etoposide in children with poor-risk relapsed Wilms tumor (45). Cisplatin is a well-known chemotherapeutic drug and is effective against various types of cancers. Combination therapies of cisplatin with other drugs have been highly considered to overcome drug resistance and to reduce toxicity (46). It is ideal to administer cisplatin intra-arterially because it has a very high affinity for tissue protein, which leads to the effective binding of cisplatin to the tumor tissue during its first pass (47, 48).

Almgard et al. (5) performed first embolization for the treatment of renal adenocarcinoma in 1973. Since then, renal artery embolization is increasingly being used for the treatment of advanced or unresectable renal tumors in adults. Clinical studies have shown that preoperative renal embolization significantly reduces blood loss during nephrectomy, especially in large hypervascular tumors (6–20). Renal artery embolization also has been used in the management of Wilms tumor in children (49–54). Although the value of preoperative embolization of Wilms tumor has been documented by many authors, opinions on its indication have differed, and its use in practice has remained relatively limited.

TACE has significantly contributed to the evolution of interventional radiology. TACE may effectively deliver highly concentrated doses of chemotherapy to the tumor bed. The merits of renal chemoembolization are based on the concept that the blood supply to tumor only comes from the renal artery. The anticancer drug and embolizing material are injected into the tumor-feeding artery, increasing the effect of the chemotherapy agents in the ischemic

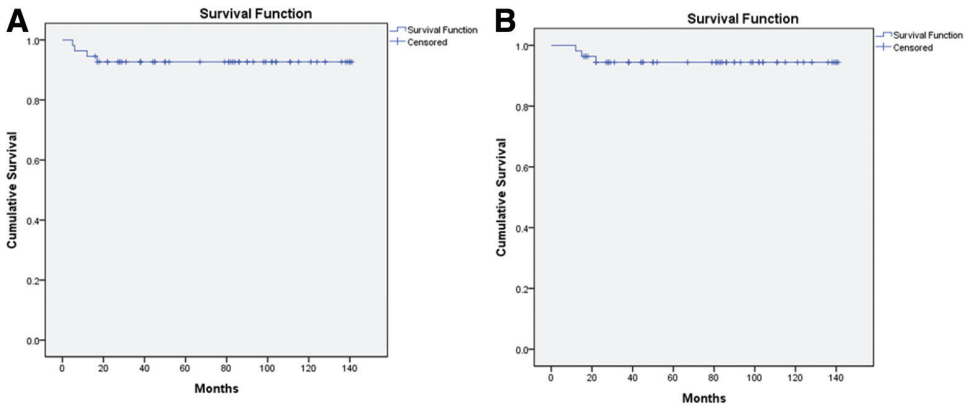

Figure 5. Event-free survival and overall survival rate by Kaplan–Meier estimates. (A) EFS, 92.7% (95% CI: 85.8–99.6%). (B) OS 94.5% (95% CI: 88.5–100%). EFS, event-free survival; OS, overall survival. (All the images in this chapter have not published previously and do not violate the copyright of the original publisher.)

tissue and reducing the risk of bleeding during surgery. In patients with extended renal carcinoma, survival was significantly higher after chemoembolization than after standard embolization of the renal artery (55–58). Animal experiments revealed that renal arterial chemoembolization can maintain high local concentrations of the anticancer drug, while maintaining low blood levels of the anticancer drug (59, 60).

We performed preoperative TACE for the treatment of advanced Wilms tumors since 1995 (21–24). The benefits of TACE for the treatment of advanced Wilms tumor are based on the concept that the anticancer drugs were directly injected into the tumor-feeding artery, increasing the effect of the chemotherapy agent within the tumor, while avoiding concomitant systemic toxicity. In our previous studies, we found preoperative chemoembolization combined with systemic chemotherapy for the treatment of advanced Wilms tumor showed a higher response rate than TACE alone (25). We used neoadjuvant TACE and systemic chemotherapy as for the treatment of unresectable, metastatic, or diffuse AH Wilms tumor since 2003. Our regimen is a platinum-based combination chemotherapy. The scientific rationale for the use of combination chemotherapy is to overcome drug resistance to individual agents. In addition to providing a broader range of coverage against naturally resistant tumor cells, combined chemotherapy may also prevent or delay the development of acquired resistance in initially responsive tumors and provide additive or synergistic cytotoxic effects. This regimen is also a multimodal combination therapy consisting of localized arterial chemotherapy, arterial embolization, and intravenous chemotherapy. This combination can induce more massive necrosis of tumor, eliminate the distant metastases, improve the complete resection rate of tumor, and achieve excellent survival rate.

Conclusion

The preliminary results in this phase II study suggest that the use of neoadjuvant TACE and systemic chemotherapy is well tolerated and may provide a promising choice in the treatment of unresectable, metastatic, or diffuse anaplastic Wilms tumor in children.

There were limitations in this study. Because of the small number of cases in this group and the short observation period, long-term effects warrant further investigation.

Conflict of Interest

The authors declare that they have no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

Acknowledgments

This study was approved by our institutional review board; the need for informed consent for publication of data was waived. The authors thank all the children and their parents for allowing us to publish the data collected during this research project. The authors also thank the staff of the Department of Pediatric Surgery, Radiology, and Pathology for their cooperation.

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