Treatment of Wilms Tumor Using Carboplatin Compared to Therapy Without Carboplatin

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Background. Wilms tumor (WT) is the most common pediatric malignant primary renal tumor. One of the main drugs used in treatment is actinomycin-D. This was not readily available in Turkey at one time. Carboplatin was used in the primary treatment of WT in order to prevent delays in treatment. The aim of this study is to present the results of patients with WT receiving carboplatin or actinomycin-D therapy. Procedure. Forty-eight consecutive patients with WT treated between July 2005 and December 2011 were included in this retrospective study. The patients were treated according to Turkish Pediatric Oncology Group guidelines. Nineteen patients were treated with actinomycin-D and 29 with carboplatin (500 mg/m²/dose). The two groups were then compared in terms of 2- and 4-year overall survival (OS), event-free survival (EFS) and disease-free survival (DFS). Results. Two- and four-year OS rates in the carboplatin group were 90.0% and 90.0%, compared to 100.0% and 88.0%, respectively, in the non-carboplatin group. Two- and four-year EFS levels in the carboplatin group were 92.0% and 88.0%, respectively, compared to 82.0% and 76.0% in the non-carboplatin group. Two-and four-year DFS levels in the carboplatin group were 92.0% and 86.0%, respectively, compared to 77.0% and 77.0% in the non-carboplatin group. Conclusions. The findings show that the carboplatin can be used as an alternative drug in the primary treatment of WT in the event that actinomycin-D is unavailable or not tolerated. Pediatr Blood Cancer © 2014 Wiley Periodicals, Inc.

INTRODUCTION

Wilms tumor (WT) is the most common pediatric malignant primary renal tumor [1]. This renal cancer particularly affects children in the first 2 years of life. Overall survival (OS) rates in patients with WT have risen to 85% due to the ongoing success of clinical trials over the last 30 years. Treatment-associated morbidity has also declined. Duration and intensity of treatment depend on the stage of the disease and histopathological findings. WT treatments include pre-operative and post-operative vincristine and actinomycin-D, with or without doxorubicin or radiotherapy. Salvage chemotherapy involving ifosfamide, carboplatin, and etoposide (ICE protocol), in addition to high-dose chemotherapy regimens and autologous hemopoietic stem-cell rescue, are also available in relapsed patients [2].

Carboplatin entered into clinical use in 1981 [3]. It has since come to represent a practicable alternative to cisplatin for the treatment of various solid tumors. Carboplatin is a second-generation analog of cisplatin, with which it shares various structural and pharmacological characteristics. However, carboplatin has a better toxicity profile and causes significantly less nephrotoxicity than cisplatin. Cisplatin is a much more emetogenic chemotherapeutic agent, compared to carboplatin. The dose-limiting factor in conventional carboplatin therapy is hematological toxicity, and the resulting thrombocytopenia is more severe than leukopenia or anemia [3,4].

In this study, carboplatin was used instead of actinomycin-D when the latter was unavailable for the treatment of patients with WT. The aim was to evaluate the results of carboplatin combination treatment modalities from our institution in Adana, Turkey.

METHODS

Forty-eight consecutive patients with WT treated between July 2005 and December 2011 were retrospectively included in the study. Data were obtained from patients’ medical charts. Written consent was obtained from the patient’s family or legal guardian.

Since the study was not planned prospectively ethical committee approval could not be obtained before treatment began. We decided that treatment should not be continued with a deficient drug at a time when actinomycin-D was unavailable in Turkey, and carboplatin, used in relapsed Wilms tumor, was employed instead. The results of carboplatin therapy were good. We therefore thought that the scientific presentation of this research in the form of a paper would be of use to other physicians. Approval for the study was granted by the ethical committee. Such approval is not required for retrospective studies. Complete physical examination including blood pressure measurement, laboratory tests including urine analysis, complete blood count and blood biochemistry, cardiac evaluation with electrocardiogram (ECG), and echocardiography (ECHO), and imaging techniques including chest X-ray, abdominal ultrasonography (USG), Doppler USG, and abdominal computerized tomography (CT) were performed for each patient. CT scans were used to determine the origin of the tumor within the kidney, evaluate the possible presence of a second WT in the contralateral kidney, assess caval extension, and identify metastases. The combination of CT scan and USG was the most useful and accurate method for diagnosing and assessing patients before surgery.

Histopathological classification and clinical staging were performed on the basis of the Turkish Pediatric Oncology Group (TPOG) system [5]. Clinical records were surveyed for all patients, and data including age, gender, and symptoms at presentation, sites of initial involvement, laboratory results, initial treatment, therapeutic response and date of diagnosis, date of first treatment,
date of relapse, date of death or last follow-up were collected. Vincristine and actinomycin-D (VA) in combination have long been used in preoperative chemotherapy in newly diagnosed WT patients in Turkey. Preoperative chemotherapy consisted of vincristine, 1.5 mg/m² (max. 2 mg), once weekly, for 4 weeks, and actinomycin-D, 0.015 mg/kg for 5 days, in the first week (Fig. 1). Post-surgical tumor staging was based on the TPOG staging system (5). Histopathological examinations were performed by pathologists and tumors were classified as having favorable (FH) or unfavorable histology (UH = anaplastic WT). As recommended by the TPOG, Stage I (FH) and (UH), IIa FH tumors were treated with vincristine (1.5 mg/m² weekly for 10 weeks, and then two times every 6 weeks) and actinomycin-D (0.015 mg/kg for 5 days every 6 weeks) for a total period of 6 months (Fig. 2). Stage IIB FH tumors were treated with the same regimen for 12 months, accompanied by radiotherapy (1,080 cGy to the hemiabdomen) (Fig. 3). Stage III and IV FH tumors were treated with vincristine (1.5 mg/m² weekly for 10 weeks, and then two times every 6 weeks), actinomycin-D (0.015 mg/kg, for 5 days every 6 weeks), and doxorubicin (20 mg/m² 3 days every 6 weeks, up to a maximum cumulative dose of 360 mg/m²) for 12 months, accompanied by radiotherapy (1,080 cGy to the hemi abdomen or whole abdomen) (Fig. 4). Stages II, III, and IV UH tumors were treated with vincristine 1.5 mg/m² (max. 2 mg), once weekly, actinomycin-D (0.015 mg/kg, for 5 days every 6 weeks), doxorubicin (20 mg/m² 3 days every 6 weeks, and etoposide (100 mg/m²/day 3 days every 6 weeks) for a total of 18 months and external radiotherapy to the abdomen (Fig. 5). Dosages for children under 12 months of age were lowered to 50% of those employed in older children. Bilateral tumors were staged at surgery, and histopathological examinations of each
kidney were performed. Treatment was designed according to the stage and resection margin of each kidney.

Nineteen patients received combined therapy with actinomycin-D and 29 received combined therapy with carboplatin. Carboplatin and actinomycin-D were given during the entire protocol. Carboplatin was administered at the dose used in the ICE protocol (250 mg/m² on days 1 and 2) [6]. The patients were divided into carboplatin and non-carboplatin groups. The treatment regimes in the groups receiving carboplatin and actinomycin-D were determined according to the TPOG WT staging system. Carboplatin was used in the carboplatin group where actinomycin was used in the original protocol. Schemas for the two treatment regimes are given in Figures 1–5. Two- and four-year survival rates were then compared between the two groups. After the actinomycin-D and carboplatin regimen had been administered, the effect of the treatment was assessed by determining the response of the target lesions on abdominal USG and CT images. Objective response to the actinomycin-D and carboplatin regimen was evaluated using CT every 2 months. Response rate was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and the results were reported as complete response (CR; complete disappearance of the tumor), partial response (PR; at least 50% reduction in the tumor), stable disease (SD; any tumor size between criteria for partial response and progressive disease) or progressive disease (PD; at least 25% increase in the tumor) [7].

Hematological and non-hematological toxicities were graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [8]. The two regimens were compared according to grade 3, 4, or 5 hematological and non-hematological toxicity.

Statistical Analysis

The data were analyzed on SPSS software, version 15. Descriptive statistics and frequency distributions were reported for patient characteristics. Values are presented as median (minimum–maximum). Univariate analyses of patient characteristics and tumor responses were performed using Pearson’s chi-square test, Fisher’s exact test or the Mann–Whitney U-test as necessary.

Fig. 3. Treatment protocols were applied in patients with Stage-lib (FH) WT. External radiotherapy was applied to the primary tumor bed. (A) Actinomycin-D therapy; (B) Carboplatin therapy. This treatment protocols were applied for 12 months. VCR was started on the 7th day postoperatively. VCR, vincristine; Act-D, actinomycin-D.

Fig. 4. Treatment protocols were applied in patients with Stage-III–IV (FH) WT. (A) Actinomycin-D therapy. (B) Carboplatin therapy. External radiotherapy was applied to the primary tumor bed. This treatment protocols were applied for 12 months. VCR was started on the 7th day postoperatively. VCR, vincristine; Act-D, actinomycin-D; ADR, doxorubicin.
appropriate. DFS, EFS, and OS were calculated according to the Kaplan–Meier method. Events included death, progression and relapse. The log-rank test was used to compare survival curves. \( P \) values less than 0.05 were regarded as significant.

**RESULTS**

Of the 48 patients, 20 (41.7%) were male and 28 (58.3%) female (M/F = 0.7). Median age at diagnosis was 26.0 months (range 5.5–120.0 months). In terms of clinical stage, 6.3% were stage I, 56.3% stage II, 22.8% stage III, 6.3% stage IV, and 8.3% stage V. Favorable histology was diagnosed in 38 (79.2%) patients and UH in 10 (20.8%). Patients were treated according to TPOG guidelines. Twenty-nine patients (60.4%) received carboplatin and 19 (39.6%) did not. Age, sex, stage, and histology in the carboplatin group were similar to those in the non-carboplatin group, but the mean duration of follow-up was lower than that in the carboplatin group \( (P < 0.05) \), as outlined in Table I.

Median duration of follow-up in the carboplatin group was 33.0 ± 15.6 months (range 5.0–69.0 months), and 48.0 ± 21.9 months (range 3.0–80.0 months) in the non-carboplatin group \( (0.0001) \). Two (6.9%) patients died in the carboplatin group and 3 (15.8%) in the non-carboplatin group. In the actinomycin-D group, two of the three patients died from pulmonary metastases and one due to sepsis developing during treatment for relapse in the primary diagnosis site (abdomen). One patient in the carboplatin group died from relapse in the primary diagnosis site (abdomen) and the other due to sepsis developing during chemotherapy.

At the second month after pre-operative chemotherapy the CR, PR, SD, and PD response rates were 89.7% \( (n = 26) \), 10.3% \( (n = 3) \), 0.0% \( (n = 0) \), and 0.0% \( (n = 0) \), respectively, in the carboplatin group, and 89.4% \( (n = 17) \), 5.3% \( (n = 1) \), 0.0% \( (n = 0) \), and 5.3% \( (n = 1) \) in the non-carboplatin group; the differences were not significant \( (P = 0.39) \). After surgery, according to the results of the latest assessment of patients, the CR, PR, SD, and PD response rates were 89.7% \( (n = 26) \), 0.0% \( (n = 0) \), 0.0% \( (n = 0) \), and 10.3% \( (n = 3) \), respectively, in the carboplatin group and 68.4% \( (n = 13) \), 0.0% \( (n = 0) \), 0.0% \( (n = 0) \), and 31.6% \( (n = 6) \) in the non-carboplatin group; the differences were also not significant \( (P = 0.65) \).

Of the 29 patients receiving carboplatin, serious toxicities (grade 3/4) were mainly hematological \( (n = 24, 82.8\%) \), thrombocytopenia \( (n = 14, 48.3\%) \), anemia \( (n = 19, 65.5\%) \), and neutropenia \( (n = 17, 58.6\%). Febrile neutropenia developed in 15 patients. The non-hematological serious adverse events (grade 3/4) were gastrointestinal disorders (mucositis, \( n = 2 \), 6.9%) and infections \( (n = 12, 41.4\%) \). Sepsis developed in 5 cases at grade 4/5. Grade 3 anorectal infection occurred in one case, grade 3 lung infection in seven cases and grade 3 appendicitis in one patient. Grade III left ventricular systolic dysfunction developed in one patient and Grade II oculomotor nerve disorder in one patient.

Of the 19 patients receiving actinomycin-D, thrombocytopenia developed in 9 cases (47.4%), anemia in 10 (52.6%), neutropenia in 8 (42.1%), and febrile neutropenia in 8 (42.1%). The non-hematological serious adverse events (grade 3/4) were gastrointestinal disorders (mucositis, \( n = 4, 21.1\%) \) and infections \( (n = 4, 21.1\%) \). Sepsis occurring in three cases was grade 4/5. Grade 3 lung infection developed in one patient and acute kidney injury (grade 5; fatal) in one. There were no significant differences between the two groups” in terms of hematological and non-hematological toxicities \( (P > 0.05) \).

Two- and four-year OS levels were 90.0% and 90.0% in the carboplatin group and 100.0% and 88.0%, respectively, in the non-carboplatin group; the differences were not significant \( (P = 0.92) \). Two- and four-year EFS were 92.0% and 88.0%, respectively, in the carboplatin group and 82.0% and 76.0% in the non-carboplatin group; the differences were again not significant \( (P = 0.44) \). Two- and four-year DFS levels were 92.0% and 86.0%, respectively, in the carboplatin group and 77.0% and 77.0% in the non-carboplatin group; the differences were not significant \( (P = 0.42) \). OS and EFS levels for the two treatment regimes are shown in Figure 6.

**DISCUSSION**

WT mainly appears in children under 5 years of age. Several protocols are employed in the treatment of WT. Collaborative groups such as the National Wilms Tumors Study Group (NWTSG), The International Society of Pediatric Oncology (SIOP), and the United Kingdom Children’s Cancer Study Group (UKCCSG) have published large randomized controlled trials. As a result of these
studies, WT treatment has been modified to reduce morbidity to a minimum for low-risk patients and to maximize prognosis for high-stage, high-risk individuals. Treatment is currently based on daunomycin, vincristine, and doxorubicin as first-line chemotherapy. Cyclophosphamide, ifosfamide, cisplatin, carboplatin, and etoposide have also been shown to be active against WT. Multiagent regimens containing these drugs, and particularly the ICE combination (ifosfamide, carboplatin, and etoposide), have raised post-relapse survival levels to approximately 50–60% [2,9–11]. A number of highly effective chemotherapy regimens, including ifosfamide-carboplatin-etoposide, cyclophosphamide-etoposide, and carboplatin-etoposide, are regarded as the treatment of choice in recurrent cases [12]. Abu-Ghosh et al. [13] reported that ifosfamide, carboplatin, and etoposide chemotherapy produced an overall response rate of 82% in a small group of 11 patients. Ifosfamide was administered to patients with high-risk WT at 1,800 mg/m² per day for 5 days, carboplatin at 400 mg/m² per day for 2 days, and etoposide at 100 mg/m² per day for 5 days.

Our patients were treated in line with the TPOG system [5].

**TABLE I. Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 48)</th>
<th>RC (n = 29)</th>
<th>RA (n = 19)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>Median, months (range)</td>
<td>26 (5.5–120.0)</td>
<td>25 (8.0–108.0)</td>
<td>27 (5.5–120.0)</td>
<td>0.92*</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Males</td>
<td>20 (41.7%)</td>
<td>10 (34.5%)</td>
<td>10 (52.6%)</td>
<td>0.22**</td>
</tr>
<tr>
<td>Females</td>
<td>28 (58.3%)</td>
<td>19 (65.5%)</td>
<td>9 (47.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stage (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (6.3%)</td>
<td>1 (3.5%)</td>
<td>2 (10.5%)</td>
<td>0.17**</td>
</tr>
<tr>
<td>II</td>
<td>27 (56.3%)</td>
<td>16 (55.2%)</td>
<td>11 (57.9%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>11 (22.8%)</td>
<td>9 (31.0%)</td>
<td>2 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3 (6.3%)</td>
<td>0 (0.0%)</td>
<td>3 (15.8%)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>4 (8.3%)</td>
<td>3 (10.3%)</td>
<td>1 (5.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH</td>
<td>38 (79.2%)</td>
<td>23 (79.3%)</td>
<td>15 (78.9%)</td>
<td>0.98***</td>
</tr>
<tr>
<td>UH</td>
<td>10 (20.8%)</td>
<td>6 (20.7%)</td>
<td>4 (21.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up median, months (range)</strong></td>
<td>4 (3.0–80.0)</td>
<td>33 (5.0–69.0)</td>
<td>48 (3.0–80.0)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

RC, received carboplatin; RA, received actinomycin-D; FH, favorable histology; UH, unfavorable histology. *Mann–Whitney U-Test. **Pearson’s Chi-Square test. ***Fisher’s exact test.

**Fig. 6.** Kaplan-Meier estimations of survivals for the two groups with WT patients. (A) Overall survival (OS). (B) Event-free survival (EFS). Log-rank test were \( P = 0.92 \) (OS) and \( P = 0.44 \) (EFS). Solid line: Received carboplatin (n = 29). Dashed line: Received Actinomycin-D (n = 19).
Carboplatin has been evaluated for treatment of most malignancies in which cisplatin has already been shown to be efficacious. It is also better tolerated [2,14]. Carboplatin therapy, by itself or in combination, has been successfully used in the treatment of WT. Pietras [15] reported that the high level of toxicity in high-risk patients in the SIOPEN 93-01 protocol resulted in treatment delays and modifications. Changes were therefore introduced in the current protocol (SIOPEN 9) [16]. In this protocol new cytotoxic drugs, whose effectiveness has been confirmed in previous pilot studies, such as etoposide, carboplatin, ifosfamide, and epirubicin were taken into account. Patients with unfavorable histology received intensified therapy with ifosfamide, doxorubicin, carboplatin, and etoposide for 34 weeks. Patients with metastases were stratified according to the response to preoperative chemotherapy treated as in the SIOPEN 9 study. VP16 and carboplatin are administered for 3 days in reduced doses (VP16 of 5 × 100 mg/m² has been changed to 3 × 150 mg/m² and 600 mg/m² and CARBO to 3 × 200 mg/m²) [15]. Naguib et al. [10] published a retrospective analysis of clinico-pathological features and treatment results for 53 previously untreated pediatric patients with WT. They treated relapsing and resistant cases of stage I–IV rhabdoid tumor of the kidney with untreated pediatric patients with WT. They treated relapsing and resistant cases of stage I–IV rhabdoid tumor of the kidney with carboplatin and etoposide de Camargo et al. [17] administered carboplatin by itself to 15 patients with relapsed WT. The regimen consisted of carboplatin I.V. administered as a single agent at 550 mg/m² for 1 hour every 3 weeks. They reported 4 (26%) complete responses, 4 (26%) partial responses, one stable disease, and six with progressive disease. Küpeili and Bilici [18] used doxorubicin instead of actinomycin-D in the preoperative treatment of WT when the latter was unavailable in Turkey. They described this as effective. Similarly, our study showed that carboplatin treatment is well tolerated and effective for WT. Carboplatin has cost advantages over actinomycin-D and is more economical. We found no difference between the two regimens in terms of toxicity or results. There were no significant differences between the two groups in terms of serious hematological and non-hematological toxicities. The toxic effect of actinomycin-D is hepatotoxicity, particularly in terms of veno-occlusive disease [19]. Carboplatin could be used if actinomycin-D is too toxic in patients with WT. In conclusion, our data demonstrate the carboplatin can be used as an alternative to actinomycin-D chemotherapy in the treatment of WT in countries where the supply of actinomycin-D is problematic and prone to delay, or in patients with excess toxicity on Act-D. These results need confirmation with by further studies.

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REFERENCES