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Background: The outcome of children with relapsed Wilms’ tumor is poor, especially with poor-risk factors such as unfavorable histology, early recurrence, previous three-drug therapy, relapse not confined to lungs and abdominal relapse following abdominal radiotherapy. We report the overall response rate, progression-free survival and overall survival of 11 children with relapsed and poor-risk Wilms’ tumor following ifosfamide/carboplatin/etoposide (ICE) chemotherapy.

Patients and methods: ICE therapy consisted of ifosfamide 1800 mg/m²/day (on day 0–4), carboplatin 400 mg/m²/day (on day 0–1) and etoposide 100 mg/m²/day (on day 0–4). The median age at diagnosis was 39 months (range from 13 months to 16 years) and the median time to relapse after initial diagnosis was 9 months (range 4–72 months). All but one patient had at least one poor prognostic feature, with eight patients showing three or four.

Results: After ICE chemotherapy the number of patients showing a complete response (CR) was three (27%) and a partial response (PR) was six (55%). The overall response rate (CR+PR) was 82%. Five of the six patients with a PR subsequently achieved a CR with further therapy. The 3-year event-free survival and overall survival were 63.6 ± 14.5%.

Conclusions: The response rate in children with relapsed and poor-risk Wilms’ tumor is >80% with ICE re-induction chemotherapy followed by post-ICE therapy. The optimal approach for post-ICE consolidation therapy has yet to be determined.

Key words: chemotherapy, childhood, recurrent, solid tumors, survival

Introduction

Results from the Second and Third National Wilms’ Tumor Studies have suggested that the outcome of patients with relapsed Wilms’ tumor remains poor, with a 3-year post-relapse survival of only 30 ± 3% [1]. The prognosis and progression-free survival in relapsed patients is dependent on several risk factors including initial stage, tumor histology, length of initial remission, initial therapy with two compared with three drugs and site of relapse [1]. New retrieval therapy is needed for patients with relapsed Wilms’ tumor who have poor prognostic features such as unfavorable histology, advanced stage (>1), abdominal relapse at site of previous abdominal radiation therapy, early recurrence (<12 months) after initial diagnosis or previous treatment with three drugs.

Pre-clinical studies have shown the efficacy of etoposide, a semi-synthetic derivative of podophyllotoxin, on different tumor cell lines including acute leukemia, lymphoma, germ cell tumors and small-cell lung cancer [2]. Ifosfamide has been demonstrated in pre-clinical animal trials to be more effective than cyclophosphamide against different carcinomas, sarcomas, nephroblastosomas and leukemia cell lines [3]. Pre-clinical trials using carboplatin have also demonstrated anti-tumor effects comparable to cisplatin in several tumor models, but less non-hematological toxicity [4–6]. Each of the above chemotherapy agents (ifosfamide, etoposide and carboplatin) has been demonstrated to have activity as a single agent in several phase II pediatric solid tumor clinical trials. The use of ifosfamide as a single agent in relapsed or resistant pediatric solid tumors has been associated with excellent response rates of 30, 50 and 86% in children with relapsed solid tumors, Wilms’ tumor or unresectable rhabdomyosarcoma, respectively [7–9]. The use of etoposide as a single agent in children with relapsed solid tumors [10] and in children with relapsed Wilms’ tumor [11]...
has also shown a wide response range (5.8 and 73%, respectively). Furthermore, the use of carboplatin as a single agent in children with relapsed Wilms’ tumor has additionally resulted in an overall response rate of 40–53% [12, 13].

The combination of either etoposide/carboplatin or ifosfamide/etoposide has been evaluated in multiple pediatric phase II trials for possible additive or synergistic anti-tumor effects in the treatment of relapsed pediatric solid tumors. The combination of etoposide and carboplatin resulted in overall response rates of 43–83% when used in children with a variety of pediatric solid tumors [14–22]. Similar response rates have been seen with the combination of ifosfamide/etoposide in pediatric phase II solid-tumor trials with overall response rates of 55 and 39.5% [18, 19].

The combined use of ifosfamide, carboplatin and etoposide (ICE) in children with refractory or relapsed solid tumors has increased over the past 10 years and resulted in good overall response rates (>50%) in a variety of recurrent/refractory pediatric solid tumors [20–22]. In this study we report the overall response rates and long-term progression-free survival for children with relapsed Wilms’ tumor treated with ICE re-induction therapy and post-ICE hematopoietic growth factors, treated initially using Children’s Cancer Group (CCG) protocols 0894, 0924 and Genetics Institute (GI) protocol C9305-14 and post-ICE chemoradiotherapy ± autologous peripheral blood stem cell (PBSC) transplantation.

Patients and methods
Patient eligibility
Patients with relapsed Wilms’ tumor were enrolled in one of three protocols, which included treatment with ICE re-induction chemotherapy followed by G-CSF or PIXY321 (a hybrid GM-CSF/IL-3 fusion protein) in CCG-0894 and CCG-0924, respectively, or rhIL-11 (Neumega®; Genetech) followed by G-CSF or PIXY321 (a hybrid GM-CSF/IL-3 fusion protein) in CCG-0894 and CCG-0924, respectively, or rhIL-11 (Neumega®; Genetech) followed by G-CSF or PIXY321 (a hybrid GM-CSF/IL-3 fusion protein) in CCG-0894 and CCG-0924, respectively, or rhIL-11 (Neumega®; Genetech) followed by G-CSF or PIXY321 (a hybrid GM-CSF/IL-3 fusion protein) in CCG-0894 and CCG-0924, respectively, or rhIL-11 (Neumega®; Genetech) followed by G-CSF or PIXY321 (a hybrid GM-CSF/IL-3 fusion protein) in CCG-0894 and CCG-0924, respectively, or rhIL-11 (Neumega®; Genetech) followed by G-CSF or PIXY321 (a hybrid GM-CSF/IL-3 fusion protein) in CCG-0894 and CCG-0924, respectively. G-CSF was kindly supplied by Amgen (Thousand Oaks, CA, USA) and was distributed by the National Cancer Institute (NCI). PIXY321 was kindly provided by Immunex (Seattle, WA, USA) and was distributed by the NCI. PIXY321 causes a day 21 and 30 hematopoietic recovery (ANC ≥1000/mm3 and platelet count ≥100,000/mm3). No modification of ICE chemotherapy was allowed during the first and second courses. For subsequent courses if hematopoietic recovery failed to occur by day 21, ICE chemotherapy was reduced by 25%, and if hematopoietic recovery failed to occur by day 35, patients were taken off study. Ifosfamide and carboplatin were reduced by 25 or 50% if the creatinine clearance or glomerular filtration rate (GFR) were reduced to 50–74% or 25–49% of normal, respectively. Patients were taken off the C9305-14 study if the creatinine clearance (or GFR) was reduced to <25% of normal or if patients developed renal tubular acidosis. Ifosfamide was discontinued if patients on CCG-0894 or CCG-0924 developed Fanconi’s syndrome or a creatinine clearance of <25% of normal. Patients did not receive radiation therapy while on protocol therapy and did not have any surgery until the completion of the fourth course of therapy.

Chemotherapy administration
Ifosfamide was administered at a dose of 1800 mg/m2/day for 5 days, carboplatin 400 mg/m2/day for 2 days, carboplatin 400 mg/m2/day for 2 days, and etoposide 100 mg/m2/day for 5 days. Patients received intravenous hydration and mesna during each of the 5 days of ifosfamide infusion. Chemotherapy cycles were repeated every 21 days and after hematopoietic recovery (ANC ≥1000/mm3 and platelet count ≥100,000/mm3). No modification of ICE chemotherapy was allowed during the first and second courses. For subsequent courses if hematopoietic recovery failed to occur by day 21, ICE chemotherapy was reduced by 25%, and if hematopoietic recovery failed to occur by day 35, patients were taken off study. Ifosfamide and carboplatin were reduced by 25 or 50% if the creatinine clearance or glomerular filtration rate (GFR) were reduced to 50–74% or 25–49% of normal, respectively. Patients were taken off the C9305-14 study if the creatinine clearance (or GFR) was reduced to <25% of normal or if patients developed renal tubular acidosis. Ifosfamide was discontinued if patients on CCG-0894 or CCG-0924 developed Fanconi’s syndrome or a creatinine clearance of <25% of normal. Patients did not receive radiation therapy while on protocol therapy and did not have any surgery until the completion of the fourth course of therapy.

Hematopoietic growth factors
Patients enrolled on CCG-0924 received PIXY321 by subcutaneous injections at four dose levels 500, 750, 1000 µg/m2/day or 500 µg/m2 twice a day. PIXY321 was kindly provided by Immunex (Seattle, WA, USA) and was distributed by the National Cancer Institute (NCI). PIXY321 causes a significant increase post-ICE therapy in peripheral blood granulocyte-macrophage CFUs, erythrocyte BFUs, CFU-GM and CD34+ cells compared with baseline [23]. PIXY321 is also more potent than either GM-CSF or IL-3 alone in inducing hematopoiesis in vitro [24]. PIXY321 was started after day 5 of each cycle and continued until day 18, unless the ANC was ≥2000/mm3 or the platelet count was ≥90,000/mm3 for 2 days between days 13 and 18, at which time PIXY321 was discontinued. However, if the ANC did not reach ≥1000/mm3 by day 18, PIXY321 was continued until hematopoietic recovery was achieved (ANC ≥1000/mm3 and platelet count ≥100,000/mm3) to a maximum of 25 days for any course. PIXY321 was permanently discontinued for patients who developed grade IV dose-limiting toxicity.

Patients enrolled on CCG-0894 were randomized to receive either 5 or 10 µg/kg/day of G-CSF. G-CSF was kindly supplied by Amgen (Thousand Oaks, CA, USA) and was distributed by the NCI. G-CSF was started after day 5 and continued until day 18 of each cycle if the patient achieved an ANC of ≥1000/mm3; otherwise G-CSF was continued until the ANC reached ≥1000/mm3. The dose of G-CSF was reduced by 50% for grade III toxicity secondary to G-CSF or was permanently discontinued and patients were taken off protocol therapy if grade IV toxicity developed.

Patients enrolled on C9305-14 were started on rhIL-11 after day 5 of chemotherapy and continued for up to 28 days. Patients were enrolled in cohorts during rhIL-11 dose escalation (25–125 µg/kg/day). rhIL-11 was
discontinued after 14 days if the platelet count did not decrease to \( \leq 100,000 \text{ mm}^3 \) post-ICE. If the platelet count decreased to \( < 100,000 \text{ mm}^3 \) post-ICE, rhIL-11 was continued until the platelet count recovered to \( \geq 100,000 \text{ mm}^3 \). The next cycle of chemotherapy was started 2 days after the discontinuation of rhIL-11. Patients were also given G-CSF at 5 \( \mu \)g/kg/day starting after day 5 of chemotherapy and continuing until the ANC was \( \geq 1000 \text{ mm}^3 \) for 2 consecutive days.

**Assessment of response**

Tumor size was evaluated by institutional investigators at study entry and following two cycles of ICE chemotherapy and after every other cycle. The sum of the products at the greatest length and maximal perpendicular width for each tumor mass was used as the definition of tumor size. Complete response (CR) was defined as total disappearance of tumor as determined by specific diagnostic testing. Partial response (PR) was defined as a reduction of at least 50% of tumor size without any evidence of the appearance of new lesions, disease progression or symptoms from osseous lesions. Stable disease was defined as \( < 50\% \) reduction of tumor size or \( > 25\% \) increase in the size of any measurable tumor area. Progressive disease was defined as \( > 25\% \) increase in any measurable tumor and/or the appearance of new lesions or the appearance of symptoms from osseous lesions. Patients’ complete blood count, differential and platelet counts were closely monitored with each cycle of ICE. Neutrophil and platelet recovery were defined as the number of days from the start of any cycle until the first day of an ANC count of \( \geq 1000 \text{ mm}^3 \) and platelet count of \( \geq 100,000 \text{ mm}^3 \), respectively, after the nadir of chemotherapy.

**Grading of toxicity**

The World Health Organization recommendations were used to assess and grade acute and sub-acute toxic effects in GI protocol C9305-14 and the NCI criteria were used to grade toxicity in CCG-0894 and CCG-0924.

**Statistical analysis**

A total of 11 Wilms’ tumor patients were treated with ICE chemotherapy and followed for 2–7 years. The response rate among these patients was reported for CR, PR and overall response (CR + PR). Overall response rate was calculated as the number of patients who demonstrated a PR or CR divided by the number of evaluable patients. Patients were considered evaluable for statistical analysis if they had measurable disease at study entry, completed at least two cycles of ICE therapy and were evaluated for response. Patients with progressive disease during the first two cycles of ICE were also evaluable for response. Survival was taken to be the time from study entry until the last patient contact. Patients alive at last contact were considered censored. A death, regardless of cause, was considered an event.

Time to hematological recovery was calculated for each course administered during protocol therapy but recovery results for the first two cycles of chemotherapy will be presented. Recovery of ANC was considered to be the time from the start of the course until the first date that the ANC reached \( \geq 1000 \text{ mm}^3 \) after day 5 of chemotherapy or the date the next course of chemotherapy was delivered, whichever came first. Recovery of platelets was similarly defined, except the target blood count for platelet count was \( \geq 100,000 \text{ mm}^3 \). The cumulative proportion recovered was calculated as 1 minus Kaplan–Meier [25] and estimated for the cumulative proportion not recovered. Any patient who was withdrawn from study prior to documented recovery was censored for the time to recovery estimation. The 3-year survival estimates and median times to recovery were reported. Progression-free survival was defined as the survival in months without evidence of disease progression as defined above, from the time of study entry until November 1999. The overall and progression-free survival curves as well as time-to-recovery curves for both platelets and neutrophils were estimated using the method of Kaplan and Meier [25].

**Results**

**Patients’ characteristics**

Eleven patients with relapsed Wilms’ tumor were enrolled on CCG-0894 (four patients), CCG-0924 (one patient) and GI C9305-14 (six patients). The median age at diagnosis was 36 months (range from 13 months to 16 years). Staging at initial diagnosis showed two patients (18%) with stage I, one patient (9%) with stage II, four patients (36%) with stage III, three patients (27%) with stage IV and one patient (9%) with stage V. Histological evaluation at initial diagnosis showed favorable histology in nine patients (82%) and unfavorable histology in two patients (18%). Patients were initially treated according to the Third and Fourth National Wilms’ Tumor Study (NWTS) trial protocols [26–28]. The median time to relapse was 9 months (range 4 months–6 years) and the sites of relapse were pulmonary in 36%, pleural in 9%, renal in 18%, renal/pulmonary in 18% and hepatic in 9% (Table 1).

Poor prognostic features reported previously in patients with relapsed Wilms’ tumor were also examined in our group of patients and included unfavorable histology at initial diagnosis, advanced initial stage, early recurrence (<12 months), abdominal relapse with previous abdominal radiation therapy, abdominal and lung relapse, and previous three-drug therapy [1]. Of the patients 91% had at least one poor prognostic feature and the median number was three (Table 2).

**Hematological recovery**

Following the first cycle of ICE the median number of days to ANC recovery was 18 (range 15–26) and the median number of days to platelet recovery was 21 (range 12–33). Similarly, following the second cycle of ICE, ANC recovery occurred at a median of 19.5 days (range 16–36) and platelet recovery occurred at a median of 19 days (range 13–43) (Figure 1A and B).

**Response to ICE**

Patients received a median of four cycles of ICE chemotherapy (range 1–12) and response to ICE was evaluated after two or more cycles of ICE. Three patients (27%) developed a CR, six patients (55%) had a PR, one patient had stable disease (9%), and one patient had progressive disease (9%) with a response rate (CR + PR) of 82% (nine of 11 patients) (Table 3).

**Response to post-ICE therapy**

Two of the three patients who attained a CR continued to be in CR, while the third patient with initial CR relapsed and died 4 months post-ICE. Five of the six patients with an initial PR
following ICE attained a CR. Complete response was attained without any further therapy for one patient, with surgical excision of residual tumor for another, with chemotherapy and/or radiation therapy in two patients and with high-dose chemotherapy followed by autologous PBSC transplantation in one patient. Only one patient with an initial PR developed progressive disease following autologous bone marrow transplantation (Table 3).

Table 1. Characteristics of patients

<table>
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<th>Protocol</th>
<th>Cytokine dose</th>
<th>Age</th>
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<th>Initial histology</th>
<th>Previous Rx</th>
<th>Time to relapse</th>
<th>Site of relapse</th>
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<td>IL-11 50µg/kg/day</td>
<td>54 months</td>
<td>IV</td>
<td>F</td>
<td>NWTS 4</td>
<td>10 months</td>
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<td>IL-11 75µg/kg/day</td>
<td>53 months</td>
<td>IV</td>
<td>U</td>
<td>NWTS 4</td>
<td>9 months</td>
<td>Pulmonary</td>
</tr>
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<td>I</td>
<td>F</td>
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<td>F</td>
<td>NWTS 3</td>
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<td>Liver</td>
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<td>16 months</td>
<td>III</td>
<td>F</td>
<td>NWTS 4</td>
<td>5 months</td>
<td>Kidney/lung</td>
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<td>16 months</td>
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<td>NA</td>
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<td>Kidney/lung</td>
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<td>F</td>
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<td>26 months</td>
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<td>F</td>
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Table 2. Prognostic features and survival

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<th>Recurrence &lt;12 months</th>
<th>Abdominal only and prior abdominal XRT</th>
<th>Abdominal and lungs</th>
<th>Previous three-drug therapy</th>
<th>No. of risks</th>
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<td>Y</td>
<td>Y</td>
<td>4</td>
<td>D (4)</td>
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*All patients with an abdominal relapse had a kidney relapse except for patient no. 5 who had a liver relapse only.

XRT, radiation therapy; A, alive; D, deceased.
Figure 1. Proportion of patients with ANC recovery (≥1000/mm^3) and platelet recovery (≥100,000/mm^3) following the first (A) and second (B) cycle of ICE by method of Kaplan and Meier. (A) Myeloid recovery occurred at a median of 18 days (n = 11), and platelet recovery occurred at a median of 21 days (n = 10). (B) Myeloid recovery occurred at a median time of 19.5 days, and platelet recovery occurred at a median time of 19 days (n = 9). n, number of evaluable patients.
Survival

To date seven patients are alive and disease-free with a median follow-up for surviving patients of 4.28 years. The 3-year progression-free survival and overall survival were similar at 63.6 ± 14.5% (Figure 2).

Hematological toxicity

Both grade IV neutropenia (ANC <500/mm³) and grade IV thrombocytopenia (platelet count <20000/mm³) were seen in 100% of patients.

Non-hematological toxicity

Grade IV non-hematological toxicity was reported in five patients (45%) and included septic shock in three patients (three events out of 46 cycles, 6.5%), pulmonary in one patient (one event out of 46 cycles, 2.2%) and gastrointestinal in one patient (one event out of 46 cycles, 2.2%). All grade IV toxicities were reversible. Four patients with grade IV toxicity were on C9305-14 and one patient was on CCG-0894.

Transient grade III hepatotoxicity occurred in two patients, one with elevated aspartate aminotransferase (AST) and the second with elevated serum bilirubin. Transient grade III proteinuria and hypophosphatemia were reported in one patient and transient grade III hypokalemia was reported in another. Renal tubular acidosis was reported in one patient and resolved (grade II). A transient decrease in the creatinine clearance to 41% of baseline was reported in only one patient following the seventh cycle of ICE. One patient (with normal kidney function during ICE therapy) developed chronic renal failure 2.5 years following ICE chemotherapy secondary to ifosfamide therapy and a solitary kidney. No patients developed grade III or IV renal tubular acidosis. No regimen related mortality was reported in this group of patients.

Discussion

When used as single agents, etoposide, ifosfamide and carboplatin have shown anti-tumor activity in children with relapsed Wilms’ tumor [8, 11, 12]. The French Society of Pediatric Oncology (SFOP) reported a response rate of 50% (median duration of 2 months) to ifosfamide (3 gm/m² over 2 days, every 2 weeks) in children with relapsed Wilms’ tumor [8]. The use of etoposide (200 mg/m²/day for 5 days) as a single agent in relapsed Wilms’ tumor has resulted in a response rate of 42% as reported by a phase II trial of the SFOP and the UK Children’s Cancer Study Group (UKCCSG) [11]. Furthermore, the Brazilian Wilms’ Tumor Study Group reported that carboplatin, given as a single agent at a dose of 550 mg/m² over 2 days, every 2 weeks in children with relapsed Wilms’ tumor [12]. The use of etoposide (200 mg/m²/day for 5 days) as a single agent in relapsed Wilms’ tumor has resulted in a response rate of 42% as reported by a phase II trial of the SFOP and the UK Children’s Cancer Study Group (UKCCSG) [11]. Furthermore, the Brazilian Wilms’ Tumor Study Group reported that carboplatin, given as a single agent at a dose of 550 mg/m² over 2 days, every 2 weeks, resulted in a response rate of 53% [12]. The long-term progression-free survival with single-agent chemotherapy, however, is poor.

The use of a combination regimen of etoposide (100 mg/m²/day for 5 days) and carboplatin (160 mg/m²/day for 5 days) every 21 days for two courses in patients with refractory or relapsed Wilms’ has resulted in a CR in eight patients (31%) and a PR in 11 patients (42%) with a response rate of 73% [17]. However, only eight patients (31%) remain disease-free.

Table 3. Response to ICE

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Protocol</th>
<th>No. of cycles</th>
<th>BR to ICE</th>
<th>No. of cycles to BR</th>
<th>Therapy post-ICE</th>
<th>FR</th>
<th>Survival post-ICE (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C9305-14</td>
<td>1</td>
<td>PD</td>
<td>NA</td>
<td>None</td>
<td>PD</td>
<td>D (3)</td>
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<tr>
<td>2</td>
<td>C9305-14</td>
<td>6</td>
<td>PR</td>
<td>2</td>
<td>VAD/XRT</td>
<td>CR</td>
<td>A (52)</td>
</tr>
<tr>
<td>3</td>
<td>C9305-14</td>
<td>2</td>
<td>PR</td>
<td>2</td>
<td>ABMT</td>
<td>PD</td>
<td>D (15)</td>
</tr>
<tr>
<td>4</td>
<td>C9305-14</td>
<td>3</td>
<td>CR</td>
<td>2</td>
<td>None</td>
<td>CR</td>
<td>A (48)</td>
</tr>
<tr>
<td>5</td>
<td>C9305-14</td>
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<td>PR</td>
<td>1</td>
<td>None</td>
<td>CR</td>
<td>A (42)</td>
</tr>
<tr>
<td>6</td>
<td>C9305-14</td>
<td>2</td>
<td>PR</td>
<td>2</td>
<td>APBSCT</td>
<td>CR</td>
<td>A (20)</td>
</tr>
<tr>
<td>7</td>
<td>CCG-0924</td>
<td>5</td>
<td>PR</td>
<td>3</td>
<td>VD</td>
<td>CR</td>
<td>A (69)</td>
</tr>
<tr>
<td>8</td>
<td>CCG-0894</td>
<td>6</td>
<td>CR</td>
<td>2</td>
<td>IE/XRT</td>
<td>CR</td>
<td>A (82)</td>
</tr>
<tr>
<td>9</td>
<td>CCG-0894</td>
<td>4</td>
<td>SD</td>
<td>4</td>
<td>VAD/XRT, surgery</td>
<td>PD</td>
<td>D (11)</td>
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<td>10</td>
<td>CCG-0894</td>
<td>12</td>
<td>PR</td>
<td>2</td>
<td>Surgery</td>
<td>CR</td>
<td>A (79)</td>
</tr>
<tr>
<td>11</td>
<td>CCG-0894</td>
<td>4</td>
<td>CR</td>
<td>2</td>
<td>None</td>
<td>PD</td>
<td>D (4)</td>
</tr>
</tbody>
</table>

*Patient was in PR after VAD/XRT and surgery, but eventually developed PD.

*ABMT, autologous bone marrow transplantation; APBSCT, autologous peripheral blood cell transplantation; XRT, radiation therapy; I, ifosfamide; E, etoposide; V, vincristine; A, anthracycline; D, dactinomycin.

*Calculated from the first day of study entry until November 1999. A, alive; D, deceased.

BR, best response; CR, complete response; FR, final response; PD, progressive disease; PR, partial response; NA, not applicable.
and in CR at a median of 40 months of follow-up (range 24–56). The combination of ifosfamide (1800 mg/m²/day for 5 days) and etoposide (100 mg/m²/day for 5 days) has resulted in a CR rate of 15%, a PR rate of 54% and an overall response rate of 69% in children with relapsed Wilms’ tumor as reported by Miser et al. [29]. However, the 4-year survival was 29% and the 4-year progression-free survival was only 24%. These results suggest that three-drug therapy may improve long-term progression-free survival compared with two-drug therapy. However, a randomized study between a two- versus three-drug regimen with a similar post-ICE consolidative approach is required to best answer this question.

Kung et al. reported the results of a Pediatric Oncology Group (POG) study on the response rate of children with relapsed or resistant solid tumors to a combination of ifosfamide (1500 mg/m²/day for 3 days), etoposide (100 mg/m²/day for 3 days) and carboplatin (escalating dose from 300 mg/m² for 1 day) [22, 30]. At the maximal tolerated dose of 635 mg/m² for carboplatin, a CR rate of 32% and a total response rate of 63% were reported [22]. The use of ICE chemotherapy by the POG group in patients with relapsed Wilms’ tumor has shown a good response rate of 71%, but a low ≥3-year survival (<40%) [22, 30]. The previous POG reports by Kung et al. [22, 30, 31] have used a lower ifosfamide (50%) and etoposide (60%) dose than the current doses of our ICE regimen. Utilizing our doses of ICE we have recently reported excellent response rates in other recurrent pediatric solid tumors including central nervous system tumors (response rate of 43%) and recurrent sarcomas (response rate of 50.5%) [32, 33], as well as an excellent response in children with relapsed Wilms’ tumor (82%) and a better long-term survival (63.6%) than reported previously. Other investigators have also reported a good response rate in patients with relapsed resistant solid tumors including Wilms’ [34, 35]. However, it remains to be determined whether the higher doses of ICE as used in this study compared with the lower doses used in the POG studies are required to achieve both a high response rate and maintain an enhanced progression-free survival.

The second and third NWTS studies have identified subgroups of relapsed Wilms’ tumor patients with poor prognostic features and included, as discussed previously, patients with unfavorable histology, abdominal recurrence with previous radiation therapy, advanced disease stage, early recurrence (<12 months) and previous three-drug therapy [1]. Recently Pein et al. reported the results of a multivariate analysis of eight adverse prognostic factors in children with relapsed
Wilms' tumor and showed a significant effect on 3-year survival of unfavorable histology, early recurrence ≤6 months, multiple organ recurrence and lymph node involvement at recurrence [36]. The median number of poor prognostic factors in our group of patients with relapsed Wilms' tumor was three, with 91% of patients having at least one factor. However, the use of ICE chemotherapy in our patients resulted in a high response rate of 82% with long-term overall and progression-free survival (63.6 ± 14.5%) of all the patients who attained a CR initially or subsequently, either following further chemotherapy, radiotherapy, or high-dose chemotherapy and PBSC transplantation. This dose-intensive therapy allows patients with high-risk disease and poor prognostic features to enter into a CR or a PR with the probability of further therapy with newer therapeutic agents and/or novel therapeutic approaches (i.e. high-dose chemotherapy followed by PBSC transplantation). Although both patients with unfavorable histology had a poor outcome a larger number of patients with unfavorable histology are needed to better evaluate the efficacy of ICE in this subgroup. In comparison, Tannous et al. recently reported the results of an intergroup CCG and POG trial of a retrieval study in children with relapsed Wilms' tumor [37]. High-risk patients similar to our patient population were treated with chemotherapy regimens containing cyclophosphamide (2200 mg/m²)/etoposide (500 mg/m²) and carboplatin (1 gm/m²)/etoposide (300 mg/m²) during induction and maintenance in addition to local radiotherapy and surgery. CR was seen in 42% of patients and PR in 36% following two cycles of induction therapy (overall response rate 78%). Patients in CR after surgery were treated with maintenance chemotherapy cycles of alternating cyclophosphamide/etoposide and carboplatin/etoposide. The reported event-free survival and survival in this group of patients was 59 and 64%, respectively. These results compare favorably with this current ICE trial and use similar agents (carboplatin and etoposide) and cyclophosphamide instead of ifosfamide.

The use of high-dose chemotherapy followed by autologous stem cell transplantation may be effective in salvaging patients with relapsed Wilms' tumor and poor prognostic features. A 3-year disease-free survival and overall survival of 50 ± 17% and 60 ± 18%, respectively, were reported after high-dose chemotherapy and autologous stem cell transplantation in a group of patients with high-risk relapsed Wilms' tumor transplanted in post-relapse CR or PR [38]. In our group of patients, only two patients underwent autologous stem cell transplantation; one is alive and disease-free 20 months post-ICE therapy and one patient died of progressive disease post-autologous bone marrow transplantation. Further clinical trials are needed to determine those patients who require high-dose chemotherapy and stem cell transplantation after successful re-induction chemotherapy (CR or PR) in poor-risk relapsed Wilms' tumor.

Hematopoietic toxicity is the major factor limiting the use of more dose-intensive chemotherapy regimens for children with recurrent/relapsed solid tumors. The incidence of grade III/IV neutropenia was 81% for patients treated with ifosfamide/etoposide (ifosfamide at 2000 mg/m²/day for 3 days, etoposide at 100 mg/m²/day for 3 days) therapy for recurrent pediatric solid tumors [18] and the incidence of grade III/IV thrombocytopenia was 25.5%. Similarly, Miser et al. reported a high incidence of grade III/IV neutropenia (96% of cycles) following the ifosfamide/etoposide combination and a lower incidence of thrombocytopenia (20–30%) [19, 29]. The carboplatin/etoposide combination has resulted in a 92% incidence of grade III/IV neutropenia, and a higher incidence of grade IV thrombocytopenia (100% of patients treated) when compared with ifosfamide/etoposide regimens [17]. The combination of ICE therapy in pediatric patients has resulted in similar grade III/IV neutropenia (83–84%) as reported by both POG and CCG [20–22, 30]. Grade III/IV thrombocytopenia was 59 and 84% in both POG and CCG study groups, respectively. The use of the ICE regimen in our group of children with relapsed Wilms' tumor resulted in a high incidence of severe neutropenia (100% of patients) similar to that reported previously following two-drug combinations of ifosfamide/etoposide or carboplatin/etoposide. However, a higher incidence of severe thrombocytopenia (100%) was seen in our group of patients when compared with ifosfamide/etoposide regimens only but not to carboplatin/etoposide regimens. Too few patients were treated with either PIXY321 or the combination of IL-11/G-CSF to determine if either regimen resulted in enhanced platelet recovery and/or a decrease in platelet transfusion requirement.

The percentage of grade IV septic episodes (6.4%) to the total number of ICE cycles was similar to earlier reports by Miser et al. (6 compared with 7%) following ifosfamide/etoposide chemotherapy [19, 29]. No deaths secondary to regimen-related toxicity were reported in our group of patients. Renal toxicity is of major concern in patients with relapsed Wilms' tumor and a single kidney. A recent report by Marina et al. showed that severe renal tubular toxicity occurred more frequently in patients with newly diagnosed sarcoma treated with ifosfamide/carboplatin regimens compared with ifosfamide alone or ifosfamide/cisplatin combination. Delayed renal tubular toxicity (1 year following therapy) was seen more frequently in patients treated with ifosfamide/cisplatinum combinations [39]. In our group of patients with relapsed Wilms’ tumor transient grade III hypophosphatemia, proteinuria and hypokalemia were reported in two patients (18%) but no grade IV renal toxicity or renal tubular acidosis was seen during ICE chemotherapy. Our results are similar to earlier reports of renal toxicity in patients with relapsed Wilms’ tumor receiving ifosfamide/etoposide therapy (20%) [29] but were lower than previously reported following ICE therapy. Recent reports by Kung et al. [31] and Daw et al. [40] have shown a 29% incidence of Fanconi syndrome following ICE therapy in children with relapsed Wilms’, and a significant decrease in GFR when ICE was followed by nephrectomy and radiation therapy. Further studies are needed to determine whether there is any increase in nephrotoxicity with the use of ICE therapy compared with ifosfamide/etoposide therapy.
In summary, the use of a more intensive re-induction ICE regimen in children with refractory or recurrent Wilms’ tumor has proven to be substantially effective with an overall response rate of 82% without an increase in renal toxicity. This excellent response rate has allowed further consolidative interventions post-ICE such as high-dose chemotherapy and stem cell transplantation, chemotherapy, chemo-radiotherapy and/or surgery, and a historically improved 3-year overall survival and progression-free survival (63.6%). We realize that this response rate was analyzed in only 11 patients, but the limited availability of patients with relapsed Wilms’ tumor, especially at any one single institution, makes larger phase II trials somewhat difficult. The high incidence of severe hematopoietic toxicity necessitates the need for optimizing the use of hematopoietic growth factors following ICE, such as G-CSF, IL-11, PIXY 321, thrombopoietin and/or stem cell support to reduce the toxicity and/or duration of myelosuppression. Further studies are required to determine the optimal consolidative approach after successful ICE re-induction (CR and/or PR) in children with poor-risk relapsed Wilms’ tumor. Furthermore, future studies are needed to determine whether all three chemotherapy drugs are required in the ICE regimen, and the role of ifosfamide versus cyclophosphamide should be addressed.

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References

21. Cairo MS, Kralio M, Misir J et al. Excellent results of the use of ifosfamide, carboplatin, etoposide (ICE) in children with recurrent or...


