Clear Cell Sarcoma of the Kidney: Patients’ Characteristics and Improved Outcome in Developing Countries

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INTRODUCTION

Pediatric renal tumors are the second most common abdominal malignancies seen in infants and children, and represents about 6.3% of all pediatric cancers [1]. They are classified as Wilms tumor (WT) representing 85% of pediatric renal malignancies; congenital mesoblastic nephroma (5%); clear cell sarcoma of the kidney (CCSK) (4%); and rhabdoid tumor of the kidney (2%) [2–4]. CCSK is considered one of the high risk unfavorable renal tumors. According to NWTS-5, localized stage I tumors account for 25%, stage II 37%, stage III 34%, and stage IV 4% of CCSK at diagnosis [5], with a few patients diagnosed at stage V [6,7]. CCSK’s overall survival has reached 69%—according to the National Wilms Tumor Study (NWTS) in 2000. The International Society of Paediatric Oncology (SIOP) studies showed a five year event-free survival (EFS) and overall survival (OS) of 79% and 86%, respectively in 2013 [8]. In the past, CCSK was initially recognized by its high tendency to bone metastasis with poor prognosis [9–11]. The most frequent metastases sites are lymph nodes, bone, and the lungs [5]. There are few publications that have reported the status of CCSK in developing countries [12].

The aim of this study is to report the clinico-pathological presentation and correlate it to treatment outcomes in one of the largest Middle East childhood cancer referral centers, emphasizing on the pattern of metastasis and improved outcome in developing countries.

PATIENTS AND METHODS

Case report forms of pediatric patients (age 0–18 years) diagnosed with CCSK between July 2007 and March 2012 at Children’s Cancer Hospital Egypt (CCHE) were reviewed and followed up till April 2013. Collected data included demographics, clinical presentation, radiological, surgical, medical management, and pathological features in addition to clinical outcome. All patients involved in the study were classified according to the Children’s Oncology Group (COG) classification system [13,14].

Background. Clear cell sarcoma of the kidney (CCSK) is a rare and aggressive tumor accounting for 5% of pediatric renal tumors with an incidence of 20 patients per year in the USA. It is bone metastasizing with poor prognosis. Our aim was to show characteristics of patients in relation to improved outcome in one of the developing countries.

**Procedure.** We included all patients diagnosed as CCSK in the period between July 2007 and March 2012 at Children’s Cancer Hospital, Egypt. Patients’ demographics, clinical presentation, pathology, and management were reviewed. Follow up was continued until April 2013. **Results.** Twenty-five patients were identified in the defined time interval, accounting for 7% all renal tumors diagnosed at the hospital. Mean age was 36 months. Abdominal swelling and herniuma were the most common presentations. Stages I, II, III, IV, and V represented 9 (36%), 3 (12%), 8 (32%), 3 (12%), and 2 (8%), respectively. Twenty-four patients had radical nephrectomy either upfront or after neo-adjuvant chemotherapy. Surgery was followed by adjuvant chemotherapy. Abdominal radiotherapy was given for local stages II and III. Twenty-two patients reached complete remission, while one patient had stationary disease and two patients died due to progression and relapse. Overall survival was 88.5% and event-free survival was 87.8% at 45 months. **Conclusion.** Although previous studies indicate poor prognosis of CCSK, our experience shows that those patients can be treated using extensive chemotherapy combined with proper local control. Pediatr Blood Cancer © 2014 Wiley Periodicals, Inc.

Key words: clear cell sarcoma; including soft tissue sarcomas; non-rhabdoid; pediatric oncology; rare tumors; sarcomas; solid tumors
Among 357 patients diagnosed at CCHE with renal tumors, 25 patients were diagnosed pathologically as CCSK; constituting 7% of renal tumors. Presenting symptoms included abdominal swelling, 18 (62%); hematuria, seven patients (28%); pain; four patients (16%); fever, two patients (8%); vomiting, one patient (4%); and jaw swelling, one patient (4%). One girl had a medical history of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Congenital anomalies were not detected in any patient. The majority of patients were between one and five years old (19 patients; 12 of them between 1 and 3), while three patients were younger than one and another three patients older than five. More characteristics are listed in Table I.

Multi-slice abdominal and chest computerized tomography (CT) scans with contrast were done for all patients during the initial workup. Abdominal CT was assessed by the surgeon to decide if the patient could undergo upfront radical nephrectomy or if the tumor was inoperable, with the possibility of incomplete resection or tumor spillage. Patients who initially were considered inoperable underwent an ultrasound or CT-guided biopsy. Neo-adjuvant chemotherapy (vincristine/doxorubicin/cyclophosphamide/etoposide +/- carboplatin) was started after the biopsy results and radical nephrectomy was delayed. Bone scan was done initially to assess metastases.

Ten patients (40%) underwent an initial CT-guided biopsy. Two of these were initially misdiagnosed as suffering from favorable histology Wilms tumor (FHWT) and were managed accordingly until the time of definitive surgery at week 6 or 12. Another patient was diagnosed initially as FHWT with an inferior vena cava (IVC) thrombus—by CT only—and started neo-adjuvant chemotherapy for 6 weeks. Definitive diagnosis was reached for this case after radical nephrectomy. Indications for neo-adjuvant chemotherapy included large tumors crossing the midline (four patients), capsular invasion (two patients), bilateral lesions (one patient), enlarged para-aortic lymph nodes in addition to lung and bony deposits (one patient), enlarged para-aortic lymph nodes (one patient), and a malignant IVC thrombus extending to the right atrium (one patient).

## Surgery

Twenty-four patients (96%) had radical nephrectomy either upfront (14 patients) or after a neo-adjuvant chemotherapy (10 patients, 40%) and one patient died before surgery due to tumor progression. The patients who received neo-adjuvant chemotherapy (11 patients) experienced reduction in tumor volume ranging between 0% and 84.4% (mean 50.58%, median 52.39%, SD 23.52%) from the initial size prior to nephrectomy. Seven of them underwent nephrectomy at week 6 of neo-adjuvant chemotherapy. One patient had nephrectomy at week 12 after further decrease in tumor volume. Another patient with IVC thrombus extending to the right atrium needed additional time for thrombus regression. This patient was given 12 weeks of (vincristine, doxorubicin, and actinomycin D), followed by three cycles of CCE (carboplatin, cyclophosphamide, and etoposide) before definitive surgery. Another patient had a nephrectomy post 31 weeks of vincristine, doxorubicin, cyclophosphamide, etoposide, and carboplatin due to the huge size of the renal mass. This mass had decreased by 40% after 6 weeks of chemotherapy then became stationary until the end of the protocol, with slowly regressing pulmonary and bone metastases. One patient with bilateral disease died before undergoing surgery.

For patients with initially unresectable tumors, the volumetric measurements of the primary tumor—using an elliptical model—were used to assess the response to neo-adjuvant therapy. According to the RECIST criteria at the time of operation, eight of ten patients had stationary disease, while two patients had partial remission. One of the two patients with bilateral disease showed 45% reduction in the tumor volume in the kidney with the bigger mass (right) and complete disappearance of the left renal mass at the time of surgery (week 6) and complete remission at the end of treatment. The other patient suffering from bilateral tumor died from progressive disease at week 12 of neo-adjuvant chemotherapy (newly developed brain metastases), despite of marked decrease in renal volume (around 78%).

## Histopathology

**Gross features.** The tumors were usually well circumscribed, sharply demarcated from renal tissue with mean diameter of 10.98 cm. Cut section was soft, tan grey, frequently myxoid, with cystic foci range from minute cysts to large cystic spaces. Foci of...
hemorrhage and necrosis were encountered especially with patients who received preoperative therapy.

**Microscopy.** Nephrectomy specimens were available from 24 of 25 patients. Classic pattern either solely or focally represented the most common histologic pattern (92%). It was composed of a monotonous array of cells that were regular, ovoid, with fine chromatin, and scanty ill-defined cytoplasm separated by delicate arborizing blood vessels. Other encountered histologic growth patterns included myxoid (20%), spindle (16%), cellular (8%), hemangiopericytomatous (8%), palisading (4%), and anaplastic (4%) (Fig. 1).

The capsule was invaded in nine patients (36%); ureteric and vascular margins were free and six (24%) showed lymph node metastasis.

**Immunohistochemical stains.** A panel of immunohistochemical stains was done for almost (23/24) all patients using the BenchMark XT Ventana system. Tumor cells were negative for WT1, synaptophysin, myogenin, CK, and LCA excluding WT neuroblastoma, rhabdomyosarcoma, lymphoma, and rhabdoid tumor of the kidney (RTK). RTK was excluded by INI-1 positivity. Other negative markers including S100, GFAP, CD34, myeloperoxidase (MPO), CD117, and TdT were found. Focal positivity to CD99 was found in two patients for which EWS (EWSR1 break apart 22q12, Vysis) translocation by fluorescence in situ hybridization (FISH) was negative. Tumor cells were positive for vimentin and bcl-2. Both bilateral cases showed positive INI-1 and one of them showed anaplastic disease with overexpressed p53.

**Post-operative chemotherapy.** After radical nephrectomy, Stage I–III patients continued on a four-drug regimen (vincristine, doxorubicin, cyclophosphamide, and etoposide) for 25 weeks (20 patients or 80%). Patients with metastatic disease received five drugs (by adding carboplatin) for 30 weeks (three patients or 12%).

Therapy of the patient with an IVC thrombus with right atrium extension was upgraded to CCE and was continued for eight cycles.

**Local radiotherapy.** Local radiotherapy was given within 10–14 days after surgery for 15 of 24 (62.5%) patients. Table II outlines radiotherapy details.

**Radiation modality.** Thirteen patients received 1,080 cGy flank irradiation in six fractions with a boost dose to the residual para-aortic LNs and IVC thrombus. Two patients received 1,050 cGy whole-abdomen radiotherapy (WAR) due to either intra-operative tumor rupture or peritoneal deposits. Patients with lung metastases received 1,200 cGy divided over seven days (n = 3) with boost dose to residual lesions at the end of irradiation.

**Toxicity.** There was no reported perioperative mortality or morbidity. Only two patients developed late adhesive intestinal obstruction and needed re-exploration after 4–9 months of primary surgery for adhesiolyis or resection/anastomosis of the ileum. In general, the toxicity induced from chemotherapy was tolerable with no mortality. Myelosuppression grade III-IV occurred in 20 cases (80%), hepatotoxicity grade II in the form of elevated transaminases in 16 cases (64%), grade I-II nausea and vomiting in 14 cases (56%), and diarrhea grade II-III in eight cases (32%). One patient (4%) developed cardiotoxicity grade IV within seven days of doxorubicin and cyclophosphamide injection at week 19 with severe sepsis and electrolyte imbalance (hypomagnesaeemia and hypokalaemia). Ejection fraction decreased to 30% and required interruption of chemotherapy. The patient was admitted to the intensive care unit. Inotropic medications, broad-spectrum antibiotics were administered and electrolyte correction performed after which normal cardiac contractility resumed. The tolerance to radiotherapy was very good with limited toxicity to the GIT in the form of decreased appetite, nausea, vomiting and diarrhea, and skin toxicities in the form of erythema, darkness, and desquamation. Myelosuppression grade I-II was observed.

**Outcome.** Follow-up continued until April 2013 with a median follow-up period of 12 months (6 to 45 months). At the

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**TABLE II. Management and Final Outcome**

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**Fig. 1.** Histological features of clear cell sarcoma of the kidney (CCSK): (A) H & E slide of classic type (×100 magnification), (B) classic type with a huge cyst on left side (×100), (C) anaplastic CCSK (×200), and (D) classic type showing negative WT1 (×100).
end of the follow-up period, 23 of 25 patients were alive, 22 in CR and one in stationary disease (SD) according to the RECIST criteria. The two patients diagnosed with bilateral CCSK died due to disease progression; one of them relapsed systemically after 10 months of follow-up with brain infiltration while the other patient died from disease progression at week 12 with brain and cranio-spinal meningeal infiltration (Fig. 2). The three-year OS was 88.5% (95% confidence interval between 72.8% and 100%) and EFS was 87.5% (confidence interval between 71.1% and 100%) (Fig. 3). At the end of follow-up, Stage I, II, and III patients were all alive in CR with OS and EFS 100%. Even the three patients of stage IV were all alive, two in CR and one in stationary residual pulmonary metastasis with OS and EFS of 100%. Stage V had the worst OS and EFS of 0% (Table II and Fig. 3).

The only patient diagnosed as anaplastic CCSK showed a very aggressive disease presentation with bilateral renal masses and metastases to the bones, lung, and liver and showed progressive disease after 12 weeks of treatment with brain and cranial-spinal lepto-meningeal infiltration.

DISCUSSION

This is a single institution analysis report of 25 pediatric patients diagnosed pathologically as CCSK and treated at CCHE during the period between July 2007 and March 2012. CCSK accounts for 5% of pediatric renal tumors with tendency to bone metastasis [3,19] and is associated with aggressiveness and higher recurrence rates compared to Wilms tumor [20,21]. In this study, it accounted for 7% of all renal tumors presenting in one period. CCSK preoperative diagnosis is very difficult with a high possibility of misdiagnosis [22,23]. In this study, three out of 25 patients (12%) were misdiagnosed as FHWT resulting in the administration of mismatched neo-adjuvant chemotherapy. This may have resulted from: lack of specific radiological criteria for CCSK diagnosis using abdominal CT nonspecific morphology; lack of tumor markers; and/or inadequate tissue in the biopsy taken for initial diagnosis (if upfront nephrectomy was not done) [24]. In our study, a classic pattern either solely or focally represented the most common histologic pattern (92%) compared to other studies that showed classic pattern in 91%. Patterns seen that usually blend smoothly with classic pattern were myxoid (50%), sclerosing (35%), and cellular (26%) in addition to other patterns [5,25–28]. The only patient identified as anaplastic CCSK exhibited a very aggressive course.

Previous National Wilms Tumor Study Group (NWTSG) [5] and SIOP [8] studies reported an average age of 36 months (2 months—14 years; median 2.6 years) with male predominance and a male to female ratio of 1.9:1. The most common metastatic site was bone with rare bilateral metastasis [5,6]. In this study, we report similar age distribution with the majority of cases between one and three years, mean age 36 months, and 1.1:1 male to female ratio. Metastasis occurred in classic sites and included pulmonary, hepatic, and osseous metastases. CCSK was seen in the left kidney in most patients (n = 16) and bilaterally in two patients; with no specific syndromes reported in this series. This could be due to actual infrequent incidence or deficient reporting. Stage distribution was similar to previous SIOP Renal Tumors Study Group (RTSG) and NWTSG studies with stage I at 36% and stage III at 32% constituting the majority, with the exception that there were two patients diagnosed at stage V in this series. Due to the rare incidence of bilateral involvement and advanced presentation of the disease, metastasis from the other kidney could not be ruled out.

Chemotherapy was integrated with surgery and radiation therapy for proper local and systemic control of the disease. A four-drug regimen was administered for stages I–III and a five-drug regimen given to stage IV patients. Radiotherapy was applied to all stages except stage I.

In general, the chemotherapy-induced toxicity was tolerable with no treatment related mortalities. Severe myelosuppression without serious infections and cardiotoxicity were the most serious toxicities.

Although the follow up period is short, excellent survival outcome was consistent with NWTS-5 in which the patients had
radical nephrectomy followed by local radiotherapy (1,080 cGy) and vincristine, doxorubicin, and cyclophosphamide alternating with cyclophosphamide and etoposide for 24 weeks with 5-years RFS and OS of 79% and 89%, respectively [21]. In the SIOP 93-01/2001 study, for stage I AVD with no radiotherapy was given. For stage II and III, local radiotherapy (Median: 2,520 cGy) was given followed by postoperative cyclophosphamide and doxorubicin alternating with etoposide and carboplatin, with a 5-year EFS and OS of 78% and 86% [8].

Whereas treatment in the United Kingdom WT Study group 2 trial (UKWT2) included upfront nephrectomy—whenever possible—followed by 12 months of vincristine, actinomycin D, and doxorubicin, only stage III and IV patients received local radiotherapy (3,000 cGy). The resultant 4-year EFS and OS were 82% and 88%, respectively with high local relapse in stage II patients as they did not receive local radiotherapy [29].

We believe that establishing such comprehensive cancer center as CCHE, which offers multidisciplinary care and integrating data management for the whole Middle East will accelerate the clinical research and evidence generation for better practice in pediatric oncology in our region. This region has remained for a long time dependent on such evidence from studies conducted in developed countries. Moreover, it is becoming evident for physicians in our practice that patients are coming with less advanced symptoms than 10 years ago before the establishment of the hospital. This may be due in part to the availability of best care facilities at CCHE and also the orientation campaigns that were coupled with fundraising campaigns for the

Fig. 3. Outcome of all patients with clear cell sarcoma of the kidney: (A) Event-free survival (87.8%), (B) overall survival (88.5%), and (C) overall survival in correlation to different stages.
center. Such socio-economic effect is a point for further future studies.

CONCLUSION

Patients with CCSK show an increased survival rate—even in developing countries—after using aggressive postoperative chemoradiotherapy after radical nephrectomy. Some studies indicate the presence of genetic alteration in CCSK. However, unlike WT, CCSK is not commonly associated with genetic syndromes. Avoiding radiotherapy in stage I, CCSK did not affect OS or EFS. Aggressive or alternative approaches are needed to improve survival. Special attention has to be given to anaplasia and stage as the only factors correlating with survival. On the other hand, searching for disrupted pathways including up-regulation of EGFR, sonic hedgehog, and phosphoinositide-3-kinase/AKT pathways as targeted therapies to avoid aggressive treatments—with less side effects—is needed [30–32].

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REFERENCES