ORIGINAL ARTICLE

Metastatic Renal Cell Carcinoma in Children and Adolescents: A 30-Year Unsuccessful Story

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Background: Because of the rare occurrence of renal cell carcinoma (RCC) among children very little is known about this malignancy in pediatric age. We aimed adding knowledge on the clinical characteristics and outcome of metastatic (m) RCC in children and adolescents.

Patients and Methods: The series included 14 stage 4 RCC patients with a median age at diagnosis of 155.5 months, observed at the Italian Pediatric Hematology and Oncology Association (AIEOP) centers from January 1973 to November 2010. We were able to reevaluate histopatology of 11 out of the 14 patients and perform immunostaining for TFE3 in 9 out of the 11 patients.

Results: Of the 14 patients under study, 5 (3 girls) had a translocation morphology TFE + RCC, 2 were reassigned as papillary type 1 or 2, respectively, 2 tumor specimens with primary clear cell histology had confirmed the initial histologic diagnosis, and 2—whose biopsy specimen was insufficient—had the diagnosis of RCC not further specified with subtyping. In the remaining 3 cases, the initial diagnosis of clear cell carcinoma was left. Overall, 6 patients received chemotherapy, 9 immunotherapy, and 2 adjuvant antiangiogenic therapy. Overall, 11 patients (78.5%) never achieved complete remission and died from progressive disease 1 to 16 months after diagnosis (median overall survival 5.5 mo). Three patients, 2 of whom received adjuvant antiangiogenic therapy, relapsed to lung at 3, 6, and 8 months after diagnosis, and died 18, 32, and 33 months after diagnosis, respectively.

Conclusions: Despite their possibly different biology, childhood and adult mRCC seems to be sharing comparable outcomes. Because of the very low incidence of mRCC (about 20%) in children and adolescents, an international pediatric cooperation to address biological studies and assess the novel targeted approaches is needed.

Key Words: metastatic renal cell carcinoma, rare cancer, pediatric, targeted therapy

Renal cell carcinoma (RCC) is thought to arise from epithelial cells of the renal tubule and accounts for 2% to 3% of all adult malignancies. RCC rarely occurs in pediatric age accounting for only 0.1% to 0.3% of all neoplasm[1–3] and from 1.8% to 6.3% of all malignant renal tumors in children.[2–5] RCC in adults has been the subject of large clinical trials and intensive basic research. Because of its rarity in children, studies matching the complexity and power of adult studies are impossible to conduct.

Recent data have suggested that pediatric RCC may be a different entity from adult RCC, with different clinical presentation and features,[6–9] genetics, and pathology.[6,10–13] However, the overall prognosis of children seems similar to that of adults patients for stage 1 and 2[14–17] and it worsens as tumor stage increases. Patients with tumor localized in the kidney have a good prognosis, whereas the outcome is poor in case of distant metastases.[4,14] Surgery is the mainstay of the treatment and results in cure in many of the patients with tumor localized and completely resected. No effective therapy for disseminated disease is available. Immunotherapy has until recently been considered the standard of care, but only 10% to 20% of patients show apparent response. In adults, recent biological insights have identified the clinical efficacy of new front-line multi-tyrosine kinase inhibitors that target the vascular endo-thelial/platelet growth factor receptors, VEGFRs and PGFRs, respectively.

To gain more knowledge about the disseminated disease we analyzed the characteristics and the treatment results of children with metastatic RCC (mRCC) observed in the Oncology Centers of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP).

METHODS

A retrospective review of pathologic and clinical records at the AIEOP centers identified 75 patients with RCC presenting from January 1973 to November 2010. According to the modified Robson staging classification system[7] 14 patients (18.6%) were classified as stage 4. Eleven out of the 14 cases have previously been reported in our clinicopathologic study on RCC in Italy.[8] Clinical data, surgical notes, pathologic findings, and summaries of treatment details were taken from the charts. The study was approved by the regional ethical review board at the Second University of Naples and performed in compliance with the Helsinky Declaration. A reevaluation of microscopic features on hematoxylin and eosin-stained slides and immuno-histochemistry analysis concerning TFE3[18] was possible in 11 of the 14 cases by the reference pathologist (P.C.) The histologic appearance of the papillary tumor was

subclassified as type 1 or type 2 papillary pattern based on the criteria described by Eble et al.[19] Nine cases with available and adequate biological tissue were investigated retrospectively also using commercially available antibodies to TFE3. Immunoreactivity for TFE3 (TFE3-P16, Santa Cruz, 1:250) was tested. Nuclear reactivity was scored as positive. The histologic subtype was to be reassigned according to the classification system adopted by an international consensus workshop 2004.[20]

RESULTS

Patient Characteristics

Clinical and pathologic data of the 14 cases (7 boys) are summarized in Table 1. The age of patients ranged from 16 to 194 months (median 155.5 mo). At presentation, a palpable mass was found in 1 patient (7.1%), gross hematuria in 2 (14.2%), and abdominal pain in 7 (50%). Five patients (35.7%) presented with constitutional symptoms (fever, 2 cases; significant weight loss, 1 case; pathologic fracture, 1; and hypertension, 1). Two patients had non-specific symptoms: 1, respiratory distress and the other neurological signs. In 1 patient no symptoms were retrieved from the charts. The classic triad of a palpable mass, flank pain, and hematuria was not found in any of the examined patients. The primary tumor occurred in the left kidney in 6 cases and in the right one in 6 cases (no available data in 2 cases). One patient had a renal malformation as a preexisting condition. No child had a known diagnosis of von Hippel-Lindau syndrome.

Metastatic sites included lung in 9 cases, bone in 7, liver in 5, mediastinal lymph node in 3, and diaphragm or skin or central nervous system involvement in 1 case.

Pathology

Nine cases with available and adequate biological tissue had an analysis concerning TFE3. Five of them (3 girls) had a translocation morphology TFE + RCC. One case of the 9 had papillae and tubular structures covered by small cuboidal cells with scant pale cytoplasm and small nuclei, and was reassigned as papillary type 1. One case, had papillae covered by large cells with large eosinophilic cytoplasm and large spherical nuclei with prominent nucleoli, and was reassigned as papillary type 2. Two tumor specimens with primary clear cell histology had the initial histologic diagnosis confirmed. In 2 cases, with initial biopsy of kidney and cervical mass respectively, only RCC diagnosis was possible. Finally, in 3 cases with no available and adequate biological tissue the initial diagnosis of clear cell carcinoma was taken.

Treatment

Nephrectomy was performed at diagnosis in 9 patients (64.2%), with associated retroperitoneal lymphoadenectomy in 6 cases, and partial resection of the diaphragm in 1 (patient 5). In 5 patients, a biopsy of the primary tumor (2 cases) or metastatic lesions (3 cases) was performed. Overall, 6 patients received chemotherapy according to responsible physician choices. Most of the drugs adopted were those usually included in the protocols for Wilms tumor. One patient received gemcytabine and vinorelbine (patient 7). Nine patients received immunotherapy with associated chemotherapy in 2 of them: 8 patients received α-interferon combined with interleukin-2 in 4 cases. Another patient received only interleukin-2. Four cases

(28.5%) underwent radiation therapy as a part of their treatment. Radiation was delivered to the tumor bed at doses ranging from 30 to 40 Gy. Two patients, with liver and lung/mediastinal lymph nodes disease at diagnosis, respectively, received adjuvant antiangiogenic therapy.

Clinical Outcome

Table 1 reports clinical features, disease course, and outcome of the 14 patients. Overall, 11 patients (78.5%) never achieved complete remission and died of metastatic or local progressive disease 1 to 16 (median 5 mo) after diagnosis. Three cases (21.4%), who initially had complete response after surgery and radiotherapy (patient 5) or adjuvant antiangiogenic therapy (patient 12 and 13), relapsed at lung 3, 6, and 8 months after diagnosis, and died 18, 32, and 33 months after diagnosis, respectively. Therefore, after the follow-up ranging from 1 to 33 (median 7.5 mo), none of our patients survived.

DISCUSSION

RCC is a rare disease in children and adolescents.[1] It had been speculated that RCC in children represents a different entity from its adult counterpart.[7] In the last decade, translocation RCC has emerged as a common form of pediatric RCC accounting for 60% to 70% of all pediatric cases.[21,22] However, the overall prognosis for children appears similar to the one of adults for stage 1 and 2,[6–8,14–17] whereas recent data suggest that pediatric local lymph node-positive (stage 3) RCC disease is different from that in adults. In fact, while > 70% of pediatric local lymph node-positive RCC patients remain alive and disease free,[6] only 20% of adults with lymph node-positive RCC remain alive at 5 years from diagnosis. Conversely, adult and pediatric patients with mRCC have low comparable survival rates. The dismal results in our patients with metastatic disease are in agreement with other pediatric and adults series.[8,14–17] For the patients with mRCC there has been no effective therapy, despite the use of behind surgery of immunotherapy, radiation therapy, and chemotherapy.[8,17,23–25] Significant differences in the epidemiology and the biology of adult and pediatric RCC severely limit our ability to reliably transfer the knowledge gained among affected adults to children's management. Metastatic disease at presentation is more often described in adults (25%). Several reports in children, however, have described the same incidence.[14–17] The latter incidence is confirmed by our data (18.7%), with lung and bone as the most common distant lesions.

In adults, the occurrence of occasional spontaneous remissions suggests an immunogenic nature of RCC. Nevertheless, a recent meta-analysis of 58 randomized controlled trials involving 6880 patients with mRCC concluded that only a small and well-defined fraction of these patients can benefit from immunotherapy.[24] According to other pediatric reports,[22,26] our limited experience confirms a very weak response. It has been shown that cytoreductive nephrectomy improves the survival of patients with mRCC when it is performed before immunotherapy.[27–29] Conversely, a delayed nephrectomy after systemic therapy is also a reasonable strategy.[30] Because of the small number of patients (9 patients) treated with initial cytoreductive nephrectomy and to the few prognostic variables available in the charts, little can be said about the value, if any, of the nephrectomy at diagnosis in our experience. Moreover, we recorded no reliable benefit with radiotherapy (4 cases) or

TABLE 1. Clinicopathologic Features, Evolution, and Outcome

Patients	Age (mo)	Sex	Side	Extent of Surgery	Histology	Site(s) of Metastasis	Site(s) of Tumor Failure	Relapse (mo) First Adjuvant Therapy	Other Treatment	Outcome	Follow-up (mo)
1	160	M	Right	NP + RLND	Clear cell	Lung, bone, Med, LN	Metastasis	Progression	CT + IL2 + IFN	DOD	6
2	140	M	Right	Biopsy sovraclavear lymph node	Clear cell	Lung, Med LN, bone	Metastasis	Progression	IL2 + IFN	DOD	10
3	151	M	Right	Biopsy knee	Clear cell	Lung, skin, bone	Local and metastasis	Progression	CT + IL2 + IFN	DOD	3
4	194	F	NA	Biopsy kidney	Renal cell	Lung, liver, bone	Local and metastasis	Progression	CT + RT	DOD	4
5	171	M	Left	NP + RLND + PR diaphragm	TFE3 +	Diaphragm	Lung relapse	8 no therapy	RT	DOD	33
6	187	F	Right	Biopsy cervical mass	Renal cell	CNS	Metastasis	Progression	CT + RT	DOD	16
7	142	F	Left	NP + RLND	TFE3 +	Lung, liver, bone	Metastasis	Progression	CT + RT + IL2	DOD	5
8	144	F	Right	NP + RLND	Papillary type 1	Lung	Metastasis	Progression	CT + IFN + Ac. retinoic	DOD	12
9	98	M	Na	Biopsy kidney	Clear cell	Liver	Local and metastasis	Progression	CT	DOD	1
10	187	F	Left	NP	Clear cell	Lung, liver	Local and metastasis	Progression	IFN	DOD	9
11	96	F	Left	NP	TFE3 +	Bone	Metastasis	Progression	IL2 + IFN + ASCR	DOD	5
12	167	M	Right	NP + RLND + metastasectomy	Papillary type 2	Liver	Lung relapse	3 Sun	Sor + Temsi	DOD	18
13	168	F	Left	NP + RLND	TFE3 +	Lung, Med, LN	Lung relapse	6 Sor	Bev + IFN + Sun + Ever	DOD	32
14	16	M	Left	NP	TFE3 +	Lung, bone	Metastasis	Progression	IFN	DOD	5

ASCR indicates allogenic stem cell rescue; Bev, bevacizumab; CNS, central nervous system; CT, chemotherapy; DOD, dead of disease; Ever, everolimus; IFN, interferon; IL2, interleukin-2; LN, lymph node; Med, mediastinal; NA, not available; NP, nephrectomy; PR, partial resection; RLND, retroperitoneal lymph node dissection; RT, radiotherapy; Sor, sorafenib; Sun, sunitinib; Temsi, temsirolimus.

chemotherapy (6 cases). Because of the limited sample and the retrospective design of the study, these results are of limited significance. Actually, we were unable to describe any measured response to chemotherapy. However, these treatments seemed to add a little survival benefit also in other limited series of pediatric mRCC.[22,26]

Recently, a significant survival advantage has been obtained with new front-line multityrosine kinase inhibitors that target the VEGFRs/PGFRs, VEGFR and PGFR, respectively (bevacizumab, sunitinib, sorafenib, and pazo-panib),[31–35] and mammalian target of rapamycin pathways (temsirolimus and everolimus)[36,37] in metastatic adult patients. Most notably, the results of several studies suggest that the sequential use of these tyrosine kinase inhibitors is not hampered by cross-resistance, despite partly blocking the same signaling pathways.[38–40] However, most of the clinical trials of targeted therapies enrolled patients with clear cell RCC exclusively, the most common histologic subtype of RCC in adults. In the last 2 decades, translocation RCC has emerged as a common form of pediatric RCC. Translocation (TFE +) RCC is characterized by translocation involving chromosome Xp.11.2, the locus of the TFE3 gene. These have been recognized to occur predominantly in children and young adults with a statistically significant increased risk of advanced stage at presentation.[20,21] This finding is confirmed by our data: 5/9 cases from the present study demonstrated to harbor TFE3 translocation when retrospectively analyzed on available paraffin-embedded slides. In our study, because of the few patients treated with the multityrosine kinase inhibitors (2 cases) little can be said about the value of this treatment. Nevertheless, it is worth noting that in 1 TFE3 + case, 2 months after the start of antiangiogenic therapy with sorafenib a complete remission occurred, with disappearance of pulmonary metastases and mediastinal adenopathy by computed tomography imaging. In another histologic papillary type 2 case, with no evidence of measurable disease for microscopic liver disease at initial surgery, the relapse was metastatic (lung) after 3 months of adjuvant sunitinib therapy. Moreover, a longer time of survival was recorded in both cases. The incidence of TFE3 + RCC in adults was < 5% in the Japanese study.[41] However, it is noteworthy that 2 recent studies have shown that sunitinib may have significant activity in adult patients with translocation mRCC.[42,43]

In conclusion, (1) mRCC in childhood displays superimposable outcome to mRCC in adults, although it represents a group of tumors of possibly different biology than in adults; (2) coordinated and systematic genetic analysis of patients and tumor specimens are needed to afford a clearer understanding of pediatric mRCC; (3) because of the very low incidence of mRCC (about 20%) in children, an international pediatric cooperative effort is warranted to assess the targeted approaches. The lack of significant achievements in pediatric cases, both in terms of well-collected case histories, and of well-documented response to therapies and outcome, emphasize the need of a more direct transferral of information from adult series to children.

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