RENAL CELL CARCINOMA (RCC) IN YOUNG ADULTS: A CASE REPORT AND LITERATURE REVIEW

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Abstract

Pediatric renal cell carcinoma (RCC) is a rare disease entity and found to show significant differences from adult RCC in terms of epidemiological and histological subtypes. Treatment strategies for pediatric RCC were mainly adopted from adult RCC as there's no internationally recognized standard treatment guideline to date. Data on clinical outcomes are scarce. We hereby report a case of a 14-year-old female diagnosed with advanced clear cell RCC treated with pazopanib with overall survival of 10 months. There are several case reports and case series supporting the use of anti-VEGF in adolescent RCC though not in clear cell RCC. None has incorporated immune checkpoint inhibitors in adolescent RCC. Safety and efficacy in dosing strategies of anti-VEGF in adolescents is another challenge. As cancer care advances, large scale genetic data analysis leads to the emergence of precision and personalized medicine, but its utilisation in pediatric RCC is yet to be addressed.

Keywords: Pediatric RCC, Anti-VEGF, Immune Checkpoint Inhibitors, Precision Medicine, Personalized Medicine.

Introduction

Malignant renal tumour is a rare disease entity in children accounting for 5% in all cancers occurring before the age of fifteen (1). Renal cell carcinoma (RCC), the most common renal tumour type in adult, is extremely rare in children compared to Wilms tumour (WT), occurring at 3.5% of all renal neoplasms in children. However, the incidence of RCC increased drastically with age where it accounts for 70% of the renal cancers diagnosed at the age between 15-19 (2). Recent studies have suggested that pediatric RCC differ from the adult counterparts in terms of epidemiological and histological characteristics (1).

In an international population-based study on incidences of childhood renal tumours, renal carcinoma case numbers were too small for a clear geographical or ethnic pattern of incidence conclusion. Sex related incidence of renal carcinoma in children (age 0-14) reported no difference however female adolescent (15 to 19 years old) seemed to have higher incidences compared to male adolescent. The median age of diagnosis for pediatric RCC reported to be between 9 and 12 years old. Renal carcinoma incidence increases with age where the renal carcinoma become predominant renal tumour from age 14 and onwards (1).

There are several subtypes of renal cell carcinoma with Microphthalmia family translocation RCC (MiT-RCC) being the most common in children and adolescents (41.5%), followed by papillary RCC (16.5%), renal medullary carcinoma (12.3%), chromophobe RCC (6.6%), tuberous sclerosis (TS) associated RCC (4.2%), anaplastic lymphoma kinase (ALK) rearranged RCC (3.8%), clear cell RCC (3.3%) and other rare RCC (3). On the contrary, clear cell RCC is the most common subtypes in adult renal malignancy. There are approximately 25% of pediatric RCC which cannot be readily classified due to atypical features (4). Also, there is considerably large histologic overlap among different subtypes of pediatric RCC. Hence the diagnosis of pediatric RCC needs to be carefully made based upon clinical features, histology appearance supplemented by immunohistochemistry as well as genomics analysis whenever available.

The most prominent predisposing factor to RCC in children and adolescents is genetic translocation. Commonly reported genes such as folliculin (FLCN) gene responsible for Birt–Hogg–Dubé syndrome, fumarate hydratase (FH) tumour predisposition syndrome, von Hippel–Lindau (VHL) syndrome and tuberous sclerosis complex (TSC1 and TSC2) genes are found to be associated with pediatric and adolescents RCC (2).

There is paucity of data on the outcome of pediatric RCC cases given the rarity of the disease entity. Tumour stage has been reported as a prognostic factor similarly in adults. Evidence on association of lymph node involvement with long term survival is controversial. Other reported

prognostic factors for overall survival include pathologic stage, metastases and grade (2, 3).

Here we report a case of a young adolescent diagnosed with very aggressive metastatic RCC with overall survival of less than 1 year.

Case Presentation

A 14-year-old Iban adolescent female was initially presented with a history of intermittent non-radiating dull pain at the right lumbar area for 7 months with a pain score of 3 and usually resolved spontaneously within an hour. Other accompanying symptoms included painful gross hematuria with blood clot in urine. She also had unintentional weight loss of 8kg over 4 months associated with loss of appetite. She is a non-smoker, non-alcoholic and has no other comorbidities. Her height was 148 cm and weight 42 kg upon diagnosis, which translated into a body mass index of 19.17 kg/m^2 and a body surface area of 1.31 m^2. She attained menarche at 11 years old with a regular menstrual cycle of 28-30 days. Computerized tomography (CT) imaging as shown in Figure 1 reported a lobulated right renal mass located centrally, involving predominantly the midpole extending down to the lower pole with partially exophytic measuring 8.4x7.4x10 cm with heterogenous arterial enhancement in corticomedullary phase and extensive regional and distant lymphadenopathy involving retrocaval, aortacaval and paraaortic nodes. An ultrasound guided right renal biopsy was done and the histopathology examination reported clear cell renal cell carcinoma (WHO/ISUP Grade 1) as illustrated in Figure 2. She was diagnosed with unresectable International Metastatic Renal-Cell Carcinoma Database Consortium's (IMDC) poor risk advanced renal cell carcinoma with distant lymph nodes metastasis. Pazopanib, a VEGF-inhibitor, was started at a dose of 400 mg once daily as it was reimbursable in public setting. She was tolerating pazopanib well with no adverse events reported.

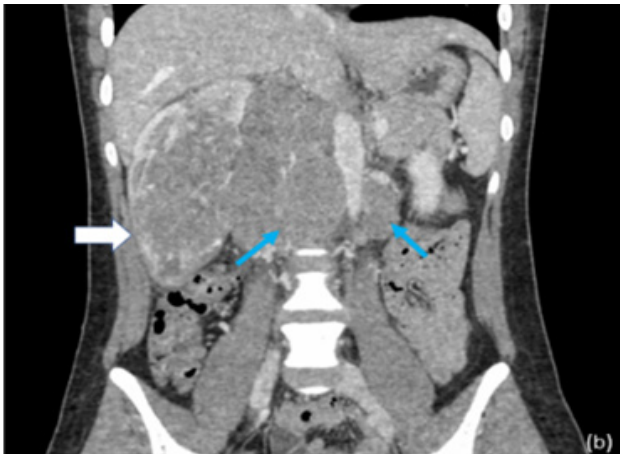

Figure 1: Baseline imaging - Baseline CT scan shows heterogeneous clear cell renal carcinoma (white arrow) with paraaortic lymphadenopathy (blue arrow).

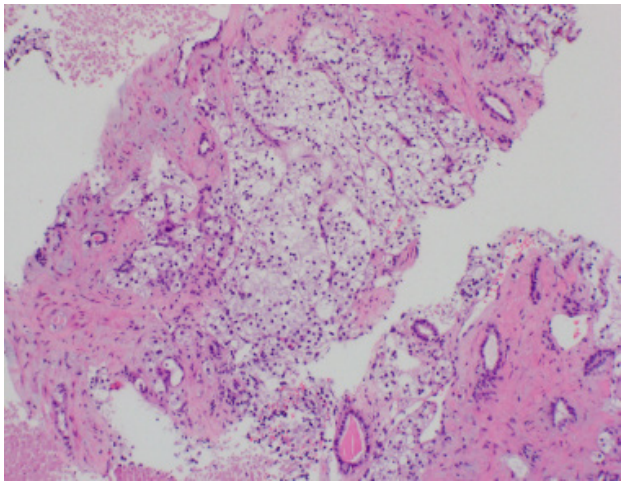

Figure 2: Histopathology of renal mass biopsy - Haematoxylin and Eosin (H&E) stain, original magnification x100, Lower-power microscopic view of right renal biopsy showing clear cell renal cell carcinoma (WHO/ISUP Grade 1).

Unfortunately, she started showing symptoms of abdominal pain and vomiting 2 months later. CT reassessment scan as shown in Figure 3 reported larger right renal mass measuring 11.5 x 8.8 x 17 cm with inferior vena cava thrombosis, worsening right paratracheal, abdominal nodal and lung metastases, new liver and bilateral ovarian metastases. She was started on tramadol for her abdominal pain and subsequently escalated to morphine for her symptoms control. At the same time, her pazopanib was increased to 800 mg once daily. At this recommended adult dose, she developed proteinuria with urine dipstick protein 1+ and 24-hour urine collection reported 0.74 g of urine protein. There was no other clinically significant adverse event reported. Thus, her pazopanib was continued at the same dose of 800 mg once daily.

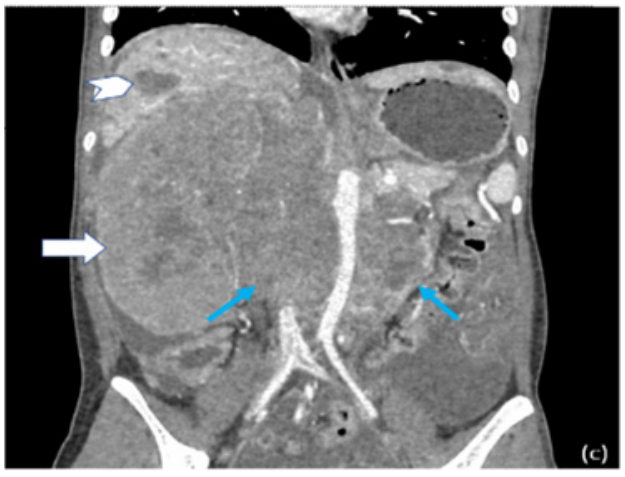

Figure 3: Treatment reassessment scan - Post pazopanib progression CT shows larger renal tumour (white arrow) with worsening paraaortic lymphadenopathy (blue arrow) and new liver metastasis (arrowhead).

Repeated CT reassessment scan after 5 months on pazopanib treatment reported worsening and new lung nodules, numerous new pleural nodules, larger and new mediastinal and hilar nodes, right renal mass marginally smaller at 7.7 x 8.3 x 18.4 cm, worsening liver, adnexal and peritoneal metastasis, overall in keeping with progressive disease. She developed symptomatic ascites requiring drainage. In view of the rapidly deteriorating physical function, she was offered best supportive care. She subsequently succumbed to her disease within a year of diagnosis.

Discussion

The treatment landscape of renal cell carcinoma has rapidly evolved over the past 2 decades from the initial cytokine therapy to targeted therapy and immunotherapy. Prior to 2005, interleukin-2 and interferon-α were the only therapeutic options available for advanced renal cell carcinoma and treatment response were only reported in 5-10% of patients. With the introduction of sorafenib in 2005 and emergence of multiple tyrosine and protein kinase inhibitors, the objective response rate rose to 30-40%. In the current era of immuno-oncology which uses the combination of immune checkpoint inhibitors or combination of tyrosine kinase inhibitor with immune checkpoint inhibitor further improve the treatment response rate to 60% (5). With the current treatment regimens, the overall survival for advanced metastatic renal cell carcinoma is reported to be 45.7 months and 55.7 months (6, 7). The recommendation by the latest local and international guidelines was not meant for patients younger than 18 years old (8, 9).

Despite several phase 3 trials report positive outcomes on metastatic clear cell renal cell carcinoma in adult patients with age 18 and above, those outcomes were not proven in pediatric renal cell carcinoma (10-14). Supporting evidence on pediatric RCC treatment is very limited as there are only case reports and reviews reporting the outcome of pediatric RCC. A single center retrospective analysis of 24 patients with mixed subtypes of pediatric RCC (age < 21 years old) reported the use of chemotherapeutic agents, antiangiogenic therapies, mammalian target of rapamycin (mTOR) inhibitors and immunotherapies. Median time to progression (TTP) is the highest with antiangiogenic therapies (70-119 days) followed by mTOR inhibitors (47 days) and chemotherapy (22-30 days) but no median TTP reported for immunotherapies. Pazopanib, although used as second-line therapy, was associated with a median TTP of 93.5 days (15).

Another report of pediatric RCC case series from Italian Pediatric Hematology and Oncology Association Centers included 14 patients with median overall survival of 5.5 months, majority treated with chemotherapy and radiotherapy while 2 patients on adjuvant antiangiogenic therapy. However, complete remission was never achieved for those 2 patients receiving antiangiogenic agents and they eventually succumbed to disease at 32 and 33 months after diagnosis (16). In addition, none of these reports explained the dosing strategy of antiangiogenic agents in the pediatric population.

There are another 2 case reports on successful treatment with sunitinib and cabozantinib in pediatric patients with translocation RCC. An 11-year-old female with advanced stage transcription factor E3 (TFE-3) positive RCC treated with sunitinib 50mg daily for 2 weeks out of every 4 weeks achieved complete radiological remission after 3 months. Toxic effects reported include mouth ulcer, loss of skin and hair pigmentation. Cabozantinib was used in 2 mesenchymal-epithelial transition factor (MET) expressed translocation RCC patients aged 12 and 17 years old, treated at a dose of 60mg once daily, showed treatment response time of 17-18 months. Adverse events reported were nausea, dry skin, cold sensation, hyperthyroidism, mucositis and palmar erythrodyesthesia (17, 18). Unfortunately, there is currently no dosing guide for targeted therapy in the pediatric population and both of these cases derived the dose from the adult population. Glade Bender JL et al. (19) summarized phase I clinical trials of VEGF inhibitors in children with refractory solid tumours with conclusion of the pharmacokinetics of VEGF inhibitors are comparable to adults with allometric dosing in children. However, with fixed tablet and capsule dosage formulations, allometric dosing can be a challenge. Furthermore, another phase I study of pazopanib in children with relapsed or refractory solid tumours reported a maximum tolerated dose of 450 mg/m^2 which justified the dose incorporated in our patient. Nevertheless, this phase I study has insufficient data on its antitumour activity (19).

Our patient has achieved menarche with regular menstruation and also a height and weight similar to an Asian adult, hence the dosing strategies of the anti-cancer agents for an adult was adopted but with lower initiation dose with an aim to escalate to recommended adult dose if there was no clinically significant safety concern. It is unknown if such a strategy had led to a poorer outcome in our patient. An observational study from Japan has reported that starting pazopanib at 400 mg once daily for adult patients over 18 years old showed effective plasma concentrations. Furthermore, the study also concluded that therapeutic drug monitoring for pazopanib might help in reducing the risk of developing adverse effects and subsequently optimising the treatment outcomes. This highlights the major gap in dose optimisation in adolescent cancer patients (20).

The relationship between cancer and the human genome has been studied for more than 20 years. As a result, precision medicine, which forms the basis of personalized cancer management, has been developed. Precision medicine is a strategy that exploits data regarding a person's genes, proteins and environment to diagnose, prevent and treat a specific disease, particularly incorporating the use of therapeutic strategies specifically tailored to the genetic profile of the cancer patient (21). The earliest discovery of germline mutation associated with RCC is VHL gene. VHL is a tumour suppressor gene that regulates hypoxia inducible

factor (HIF) protein which in turn regulates transcription of multiple genes including VEGF. Inactivation or mutation in VHL leads to accumulation of HIF and up-regulation of VEGF pathway, consequently increasing tumour proliferation, migration, permeability and angiogenesis. The prevalence of VHL mutation is reported to be between 23-52.3% in clear cell RCC. This important discovery has shifted the RCC treatment strategy from cytokine-based therapy to multikinase tyrosine kinase inhibitor and immunotherapy. The most commonly reported mutated genes other than VHL in genomic studies included polybromo 1 (PBRM1) (32.9-40%), Breast cancer gene BRCA1 associated protein-1 (BAP1) (10-15%), SET Domain Containing 2 (SETD2) (11.5%) and Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) (2-5%) (22). Besides being investigated as actionable driver mutations, common RCC genetic mutations discovered such as PBRM1, BAP1 and tumour protein p53 (TP53) were reported to have independent prognostic values based on retrospective analysis of two-phase III trials in advanced RCC (23). Incorporation of these mutational status in risk stratification model requires further investigation in prospective trials.

Gerlinger et al. (24) studied intratumoral heterogeneity (ITH) of 4 advanced RCC patients by sequencing multiple primary tumour sites and separate metastasis. Among the somatic mutations identified, less than 30% was ubiquitous, with the majority either shared (present in some but not all sites) or private (only present at one site). Besides, only VHL mutation was found to be ubiquitous. A significant ITH could be a potential factor in treatment failure hence remained a challenge in cancer treatment and its solution remained unanswered.

Owing to the aggressive nature of the disease in our case study, an attempt has been made to conduct genomic sequencing for possible personalized therapy. Unfortunately, it was not feasible due to inadequate tumour sample. Whether precision medicine can be effectively implemented in a clinical setting for RCC, especially in aggressive disease without standard treatment guidelines for pediatric population, is yet to be addressed.

With the emergence of immuno-oncology, immunotherapy such as immune checkpoint inhibitors have become first line treatment alongside with tyrosine kinase inhibitors owing to their impressive response rate and overall survival benefit (25-28). The benefit is even reported in adjuvant settings for pembrolizumab with disease free survival rate of 77.3% when compared to 68.1% in the placebo group. However, the study population in this randomised controlled trial is mainly adults (29). The advent of immunotherapy has revolutionized cancer treatment in adults but its role in pediatric malignancies is still lacking. Dinutuximab, an anti-GD2 (disialoganglioside) antibody was first approved by United States Food and Drug Administration (US-FDA) in 2015 for neuroblastoma in pediatric patients (30). Blinatumomab, bispecific antibodies, received FDA approval for use in pediatric patients with Philadelphia chromosome-negative relapsed/refractory B cell acute lymphocytic leukemia in 2016 (31). In 2017, pembrolizumab was approved for pediatric Hodgkin lymphoma and ipilimumab was approved for melanoma in pediatric patients more than 12 years old (32). Despite these successes, the use of immunotherapy in pediatric malignancies still lag behind advancements seen in adult malignancies. Several hurdles have been reported for use of immunotherapy in pediatric solid tumour. Firstly, a young age and immature immune system may hamper the effect of immunotherapy. Pediatric malignancies are often aggressive which necessitate the use of induction chemotherapy which ultimately deplete immune cells especially lymphocytes and natural killer cells. Lack of mutational drivers in pediatric solid tumour results in low T-cell clonal frequencies. Besides, there may also be potential acute and late toxicities from immunotherapy use in the pediatric population due to overreaction of the immune system. In addition, there's currently no predictive marker for the immunotherapy response in pediatric population (33). While there are still several hurdles to be addressed, the future role of immunotherapy in pediatric oncology is still promising as the knowledge of these diseases, tumour microenvironment complexities, and intricacies of pediatric immune system come into sharper focus.

Conclusion

Pediatric RCC although a rare disease entity, the incidence is on the rise worldwide. The distinct clinical, molecular and histological characteristics of pediatric RCC has been proven to be different from adult RCC. The translation of adult RCC treatment guidelines to the pediatric population is contentious in terms of response rate, dosing strategy and adverse events especially in the long-term safety data. In this era of precision and personalized medicine, use of genotyping and genomics provides insights on treatment strategy and disease prognostication in advanced RCC. However, ITH may confound its benefit. Given the poor outcome and scarcity of proven effective treatment especially in advanced disease stages, future research should focus on revealing the gaps of knowledge and development of standard treatment guidelines for pediatric RCC.

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Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

Consent obtained from the subject's parent in written form.

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