Targeted therapy in Xp11 translocation renal cell carcinoma

Cielená liečba Xp11 translokačného renálneho karcinómu

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Summary

Background: Translocation renal cell carcinoma (TRCC) is a rare form of RCC affecting mostly children and young adults with the occurrence of only 1–5% of all renal cell carcinomas. These carcinomas are associated with different translocations on a short arm of chromosome X in the region 11.2, which results in genetic modification of the p arm containing the transcription factor E3 gene. ***Methods:*** Herein we report a case of a patient who was diagnosed with TRCC with *c-Met* overexpression and was treated with multiple targeted therapy agents and immunotherapy. ***Case:*** A 28-year old woman without a significant past medical history underwent left sided total nephrectomy for TRCC. Seven months later, she developed systemic relapse and was treated with multiple lines of targeted therapy including sunitinib, everolimus, sorafenib, crizotinib, and pazopanib as well as with anti-PD-L1 antibody nivolumab, with stable disease as a best response. The most pronounced disease stabilization was achieved with sorafenib, which lasted 18 months. The patient died 81 months after initial diagnosis and 74 months from the diagnosis of metastatic disease. ***Conclusion:*** Improved survival observed in our patient could be related to the effectivity of tyrosine-kinase inhibitors, but not m-TOR inhibitors, even though disease stabilisation was observed as a best response. Identification of new treatment targets are warranted in this rare disease.

Key words

translocation renal cell carcinoma – Xp11.2 translocation – c-Met – immunotherapy – targeted therapy – crizotinib – sorafenib

Súhrn

Východiská: Translokačný renálny karcinóm (TRCC) je raritná forma RCC postihujúca predovšetkým deti a mladých dospelých s výskytom 1–5 % všetkých karcinómov obličky. Tieto karcinómy sú asociované s translokáciami na krátkom ramene chromozómu X v regióne 11.2, ktoré vyústia do genetickej zmeny p ramienka obsahujúceho gén pre transkripčný faktor E3. ***Metodika:*** V tejto práci prezentujeme kazuistiku pacientky s diagnózou translokačného renálneho karcinómu so zvýšenou expresiou génu *c-Met*, ktorá bola liečená viacerými líniami cielenej liečby a imunoterapie. ***Kazuistika:*** Dvadsaťosem-ročná žena bez významného predchorobia podstúpila ľavostrannú nefrektómiu pre TRCC. O 7 mesiacov sa u nej vyvinula systémová recidíva ochorenia, pre ktorú bola následne liečená viacerými líniami cielenej liečby vrátane sunitinibu, everolimusu, sorafenibu, crizotinibu, pazopanibu a tiež PD-L1 protilátkou nivolumabom, pričom pri tejto terapii bolo u pacientky možné pozorovať terapeutickú odpoveď maximálne vo forme stabilizácie ochorenia. Najdlhšiu stabilizáciu ochorenia pacientka dosiahla pri liečbe sorafenibom; táto stabilizácia trvala 18 mesiacov. Pacientka zomrela 81 mesiacov od stanovenia diagnózy a 74 mesiacov od diagnostikovania metastatického ochorenia. ***Záver:*** Zlepšené prežívanie pozorované u našej pacientky môže súvisieť s efektivitou podávaných tyrozín-kinázových inhibítorov, avšak nie m-TOR inhibítora, i keď najlepšou odpoveďou na podávanú liečbu bola stabilizácia ochorenia. Pri tomto ochorení je potrebná identifikácia nových cieľov liečby.

Kľúčové slová

translokačný renálny karcinóm – Xp11.2 translokácia – c-Met – imunoterapia – cielená liečba – crizotinib – sorafenib

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Introduction

Translocation renal cell carcinoma (TRCC) is a rare form of renal cell carcinoma (RCC) believed to be indolent and affecting mostly children and young adults [1]. It represents 1–5 % of all renal cell carcinomas most predominantly in women thanks to higher incidence of translocations on two X chromosomes [2]. TRCC is characterized by translocation that affects a short arm of the chromosome X in the region 11.2 resulting in the fusion of the transcription factor for immunoglobulin heavy-chain enhancer 3 gene (*TFE3*) with at least six other partners. The most prevalent translocations are t (X;17) (p11.2; q25), t (X;1) (p11.2, p34) and t (X;1) (p11.2;p34) and t(X;1)(p11,2;q21), resulting in the fusion of the *TFE3* gene and the alveolar soft part sarcoma chromosome region, candidate 1 gene (*ASPL*), splicing factor proline and glutamine rich gene (*PSF*) or proline rich mitotic checkpoint control factor gene (*PRCC*) [3].

Histologically, TRCC shows a papillary structure formed by large polygonal cell with clear and eosinophilic cytoplasm resembling clear cell and papillary renal cell carcinoma [4]. It is characterized by overexpression of the modified *TFE3* gene, which can be identified by immunohistochemistry using specific antibodies targeting the C-end of TFE3 protein [5].

Management of RCC differs according to the disease stage. In local and locally advanced disease the cornerstone of the treatment plan is surgery and even in metastatic RCC the surgery plays an important role. The adjuvant treatment for RCC failed to show overall survival (OS) benefit and is not routinely used even in patients with a high risk for relapse [6].

RCC is fundamentally chemo-resistant and radio-resistant. The improved results in the treatment of metastatic RCC were observed with the initiation of targeted therapy and checkpoint inhibitors. Tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF) receptors are the cornerstone of the treatment for metastatic RCC [6,7]. These agents are approved in the first and subsequent lines of the systemic treatment in patients with metastatic clear cell RCC (ccRCC) as well as with non-clear cell RCC (ncRCC) [6,7]. Another treatment option is the use of inhibitors of mammalian target of rapamycin (m-TOR), which can be used in first-line treatment in poor risk ccRCC and/or in subsequent lines [6,7]. In ncRCC, m-TOR inhibitors may be considered in first-line treatment depending on specific ncRCC subtypes (papillary, chromophobe) [6,7]. Furthermore, in case of RCC with the mutation or the amplification of tyrosine-protein kinase (hepatocyte growth factor receptor) gene (*c-Met*), there is also a recommendation for the use of c-Met inhibitors such as crizotinib or cabozantinib [6,7]. Emerging treatment options represent the immune checkpoint inhibitors that should be considered a standard of care in first and subsequent lines of therapy, even though there are only limited data for ncRCC [6,7].

In rare subtypes, including TRCC, we are still gathering information; therefore, it is important to weigh in every aspect and knowledge to optimize and suite the therapy plan for each individual patient. Herein, we present a case of a patient who was diagnosed with TFE3 TRCC with *c-Met* overexpression and was treated with multiple targeted therapy agents and immunotherapy.

Case report

A 28-year-old woman presented with left sided abdominal pain and in 2012 and had otherwise unremarkable medical history. A routine diagnostic work-up was performed and the abdominal computed tomography scans uncovered a tumorous process of the left kidney. The tumour was located centrally in the left kidney with dimensions of 120 × 100 × 92 mm. On 27th November 2012, the patient underwent left-sided transperitoneal nephrectomy with histologic findings of TFE3 translocation renal cell carcinoma, grade 2, with c-Met overexpression, PD-L1 negativity and stage T2bN0M0. In June 2013, she observed a lump in her left supraclavicular region; after following imaging, there was diagnosed renal-bed recurrence. The left supraclavicular lymphadenopathy was surgically removed with a histologically proven metastasis of TRCC. Consecutively (September 2013), the patient started first-line treatment with multi-targeted tyrosine kinase inhibitor sunitinib, on which she achieved disease stabilisation for 5 months. In January 2014, however, CT-verified progression was observed in the renal-bed with dimensions of 40 × 39 × 80 mm. In March 2014, there was also observed progression of the metastasis in left supraclavicular region with characterisation of metastatic lymph nodes with dimensions of 15 × 13 × 10 mm and 29 × 21 × 20 mm. This was an incentive, which led to second-line treatment with everolimus, on which there was observed direct progression in supraclavicular lymphadenopathy in 2 months. In June 2014, the patient therefore started third-line treatment with sorafenib, during which she achieved disease stabilization for 18 months. After that the progression was again observed on control CT scans; thus, the patient started forth-line treatment with pazopanib lasting for 7 months. However, this treatment was not successful because of another progression in supraclavicular lymphadenopathy; therefore, the patient started crizotinib as fifth-line targeted therapy because of c-Met positivity. On this treatment, she achieved 12-month stabilization of the disease; however, in March 2018 we approached retreatment plan with sorafenib lasting 9 months because of asymptomatic progression (Fig. 1,2). During the retreatment with sorafenib, the patient developed clinical progression with uncontrollable cancer pain necessitating hospitalization and adjustment on chronic pain control with opioids. Thus, in December 2018, she started sixth-line treatment with nivolumab lasting for 6 months. Later on, the patient's status gradually worsened with the necessity for hospitalization because of progression in pain, fatigue, hydronephrosis necessitating nephrostomy of the right kidney, mineral dysbalance with metabolic acidosis, resulting in patient's death on 8th August 2019. The patient died 81 months after initial diagnosis and 74 months from the diagnosis of metastatic disease. This case report has been reported in line with the Case Reports Guidelines criteria.

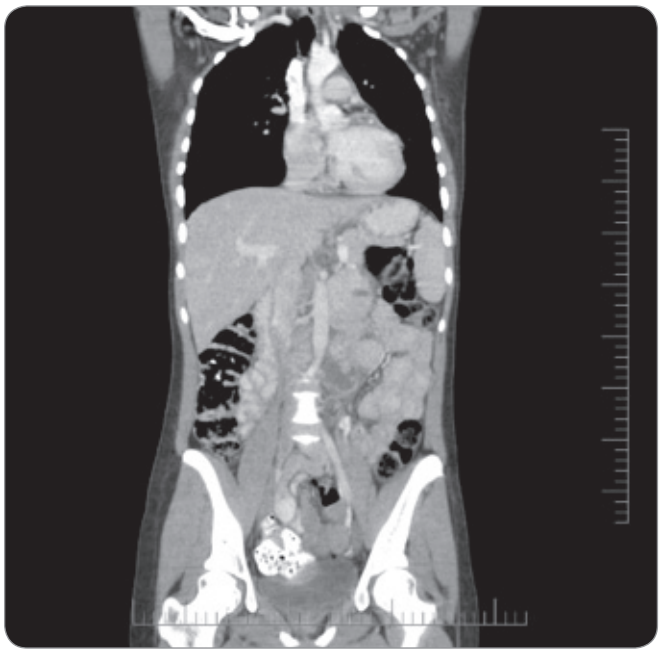

Fig. 1. CT scan showing disease progression in renal-bed.

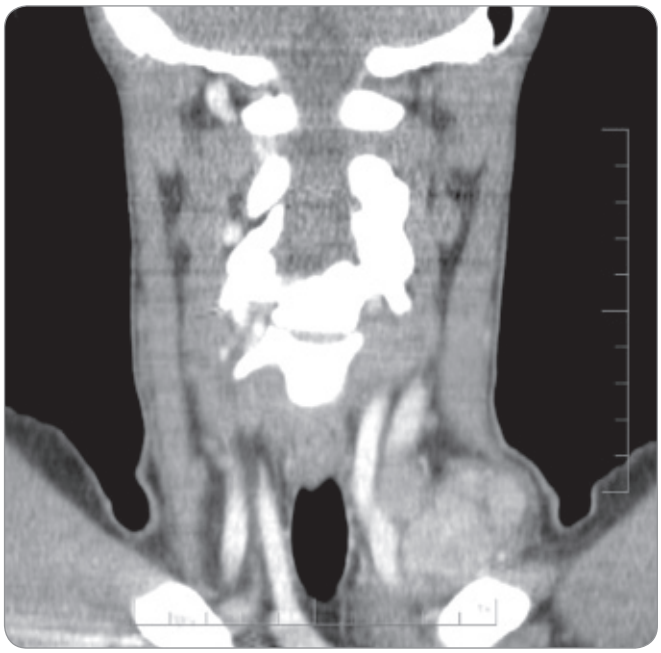

Fig. 2. CT scan showing disease progression in supraclavicular region.

Discussion

During the last decades, advances have been made regarding rare subtypes of renal cell carcinoma showing specific histopathologic and immunohistochemical characteristics. Xp11 TRCC as one of them was first described by Tomlison et al in 1991 [8]. Nowadays, it is believed to be affecting mostly children and young adults, although it may be highly under-diagnosed in adult population based on its morphologic similarity to more common RCC and more seldom use of cytogenetics in adult renal tumours compared to children [9,10].

Even though there has been an increase in the therapeutic options for either localized or metastatic renal cell carcinoma, the treatment of metastatic Xp11 TRCC remains still challenging. Currently, the recommendations for the treatment of the Xp11 TRCC are based mostly on small retrospective studies and recommendations for conventional renal cell carcinoma, as there are only limited data regarding the treatment options for TRCC [11].

Current management of localized Xp11 TRCC is similar to conventional guidelines for the treatment of RCC [9]. The surgical therapy plays a primary role and is currently focusing on organ preservation; however, this is based upon tumour localization and institutional experience [8]. The therapy of metastatic TRCC is not different from the therapy of conventional renal cell carcinoma.

In the past, there was a pursuit for chemotherapy and radiotherapy driven treatment plans; however, they proved to be ineffective. Later, researchers tried to implement cytokine therapy with the use of interferon α and interleukin-2, but they did not deliver a significant response either [3,12]. In the study by Malouf et al [11], they analysed the results of targeted therapy using VEGF or mTOR inhibitors in 21 patients with metastatic Xp11.2 renal cell carcinoma. The objective therapeutic response was observed in 7 (33.3%) patients receiving targeted therapy with VEGF or mTOR inhibitors. When sunitinib was used as first-line treatment, the median progression free survival (PFS) was 8.2 months compared to that of 2 months for cytokine therapy. When a VEGF inhibitor was used in subsequent treatment lines, patients achieved median PFS of > 6 months.

Choueiri et al [9] explored in their study the potential treatment efficacy of TRCC aiming at VEGF with sunitinib. Sunitinib was administered to 10 out of 15 patients in this study, 3 patients received sorafenib, 1 patient bevacizumab and 1 patient ramucirumab. Three (20%) patients achieved a partial response, seven (46.7%) patients had a stabilised disease and progression was observed in five (33.3%) patients. Median PFS was 7.1 months for the entire cohort with OS 14.3 months.

TFE3 TRCC is believed to have indolent course; however, there are data, including the study by Choueiri et al, showing more aggressive disease course with a shorter OS in adults compared to younger population affected by Xp11 TRCC [3,13]. In the work by Meyer et al [13], the mean life expectancy was 18 months following the diagnosis. When we compare this data to the current 5-year disease specific survival in the metastatic RCC projected by European Society for Medical Oncology based on the prognostic group, which is 0–32%, we can see the difference and higher aggressiveness of this RCC subtype in adult population [6].

Crizotinib is a multi-targeted tyrosine kinase inhibitor with a small molecule inhibiting the proto-oncogene tyrosine-protein kinase *ROS, c-Met, ALK* phosphorylation and signal transduction. This inhibition is associated with cell cycle arrest in G1 phase of the cell cycle and in-

duction of apoptosis [14]. The role of this inhibitor has not been previously studied among patients with Xp11 TRCC. We observed prolonged disease stabilization lasting for 12 months; however, no tumour shrinkage was observed [6].

Immune checkpoint inhibitors represent a novel class of drugs used in metastatic RCC, although similarly to targeted therapy, experience in metastatic TRCC is limited. In multicentre retrospective analysis, Boilève et al observed similar efficacy of the immune checkpoint inhibitors in TRCC compared to ccRCC [15,16].

Conclusion

In this case report, we present a case of 28-year-old female patient diagnosed with c-Met positive TFE3 translocation renal cell carcinoma. The prognosis of Xp11 TRCC is considered to be indolent; however, we observe more aggressive disease course in adults. Even though TFE3 TRCC is more aggressive in adults, our patient was treated for 7 years consecutively with five lines of targeted therapy and one line of immunotherapy. The best therapeutic response was observed with the use of sorafenib for 18 months and later with re-challenge for 9 months. Because of the *c-Met* mutation, we have attempted the treatment with c-Met inhibitor crizotinib in the fifth line and our patient has achieved disease stabilization for 12 months. To our knowledge, the use of crizotinib in Xp11 TRCC is described in the scientific literature for the first time. It may present a potential role in the treatment plan for either TRCC or for other types of RCC as well.

We conclude that the long survival of our patient may be regarded towards indolent course of the disease, but also towards the successful use of multiple targeted therapies. However, it is necessary to acquire further knowledge of this rare subtype of RCC to identify new treatment targets.

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