Papillary renal cell carcinoma – case report of a patient with disseminated disease treated with pazopanib with several years of survival against reviewing current literature

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ABSTRACT

Papillary renal cell carcinoma is the second most common histological type of renal cell carcinoma with distinct cytogenetics, histology and prognosis. It exhibits significantly poorer response to molecular targeted therapies, which are about the progress in clear cell carcinoma. We present an overview of the treatment trials and report a casuistic case of metastatic disease controlled for several years with pazopanib.

KEY WORDS: papillary renal cell carcinoma, molecular targeted therapies

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PAPILLARY RENAL CELL CARCINOMA – PATHOGENESIS, CLINICAL FINDINGS, THERAPY

Papillary renal cell carcinoma constitutes about 7–15% of cases of renal cell carcinoma, so it is the second most common type of cancer after clear cell type. It is separate cytogenetically, histologically and prognostically from clear cell carcinoma. It consists of two subtypes: subtype 1 and having a worse prognosis subtype 2 [1, 2]. It is more common in men, patients with acquired cystic kidney disease and those undergoing dialysis for chronic renal failure [3, 4]. Basically it develops as a single tumor, but more often than other types is multifocal and bilateral [3].

Cancer is composed of cells grouped around the capillary vessels, forming the papillary and tubulopapillary structures. Type 1 is characterized by cells with scant cytoplasm, arranged in a single layer while type 2 has large cells with eosinophilic cytoplasm. The psammomatous bodies are typically present in the papillas stroma. Type 1 (73%) of the definition is referred to the first grade (G1) according to Fuhrman staging, while type 2 corresponds with higher degrees of malignancy [2, 3].

Immunohistochemistry reveals expression of cytokeratin CK7 (type 1) and CK20 (type 2), absent in clear cell carcinoma and expression of AMACR (P504S) [3].

In terms of etiopathogenic, in sporadic cases usually trisomy of 7^{th}, 12^{th}, 16^{th}, 17^{th}, 20^{th} chromosomes is detected as well as the loss of the Y chromosome and translocation t(X;1) comprising the gene *PRCC* in 1^{st} chromosome. Hereditary disease, representing only 4%, is associated with two syndromes: hereditary papillary renal carcinoma inherited as autosomal dominant with a germline mutation in the *MET* gene on chromosome 7^{th} (7q31) and congenital leiomyomatosis with renal cell cancer (HLRCC, hereditary leiomyomatosis and renal cell cancer) passed as autosomal dominant, linked to the mutation in the gene *FH* (fumarate hydratase) [2, 3, 5, 6]. Papillary renal cell carcinoma in contrast to clear cell carcinoma is not associated with mutations in tumor suppressor gene Von Hippel–Lindau (*VHL*) [7, 8].

Significant progress that has been made in the treatment of advanced kidney cancer focuses on the most common subtype which is clear cell carcinoma. The so-called nonclear cell histological types of the disorder respond much less to novel therapies [6, 7, 9].

In the AVOREN study (phase III trial of bevacizumab + interferon α-2a vs. interferon α-2a in the treatment of metastatic renal cell carcinoma) distinguished group of patients was diagnosed with mixed histology cancer, taking into account the papillary carcinoma. These patients benefited from treatment with a combination of bevacizumab + interferon α-2a compared with interferon α-2a (PFS 5.7 months vs. 2.9 months), however, the response was lower than in patients with clear cell histology [10]. In the expanded access study with sunitinib 13% of the patients presented nonclear-cell histology with no division into subtypes, the response rate (RR, response rate) was 11% and median time to progression (PFS, progression-free survival) was 7.8 months [11]. In a small second phase study also with sunitinib, 20 patients with nonclear-cell cancer were included, 13 with papillary cancer among them. There were no objective responses and median PFS was 48 days [12]. In turn, in a retrospective analysis of 53 patients with nonclear-cell histology and 41 (77%) of papillary histology among them, the response rate for sunitinib and sorafenib in the first or second line of treatment was 15% and median PFS – 7.6 months. The subgroup analysis for papillary histology the longest median PFS of 11.9 months as a result of sunitinib treatment was demonstrated [13].

The expanded access study with sorafenib included 158 of 2504 patients (6.4%) with papillary cancer and the response rate was only 3% [14].

In a study evaluating the efficacy of temsirolimus in the first line treatment of patients with unfavourable clinical factors there was a group of 55 patients with papillary carcinoma, wherein the median PFS was 7 months and was similar to that parameter for the entire treated population [15]. In RAPTOR study with everolimus where 83 previously untreated patients were evaluated, the median PFS was 7.6 months in the assessment of individual centers and only 3.7 months after central verification [16]. In turn, in REACT study, where everolimus was assessed in the second line treatment, 75 patients (5.5%) had nonclear-cell histology with no subtype division. The response rate was 1.3% (vs. 1.7% in the overall population) and the median length of treatment was 12.14 weeks (vs. 14 weeks), it was rated that the drug is active in patients with nonclear-cell histology.

In the illnesses occurring in the families and to a lesser extent in sporadic cases MET pathway disturbances play an important role in the pathophysiology of papillary carcinoma type 1 and 2. In the preclinical models of this condition MET inhibitors proved its activity [6, 7, 17, 18]. Phase II trial with foretinib – MET and VEGFR2 inhibitor, in which 74 patients were treated, showed a 13.5% response rate and median PFS of 9.3 months [6, 8, 18].

Also EGFR (epidermal growth factor receptor) pathway is tested as a potential molecular target of therapy in papillary carcinoma. Preclinical data suggest that the absence of *VHL* mutation is associated with increased activity of EGFR inhibitors in papillary carcinoma. The Southwest Oncology Group in the second phase study tested erlotinib in a group of 39 patients with papillary carcinoma where the absence of *VHL* mutation is typical. Median follow-up time was 12.8 months, 4 patients achieved a partial response with 10% of overall response rate. Very encouraging median overall survival (OS) of 26.9 months was reported, however serious side effects in the form of pneumonia in 5th grade and 4th grade thrombocytopenia CTCAE (Common Toxicity Criteria for Adverse Events) were observed. *EGFR* mutation status and *EGFR* gene amplification seem to play a role in predicting the clinical efficacy of anti-EGFR therapy in renal papillary carcinoma, as they do in other cancer types [19].

The latest concept is to combine the MET and EGFR pathway blockades to achieve the synergistic effect. This task has taken up The Southwest Oncology Group in the second phase study with MET ARQ 197 inhibitor (tivantinib) alone and in combination with erlotinib [6, 7]. This project joined several other studies aimed to demonstrate the activity of molecular targeted therapies (bevacizumab + erlotinib, crizotinib, cabozantinib, bevacizumab + everolimus, pazopanib, rilotumumab, volitinib) in the papillary renal cell carcinoma [6, 7].

Studies on the expression of PD-L1 (programmed death ligand 1) in the tumor cell membranes and cells with single nucleus infiltrating tumour stroma in nonclear-cell renal cancer revealed a positive relationship between the intensity of PD-L1 expression and worse prognosis, advanced clinical stadium and greater degree of malignancy [20]. Papillary carcinoma accounted for 10% of the study group. Several monoclonal antibodies anti-PD-1 (programmed death-1) or its ligand (PD-L1) are currently under investigation [6].

CASE REPORT

Because of haematuria in 56-year-old man, smoker approximately 30 pack-years, suffering from chronic obstructive pulmonary disease, hypertension and spine osteoarthritis, abdominal cavity ultrasound was performed. The study found a tumor of the left kidney size approximately 20 × 13 cm. In January 2010 a radical left-sided nephrectomy was carried out. Obtained histopathological diagnosis was: papillary renal cell carcinoma G2; necrosis accounted for 40% of the tumor volume, tumor was within the capsule, the light of renal vein was filled with a plug of tumor cells. 10 months after nephrectomy in computed tomography scans a nodule in the middle lobe of the right lung and two subsequent ones in basal segments of the left lung were found, none of them exceeded 10 mm in diameter. Then ultrasound of the abdomen was performed and revealed focal lesion in the 3rd segment of the liver and pathological mass of several centimeters in the nephrectomy lodge. This clinical picture was interpreted as a spread of papillary renal cell carcinoma and after obtaining the informed consent of the patient, a refund of the therapy with pazopanib was applied. The choice of pazopanib from other VEGFR (vascular endothelial growth factor receptor) inhibitors was imposed by administrative considerations applicable at that time in Poland, which made it possible to obtain a refund of just drug, despite the lack of registration in such indication. The patient remained in good performance status without evidence of organ failure in performed laboratory tests. Treatment was started in February 2011 at a dose of 800 mg per day. During treatment adverse events in the form of diarrhea in 1st grade of CTC, neutropenia and thrombocytopenia in 1st grade of CTC were observed in the first two years of therapy. They did not require dose adjustment. To date, the patient has received 62 cycles of pazopanib, of 30 days each, 800 mg per day, so he is treated more than 5 years and tolerates the treatment very well. The result achieved is a stable disease by RECIST (Response Evaluation Criteria in Solid Tumors) in computed tomographies performed every three months.

SUMMARY

Papillary renal cell carcinoma is the second most common histologic subtype of renal cell carcinoma and has a distinct molecular basis from clear cell carcinoma. Inhibition of MET pathway alone or in combination with EGFR and VEGFR pathways inhibition sets the direction for further exploration of effective therapy of that type of cancer. The promising research on "targeted immunotherapy" on PD-1/PD-L1 inhibition also emerged.

The presented case against data available in the international literature should be considered as casuistic. It illustrates several years of effectiveness of multipotent VEGFR tyrosine kinase inhibitor – pazopanib in controlling metastatic disease, excellent tolerability, easily accepted mild side effects, enabling the patient to conduct a lifestyle not impaired by the treatment. It is a contribution to the further research on the effectiveness of molecular targeted therapies in that genetically, histologically and clinically separate type of renal cell carcinoma.

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Authors' contributions:
Agnieszka Buraczewska: 90%
Joanna Kardas: 10%.