Long-term response with everolimus for metastatic renal cell carcinoma refractory to sunitinib-sorafenib sequence

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ABSTRACT

We presented a 39-year-old male who developed progressive cancer disease 4 years after nephrectomy due to clear cell carcinoma. He was diagnosed with locally reccurence and metastases to the liver, spleen and abdominal muscles. The patient was treated with sunitinib and then after disease progression – with sorafenib. We observed 18 months of cancer control (TKI-TKI). After second progression everolimus was administered. Third line everolimus therapy helped to achieve durable stable disease with PFS 46 months till now (May 2015). The patient remains in very good performance status with minimal toxicity from the regimen. This case illustrates a long term survival for patients with metastatic renal cell carcinoma, a malignancy with historically poor prognosis. The use of three sequential targeted therapies (TKI – TKI – mTORi) helped to achieve over 5 years or disease control, with rarely seen long-term response to third line treatment (mTORi) – where stabilization is good enough. We discussed therapeutic strategies in metastatic renal cell carcinoma according to the literature and therapeutic possibilities in Poland.

KEY WORDS: clear cell carcinoma, metastatic renal cell cancer, mTOR inhibitor (mTORi), tyrosine kinase inhibitor (TKI), progression free survival (PFS), overall survival (OS)

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CASE PRESENTATION

39-year-old male reported at the beginning of June 2005 to the emergency room because of hematuria. So far, the patient hasn't been treated for a chronic diseases. An urgent ultrasonography examination (USG) of the abdomen was made. It revealed large solid tumor in the upper part of the left kidney with smooth, polycyclic outlines – the largest dimension of the tumor was 115 mm. The left renal vein was slightly extended with faint flow and the urinary bladder was filled with large blood clots. A CT scan of the abdomen revealed the tumor in the upper pole of the left kidney with a diameter of 126 mm with calcifications in the central part. The tumor has not infiltrated beyond the perirenal capsule. In June 2005, the patient has undergone left-sided nephrectomy. The entire tumor of approx. 11–15 cm with left kidney was dissected. The specimen was explored – there was no clot or tumor invasion in the renal vein and the tumor was filled with atheroma's contents. The left adrenal gland was resected. Microscopic examination revealed clear cell renal carcinoma (Grade 2, pT2). The surgery was microscopically radical (R0).

The patient remained in observation until December 2009. Then USG of the abdomen was performed. He was found three focal lesions in the liver – max. 30 mm in dimension – suspected of metastasis. MRI of the abdomen showed recurrence in the area of nephrectomy (8 mm), focal lesions within the muscles of abdominal wall (18 mm) and in adipose tissue of the abdomen (15 mm), the solid focus in the spleen (23 mm) and a numerous metastases in right lobe of the liver (max. to 30 mm).

The patient remained in very good condition (100% according to Karnofsky scale), the physical examination did not reveal abnormalities, BMI was 26.6 kg/m^2 and BSA 2.11. Within basic laboratory tests (ECG, blood morphology and biochemistry, urinalysis) only hypercholesterolemia 243 mg/dl (N: 120–200 mg/dl) and low level of TSH were beyond the norm. But FT_3, FT_4 were in the normal range (in 2008 the patient undergone fine-needle biopsy of the lump in thyroid gland: the examination revealed cytological changes as in nodular goiter). The patient met the criteria of eligibility for a therapeutic program of National Healthcare Fund – treatment with sunitinib for metastatic renal cell carcinoma. In December 2009, the patient began systemic treatment – sunitynib 50 mg per day in the typical scheme 4/6 weeks. Tolerance of the treatment was clinically very good – the patient reported no complaints. There was no abnormalities in the physical examination. In blood analysis we observed mild leukopenia with neutropenia (grade 2 CTCAE v4), trace protein in urine and an increase in serum creatinine level (1.4 mg/dl, N: 0.5–1.2) with eGFR 58 ml/min/1.73 m^2 (2 degree of toxicity according to CTCAE v4 – the Common Terminology Criteria for Adverse Events version 4). The patient received 4 courses of treatment with sunitinib. In June 2010, MRI of abdomen showed enlargement of all metastases in the liver – disease progression was diagnosed and the treatment with sunitinib was ended. Considering no other therapeutic options at that time, we have been requested to the National Health Fund for financing of treatment with sorafenib as the part of chemotherapy funding beyond the standard catalog. We received a refusal, because our patient didn't meet the criteria for inclusion in the therapeutic program with sorafenib due to progression after TKI. In August 2010, the patient started taking sorafenib (purchased from his own resources). The control MRI of the abdomen performed in November 2010 showed stable disease, compared to MRI made in August 2010. The scan revealed several metastases in the liver to max. 67 mm and numerous minor without dynamics. Other targets were stable. In most of the metastases the features of degradation were marked. Again, we have been requested to the National Health Fund for financing of treatment with sorafenib given its effectiveness in our patient. And again we received refusal. The patient tolerated the therapy very well, there was no abnormalities in the clinical examination. Laboratory tests showed mild neutropenia (1 degree CTCAE v.4), but there was no need to modify the dose of the drug.

In July 2011, MRI showed again disease progression – previously existing metastases in the liver increased up to 72 mm and new lesions appeared, the recurrence in the area of nephrectomy increased up to 25 mm. Therefore we requested to the National Health Fund for funding everolimus therapy according to registration indications (registration in the EU in August 2009). In August 2011 the patient began everolimus therapy 10 mg per day, which continues to the present day (May, 2015). The therapy is very good tolerated – the patient is professionally active and plays sports. The clinical examinations show no abnormalities. In the laboratory tests hyperlipidemia (Ch: 327 mg/dl, N < 200, T: 423 mg/dl, n < 165) and increased creatinine level (1.3 mg/dl – 1 degree of toxicity by CTCAE v 4) are observed. In control MRI of the abdomen we observe metastases with variable dynamics and no new lesions – the criteria of stable disease by RECIST 1.1 are met. Chest X-ray finds no change.

Till this time (May 2015) the patient is being treated with everolimus as part of chemotherapy funding beyond the standard catalog – patient is not eligible for the therapeutic program of National Health Fund because of a history of treatment with

two drugs from the group of TKI. The patient is treated with everolimus constantly (46months), had a short breaks in treatment due to the expectation for the approval of the National Health Fund to continue to fund the treatment (the approval needs to be prolonged every 3 months).

DISCUSSION

Renal cancer is a rare malignancy – barely 2–3% of all malignant neoplasms. Over the past decades the increase in the incidence of renal cell carcinoma is observed, which is due to widespread diagnostic imaging – mainly ultrasonography. Renal cell carcinoma limited to the kidney is usually asymptomatic and is detected incidentally on the occasion of diagnostic imaging performed for other reasons. This situation affects approximately 40–60% of patients [1, 2]. Symptoms appear when the disease is advanced locally (about 15% of cases) – in such cases a common symptom (60%) is microscopic or macroscopic hematuria. In about 20% of patients the disease is diagnosed in the metastatic stage (mRCC, metastatic renal cell cancer) – in such cases location of metastases results in specific symptoms. The only effective treatment in the disease limited to the kidney or locally advanced disease is surgery – nephrectomy or NSS (nephron sparing surgery) under certain conditions. Only a decade ago the patient with the diagnosis of mRCC was directed to the palliative care or was offered the therapy with interferon with a small benefit. Few patients were qualified to participate in sponsored clinical trials. We now live in an era of molecular targeted therapy – by knowing some of the mechanisms responsible for carcinogenesis, angiogenesis, tumor invasiveness and metastasis. Therapeutic possibilities for the treatment with molecular targeted drugs relate to patients with renal cell carcinoma in metastatic stage. In clinical practice, patients referred for molecular targeted therapy are qualified according to predictive Motzer scale – the so-called MSKCC classification (Memorial Sloan-Kattering Cancer Center) by Motzer [3]. The scale, originally fixed for patients taking immunotherapy with interferon, includes 5 clinical prognostic factors: Karnofsky performance status < 80%, corrected calcium level > 10 mg/dl, LDH > 1.5x upper limit of normal, anemia and the time since the original diagnosis up to 12 months. Patients with two or less prognostic factors are classified as favorable or intermediate prognostic group and they, after previously performed nephrectomy, benefit from treatment with molecular targeted therapy.

A characteristic feature of renal cell carcinoma is increased angiogenesis determined by high expression of vascular endothelial growth factor (VEGF). Understanding the function of the VEGF proteins family and the VEGF receptors led to invent targeted drugs, which inhibit these proteins. The VEGF proved to be a target for monoclonal antibody bevacizumab (registered in 2005 by EMA – European Medicines Agency). Bevacizumab added to interferon versus interferon alone prolonged progression free survival (PFS) and increased response rate [4]. VEGF receptor was the target for small-molecule tyrosine kinase inhibitors (TKI) – sunitinib, sorafenib, pazopanib, axitinib (registered by EMA in 2006, 2006, 2010, 2012 respectively). The mechanism of TKI is not only selective for VEGF receptors, which explains different toxicity profile. Sunitinib (registered in 2006 by EMA) proved to be more effective drug compared with interferon (PFS 11vs 5 months, mOS: 22 vs 26 months) in first line treatment [5]. Sorafenib (registered in 2006 by EMA) administered after failure of immunotherapy with cytokines significantly prolonged PFS (5.5 vs 2.8 months) [6] and OS [7], compared to placebo (impact on OS was presented in the additional analysis). Pazopanib (registered in 2010 by EMA) used in first-line therapy of mRCC compared to placebo significantly prolonged PFS (11 vs 3 months), without affecting the OS (the study design approved the use of the study drug after progression on placebo) [7]. Pazopanib used after failure of cytokine immunotherapy versus placebo was superior in PFS (7 vs 4 months), without affecting the OS (pazopanib was administered to patients progressing after placebo) [8]. Axitinib (registered in 2012 by EMA) as the second-line treatment prolonged PFS compared to sorafenib in patients receiving earlier sunitinib (4.8 vs 3.4 month) or interferon (12.1 vs 6.5 month) [9]. Another molecule of interest turned out to be a serine threonine kinase mTOR (mammalian target of rapamycin) inhibitor. It plays an important role in promoting the development of RCC. The mTOR inhibitor everolimus was registered as a drug effective in patients with metastatic renal cell carcinoma whose disease had progressed during the treatment with one or two TKI. The registration trial proved improvement in PFS compared with placebo (PFS 5.4 vs 1.9 months in the group of patients with progression after VEGF-1 TKI and PFS 4.0 vs 1.8 months in the group progressing after > 1 VEGF-TKI) [10, 11]. It seems that the first line treatment in mRCC is a choice between sunitinib and pazopanib. A phase III trial comparing these two drugs showed no difference in PFS and OS, drugs differed only in toxicity profile [12, 13]. Adverse events characteristic for the TKI group are hypertension, cardiovascular events, hypothyroidism, skin lesions, digestive disorders, hematologic toxicity. The treatment last line (2nd or 3rd, depending on the history of treatment with cytokines) is now a choice between axitinib and everolimus – there is no data on the superiority of a particular treatment (no study comparing

these two molecules). Some authors claim that this choice should be determined by the time of response for first line TKI. In case of long-term response we should use a next line TKI and in short-term responders we should use an mTOR inhibitor [14, 15]. Metaanalyzes present greater benefit (OS, PFS) from a sequence TKI–mTOR than TKI–TKI. However, these analyzes include limited data from the axitinib treatment [16]. Further prospective studies are needed. Adverse events of everolimus are mucositis (stomatitis, diarrhea), fatigue, pulmonary disorders (non-infectious pneumonitis), metabolic disorders and hematological toxicity.

When choosing the next line treatment for our patient with mRCC, an individual approach seems to be reasonable – according to patients general condition and its comorbidities. It should be the drug, which potentially will not worsen the quality of life of the patient and which the side effects we can cope with [17].

CONCLUSION

We present a young patient with clear cell carcinoma originally limited to the left kidney. He underwent nephrectomy and after 4 years he developed metastatic disease within the abdomen. The patient had no comorbidities and is in favorable prognostic group according to the Motzer scale. The patient started palliative treatment with sunitinib in December 2009 – as part of a therapeutic program of National Health Fund. He had no significant side effects beyond mild neutropenia (without hypertension and hypothyroidism which is a good predictor of response to TKIs). After 6 months of treatment with SUTENT the disease progressed – lesions in the liver enlarged (PD according Recist 1.1). Considering no other therapeutic options at that time, the patient began treatment with sorafenib and still had no side effects typical for TKI. After 12 months of treatment with sorafenib disease progression was diagnosed (new lesions in the liver). The patient had 18months of disease control using two TKIs. From August 2011 to the present (May 2015) the patient has been treated with everolimus. The patient is monitored by MRI of the abdomen and chest X-ray without evidence of metastatic disease above the diaphragm. Metastases in the liver are large (up to 98 mm) – with variable dynamics during several years of therapy. There are no new lesions inside the abdomen. The criteria of progressive disease (PD) by RECIST 1.1 are not met – patient is continuing treatment. In clinical practice not rarely we observe long-term survival of patients with mRCC treated with TKI in the first or second line. Only few reports describe cases of long term responders to the treatment with mTOR inhibitor. 46 months of PFS happens extremely rarely (the registration trial has shown 4 months PFS in the group of patients after 2 TKIs). The stabilization as the best response to the treatment is typical for this class of drugs and correlates with previous observations. The patient remains in very good condition with minimal toxicity from the regimen. He is the longest treated patient, with a full dose of 10 mg everolimus and without clinical toxicity, among patients treated in our clinic.

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Conflict of interest: nothing to declare.

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Authors' contributions:
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