Efficacy of new molecularly targeted drugs in the treatment of renal cell carcinoma (RCC), confirmed in clinical studies in relation to survival and prolongation of time to progression, has become a big chance for patients with metastatic renal cell cancer. Axitinib is a potent and selective receptor tyrosine kinase for vascular endothelial growth factor (VEGFR-1, -2, -3), platelet-derived growth factor β (PDGRF-β) and c-KIT.

This is a case report of a 57-year old female patient with a history of left nephrectomy due to clear cell renal cell carcinoma. The patient had received three prior systemic treatments (interferon – sorafenib – everolimus). After consecutive progression the patient was qualified to 4th line therapy – axitinib at a dose of 5 mg twice daily. Partial response to treatment was achieved. After 6 months therapy was stopped due to the disease progression. The total time to progression was 37.5 months. The total survival time from the disease diagnosis was 45 months.

Based on literature date and own experience we showed that sequential treatment RCC is associated with improved survival. In summary, axitinib may be an effective drug after failure of tyrosine-kinase inhibitor (TKI) therapy in previous lines of therapy.

Key words: renal cell carcinoma, sequential therapy, axitinib, targeted therapies.

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Axitinib in sequential therapy in metastatic renal cell carcinoma

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Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of all malignancies. Males predominate among patients (1.5 : 1) and peak incidence is between 60 and 70 years of age [1]. At the time of diagnosis disseminated disease is found in 30% of patients. Lungs, bones, liver and brain are the most common locations of distant metastases of RCC. Disseminated renal cell cancer is considered as incurable disease; average patient survival in the era of targeted therapy is approximately 7.8–43.2 months (depending on the Database Consortium Model risk group) and 5-year survival rate is 0–13% [2, 3].

Recent studies demonstrated that metabolic pathways associated with membrane receptors for growth factors play an important role in RCC etiology and proteins of tyrosine and serine-threonine kinase activity have become a new therapeutic target as well as monoclonal antibodies. Efficacy of new molecularly targeted drugs (sorafenib 2005, sunitinib 2006, temsirolimus 2007, bevacizumab 2009, everolimus 2009, pazopanib 2009, axitinib 2012) in the treatment of RCC, confirmed in clinical studies in relation to survival and prolongation of time to progression, has became a big chance for patients with metastatic renal cell cancer [4–8].

Case report

This is a case report of a 57-year old female patient with a history of left nephrectomy due to clear cell RCC in December 2008. The patient was in favorable prognostic categories according to Motzer et al. The patient had no family history of malignant neoplasm and no history of chronic diseases. Due to metastatic disease (metastases in lungs), interferon immunotherapy was used as a first line therapy. The best response to treatment was partial regression according to RECIST criteria (version 1.0). After 11 months immunotherapy was stopped due to the disease progression – enlargement of existing lesions. In April 2010 the patient was qualified to 2nd line therapy with a tyrosine kinase inhibitor (sorafenib). The patient received a total of 8 chemotherapy courses. The response to treatment was stable disease according to RECIST criteria (version 1.0). After 11 months immunotherapy was stopped due to the disease progression – enlargement of existing lesions. In April 2010 the patient was qualified to 2nd line therapy with a tyrosine kinase inhibitor (sorafenib). The patient received a total of 8 chemotherapy courses. The response to treatment was stable disease according to RECIST criteria. In December 2010, due to the disease progression – appearance of new focal lesions in the liver, the patient was qualified to 3rd line therapy using a selective mTOR inhibitor (everolimus). Marked toxicity was observed during the therapy – anemia grade 3 according to CTC AE that required transfusion of packed red blood cells. The treatment was stopped after 13 courses in January 2012 due to the disease progression – appearance of new lesions in lungs, left adrenal gland and the skeletal system. The patient underwent palliative radiotherapy on the tumor site, 11th rib in January 2012, and then in June 2012 on central nervous system (CNS) area due to focal lesions located in the right parietal and temporal lobes and in the right cerebellar hemisphere. In May 2012 the patient started a 4th line therapy, axitinib at a dose of 5 mg twice daily. Partial response to treatment
was achieved. The treatment was stopped in November 2012 due to the disease progression. The total time to progression was 37.5 months (Fig. 1). The patient died in December 2012. The total survival time from the disease diagnosis was 45 months.

The treatment was carried out in accordance with NCCN (National Comprehensive Cancer Network) recommendations and with polish National Health Service.

**Discussion**

In January 2012, basing on AXIS study, another drug was approved in the USA for the treatment of an advanced RCC after failure of one line of therapy – axitinib. Axitinib is a potent [50–450-fold more potent that previously used vascular endothelial growth factor receptor (VEGFR) inhibitors] and selective receptor tyrosine kinase for VEGFR-1, -2, -3, platelet-derived growth factor β (PDGFR-β) and c-KIT [9–11]. Axitinib was shown to potently inhibit VEGF-dependent proliferation and survival of endothelial cells. In blood vessel of a tumor xenograft, axitinib inhibits phosphorylation of VEGFR-2 that is expressed at the target site in vivo and retards tumor growth, results in regression and inhibition of metastases in multiple experimental models of tumors [12]. Table 1 shows summary of clinical trials of axitinib in metastatic renal cell carcinoma.

AXIS was the first phase 3 study of axitinib in the renal cell cancer. This study enrolled 723 patients with an advanced renal cell cancer who progressed during or after a first line therapy. Three hundred and eighty-nine (53.8%) of these patients previously received sunitinib based therapy, 251 (34.7%) a cytokine based therapy (interleukin-2 or interferon α), 59 (8.2%) bevacizumab based therapy, 24 (3.3%) temsirolimus based therapy. The patients were randomized in 1 : 1 ratio to groups receiving axitinib (n = 361) or sorafenib (n = 362). The primary end point of this study was progression free survival (PFS), while overall survival (OS) was secondary end point. In the whole study population, a statistically significant benefit was found for axitinib versus sorafenib with regard to the primary end point (6.7 vs. 4.7 months, HR = 0.66; p < 0.0001). In the subgroup analysis axitinib was more effective than sorafenib in patients receiving cytokines (12.1 vs. 6.5 months; HR = 0.46; p < 0.0001) and sunitinib (4.8 vs. 3.4 months; HR = 0.71; p = 0.01) as the first line therapy. No statistically significant differences with regard to PFS between the study groups were found for patients previously treated with bevacizumab or temsirolimus. No statistically significant differences with regard to the secondary end point (OS) were found between the study arms both in the whole population as well as in the subgroups defined by previous therapy. Rate of grade > 3 toxicity according to CTCAE was similar in both groups. Hand foot syndrome was more common in patients treated with sorafenib (16% vs. 5%), while diarrhea (11% vs. 7%) and hypertension (16% vs. 11%) were more common in patients treated with axitinib. The treatment was stopped due to toxicity in 4% of patients receiving axitinib and in 8% of patients receiving sorafenib.

A phase 2 study that assessed efficacy and safety of axitinib in 52 patients was published in 2007 [13]. The drug was administered as the 2nd line therapy in patients with advanced renal cell cancer who stopped treatment with interferon α, interleukin-2 or both these drugs due to the disease progression or unacceptable toxicity. Twenty-two patients belonged to the group with favorable prognosis, while 30 to intermediate one. Median time to progression was 15.7 months, and median overall survival time was 29.9 months. Two complete responses to treatment were observed and 21 partial responses, accounting for overall objective response rate of 44.2% (95% CI: 30.5–58.7). An average duration of response was 23 months. Despite the fact that 28 patients experienced grade 3 or 4 toxicity, they were managed and controlled through modifications of the drug dose and supportive therapy.

Another phase 2 study conducted in 2009 proved effectiveness of axitinib therapy in patients with an advanced renal cell cancer. This study enrolled 723 patients with an advanced renal cell cancer who progressed during or after a first line therapy. Three hundred and eighty-nine (53.8%) of these patients previously received sunitinib based therapy, 251 (34.7%) a cytokine based therapy (interleukin-2 or interferon α), 59 (8.2%) bevacizumab based therapy, 24 (3.3%) temsirolimus based therapy. The patients were randomized in 1 : 1 ratio to groups receiving axitinib (n = 361) or sorafenib (n = 362). The primary end point of this study was progression free survival (PFS), while overall survival (OS) was secondary end point. In the whole study population, a statistically significant benefit was found for axitinib versus sorafenib with regard to the primary end point (6.7 vs. 4.7 months, HR = 0.66; p < 0.0001). In the subgroup analysis axitinib was more effective than sorafenib in patients receiving cytokines (12.1 vs. 6.5 months; HR = 0.46; p < 0.0001) and sunitinib (4.8 vs. 3.4 months; HR = 0.71; p = 0.01) as the first line therapy. No statistically significant differences with regard to PFS between the study groups were found for patients previously treated with bevacizumab or temsirolimus. No statistically significant differences with regard to the secondary end point (OS) were found between the study arms both in the whole population as well as in the subgroups defined by previous therapy. Rate of grade > 3 toxicity according to CTCAE was similar in both groups. Hand foot syndrome was more common in patients treated with sorafenib (16% vs. 5%), while diarrhea (11% vs. 7%) and hypertension (16% vs. 11%) were more common in patients treated with axitinib. The treatment was stopped due to toxicity in 4% of patients receiving axitinib and in 8% of patients receiving sorafenib.

**Table 1. Summary of clinical trials of axitinib in metastatic renal cell carcinoma**

| Authors          | Phase | Number of patients | Prior therapy | Median PFS (months) | Median OS (months) |
|------------------|-------|-------------------|---------------|---------------------|--------------------|
| Rixe et al. (2007) | II    | 52                | cytokines     | 15.7 (95% CI: 8.4–23.4) | 29.9 (20.3–NR)     |
| Rini et al. (2009) | II    | 62                | sorafenib ± other | 7.4 (95% CI: 6.7–11.0) | 13.6 (95% CI: 8.4–18.8) |
| Rini et al. (2011) | III   | 723               | sunitinib other cytokines ± bevacizumab other temsirolimus | 6.7 (95% CI: 6.3–8.6) | NR |

CI – confidence interval; NR – not reached; PFS – progression-free survival; OS – overall survival
renal cell cancer with a history of sorafenib therapy [14]. The study enrolled 62 patients. For 29% of patients it as a 3\textsuperscript{rd} or higher line of therapy with antiangiogenic drugs, while all patients previously received sorafenib therapy. Partial response to treatment was observed in 14 (23%) patients, while stable disease in 11 (18%) patients. An average time to progression was 7.4 months, while an average overall survival time was 13.6 months.

The treatment toxicities were, as in the previous study, controlled and managed through modifications of the drug dose and supportive therapy.

Results of previously conducted studies indicate that sequential use of tyrosine kinase inhibitors (TKI) does not induce cross resistance. On the other hand, it may even overcome resistance to a previously used TKI. Tolerance and toxicity of sequentially used drugs is similar to that encountered for each drug used alone. Furthermore, basing on growing number of retrospective analyses, each line of therapy was shown to have additive effect on PFS and overall survival time was 13.6 months.

In summary, axitinib may be an effective drug after failure of TKI therapy failure in previous lines of therapy, which is supported by this case report and retrospective analyses. This hypothesis requires confirmation in prospective, randomized clinical trials.

The authors declare no conflict of interest.

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