Aim of the study: Due to the emergence of new therapeutic opportunities in the second-line treatment of metastatic renal cell carcinoma, the choice of the appropriate medication requires consideration. Making the selection one should take into account the likelihood of response, the probability of toxicity, properties of the drug and the clinical characteristics of the patient. Aim of the work was to confirm antitumor efficacy of axitinib in patients with metastatic clear-cell renal-cell carcinoma in the second line treatment remaining under the care of our institution. The primary objective was to determine antitumor activity, secondary – to evaluate progression free survival, safety of the treatment and to analyse clinical characteristics of treated population.

Results: Treatment records of 27 patients (9 females, 18 males) treated from October 2014 to the present (July 2016) were reviewed. The median duration of treatment which corresponds to the time to disease progression in observed population was 6 months (range: under 1 month – 16 months). 1 patient (3.7%) had got objective response (PR, partial remission). Clinical benefit rate (PR + SD (stable disease) was 66%. 9 patients (33.33%) experienced treatment toxicity only in the first degree of CTCAE (common toxicity criteria for adverse events), 11 patients (40.74%) presented the second degree toxicity and 5 patients (18.5%) – third degree. The most commonly reported treatment related adverse events were diarrhea (47%), fatigue (26%), hand-foot syndrome (26%), deterioration of blood pressure control (22.2%), abnormal liver function tests (18.5%), mucositis (11.1%). We observed 3 cases of unacceptable toxicity.

Conclusions: Axitinib confirms its effectiveness also in situation outside clinical trials, however, it is characterized by significant toxicity. Therefore, qualification for treatment should take into account the clinical patient characteristics. Effective diagnosis and treatment of side effects and dose optimization are the key skills of the attending physician.

Key words: axitinib, metastatic renal cell carcinoma, efficacy, toxicity.
clear-cell component; 2) disseminated disease; 3) failure of prior treatment with multikinase inhibitors (sunitinib, pazopanib) in the first-line treatment or after failure of cytokines; 4) prior radical nephrectomy or nephron sparing procedure; 5) absence of metastases in the central nervous system or stable state after their removal or radiation therapy; 6) Karnofsky 80–100 performance status; 7) favourable or intermediate prognosis according to MSKCC (Memorial Sloan-Kettering Cancer Center); 8) the absence of uncontrolled cardiovascular diseases, adequate organ efficiency, thyroid function within normal limits.

Treatment was ended due to progression during treatment, persistent deterioration of performance status or quality of life, unacceptable or recurrent over grade 3 CTCAE (Common Terminology Criteria for Adverse Events) toxicity, patient will or death.

Baseline assessment included medical history, physical examination taking into account performance status according to ECOG (Eastern Cooperative Oncology Group) scale, tumor imaging with computed tomography (CT), laboratory tests (hematology, biochemistry). Assessments through the treatment take into account physical examination, performance status, adverse events recording and monitoring. CT imaging every approximately 3 months of treatment, hematology and biochemistry profiles every month.

Results
A total of 27 patients (9 females, 18 males) treated from October 2014 to the present (July 2016), were reviewed. The median age was 63 years (range: 40–83) (Figs. 1, 2, Table 1). Men were twice more numerous than women. All patients were current or ex-smokers. The majority of them (23 persons, i.e. 85%) suffered from other serious illnesses (up to 7) including hypertension (19 persons – 70%), coronary artery disease (9 persons – 33%), hyperlipidemia (6 persons – 22%) and diabetes (6 persons – 22%). Other diseases occurring in the observed group were: abdominal aortic aneurysm (1 person), history of ischemic stroke (2 persons), chronic kidney disease (3 persons), benign prostatic hyperplasia (4 persons), gout (2 persons), ulcerative colitis (1 person), chronic obstructive pulmonary disease (confirmed only in 2 persons, surprisingly), asthma (1 person) (Table 2).

The median duration of treatment which corresponds to the time to disease progression in observed population was 6 months (range: under 1 month – 16 months). 12 patients (44.4% = over one third) completed treatment due to disease progression found in the imaging studies, assessed according to the RECIST 1.1. Other reasons for stopping treatment were: sustained performance status of 70 or lower on the Karnofsky scale (1 patient), significant deterioration in the quality of life during treatment (5 patients). In patients treated at our center we also noted 4 deaths of other (1) or unknown (3) causes. Eight patients are currently still treated with axitinib. We did not observe symptoms of hypersensitivity to axitinib or any of the excipients.

In the study population 1 patient (3.7%) had got objective response (partial remission – PR). Clinical benefit rate (PR+SD (stable disease) was 66%. Median PFS in this study was 6 months (24 weeks) with a range of under 1 to 15 months. Only in 3 cases (11.11%) it was possible to escalate the dose over the standard one (2 × 5 mg per day) due to very good tolerance. One of these patients was treated with the dose 2 × 10 mg per day with minimal toxicity (Figs. 3–6). Eight patients (29.62%) was unable to stand the dose of 2 × 5 mg per day, they had their dose reduced, in three cases even to 2 × 2 mg. Very good tolerance. One of these patients was treated with the dose over the standard one (2 × 5 mg per day) due to very good tolerance. One of these patients was treated with the dose 2 × 10 mg per day with minimal toxicity (Figs. 3–6). Eight patients (29.62%) was unable to stand the dose of 2 × 5 mg per day, they had their dose reduced, in three cases even to 2 × 2 mg. Sixteen patients (59%) remained on the initial dose of 2 × 5 mg daily.

Nine patients i.e. 33.33% experienced treatment toxicity only in the first degree of CTCAE (common toxicity criteria for adverse events) namely elevated transaminases, asthenia, mucositis, diarrhea, hand-foot syndrome. Eleven patients (40.74%) presented the second degree toxicity according to CTCAE and 5 patients (18.5%) – third degree.

The most commonly reported treatment related adverse events were diarrhea (11 persons – 47%), fatigue (7 persons – 26%), hand-foot syndrome (7 persons – 26%), deterioration of blood pressure control (6 persons – 22.2%), abnormal liver function tests (5 persons – 18.5%), mucositis (3 persons – 11.1%) (Figs. 3).

We observed 3 cases of unacceptable toxicity. The first one it was asymptomatic colonic perforation, disclosed in
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CT in a patient who underwent the metastasis resection from the colon a few months before. The second one it was myocardial infarction and the third one – stroke with mild neurologic deficit.

**Discussion**

Metastatic renal cell carcinoma is one of the most challenging malignancies to treat. It is resistant to cytotoxic chemotherapy and shows only limited sensitivity to radiotherapy. In the era of cytokine therapy such as interferon α or interleukin 2 approximately 15% of patients responded to that treatment [5]. This scenario changed significantly with the invention of targeted therapy. The vascular endothelial growth factor binding monoclonal antibody – bevacizumab in combination with interferon α were approved in Europe in 2007, the mammalian target of rapamycin inhibitor – everolimus in 2009. Sunitinib was approved in 2007, then joined him sorafenib and pazopanib (2010). Axitinib which inhibits the vascular endothelial growth factor receptor (VEGFR) at subnanomolar level is considered a next-generation agent [6]. All those medications have wide range of substantial side effects, some of them significantly impairing quality of life and some life-threatening. Management of these side effects represent a challenge for the physician. On one hand, dosage reduction and treatment interruption should be avoided to minimize the risk for progression, on the other hand, only mild toxicity is tolerable for the patient. Knowledge of the drug characteristics, its side effects, opportunities to optimize treatment by seeking to escalate the dose where possible seems to be crucial to conduct safe and effective treatment with axitinib [7–11].

In the pivotal trial – AXIS, treatment with axitinib resulted in significantly longer PFS (progression free survival) compared with sorafenib. The median PFS was 6.7 months with axitinib compared to 4.7 months with sorafenib (hazard ratio 0.665; 95% CI: 0.544–0.812; one-sided p < 0.0001).

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**Table 1. Patient baseline characteristics**

| Total intent to treat population | 27 (100%) |
|---------------------------------|-----------|
| Gender: man                     | 18 (66.6%)|
| Gender: woman                   | 9 (33.3%) |
| Age, median (range), year       | 63 (40–83)|
| ECOG performance status:        |           |
| 0                               | 6 (22.2%) |
| 1                               | 12 (44.4%)|
| 2                               | 9 (33.3%) |
| Prior systemic treatment:       |           |
| interferon α                    | 0         |
| sunitinib                       | 21 (77.7%)|
| pazopanib                       | 6 (22.2%) |
| Main sites of metastases:       |           |
| lungs                           | 19 (70.3%)|
| bones                           | 16 (59.2%)|
| liver                           | 8 (29.6%) |
| brain                           | 3 (11.1%) |
| the remaining kidney            | 4 (14.8%) |
| Number of metastatic sites:     |           |
| 2                               | 8 (29.6%) |
| > 2                             | 19 (70.3%)|

**Table 2. Distribution of comorbidities in the group**

| Comorbidity                        | Number of patients |
|------------------------------------|--------------------|
| Hypertension                       | 19 (70%)           |
| Coronary disease                   | 9 (33%)            |
| Hyperlipidaemia                    | 6 (22%)            |
| Diabetes                           | 6 (22%)            |
| Benign prostate hyperplasia        | 4 (14.8%)          |
| Chronic kidney disease             | 3 (11%)            |
| Gout                               | 2 (7.4%)           |
| Chronic obstructive pulmonary disease | 2 (7.4%)         |
| Ischaemic stroke                   | 2 (7.4%)           |
| Ulcerative colitis                 | 1 (3.7%)           |
| Abdominal aortic aneurysm          | 1 (3.7%)           |
| Varicose legs                      | 1 (3.7%)           |
| Gastroesophageal reflux            | 1 (3.7%)           |
| Asthma                             | 1 (3.7%)           |

![Fig. 3. Toxicity](image)

**Fig. 3. Toxicity**

Toxicity

![Fig. 4. Response to axitinib](image)

**Fig. 4. Response to axitinib**

Response to axitinib

Treatment was discontinued because of toxic effects in 14 (4%) of 359 patients treated with axitinib and 29 (8%) of 355 patients treated with sorafenib. The most common adverse events were diarrhea, hypertension and fatigue in the axitinib arm and diarrhea, palmar-plantar erythrody-saesthesia and alopecia in the sorafenib arm [12].
From Japan comes a report about the effectiveness of the drug in the first-line setting with median duration of the administration 10.8 months, 27.8% partial response and 50% disease stabilization [13].

The recommended clinical starting dose of axitinib is 5 mg twice daily, taken with or without food. Dose increase up to a maximum of 10 mg twice daily or reduction is permitted and even suggested based on individual tolerability. Axitinib pharmacokinetics are dose-proportional within 1–20 mg twice daily, which includes the clinical dose range. It has a short effective plasma half-life (range 2.5–6.1 h) and reaches maximum plasma concentration within 4 h of oral administration. It is eliminated via hepatobiliary excretion with negligible urinary excretion [14, 15].

Patients who developed diastolic blood pressure > 90 mmHg were noted to have significantly longer median overall survival and overall response rates when compared to normotensive patients [16, 17]. Therefore, the manufacturer recommends escalating the twice daily dose to 7 mg and 10 mg, as tolerated, if there is no significant increase in blood pressure on treatment [16]. Axitinib is the only targeted agent that benefits from individual titration in terms of efficacy [18]. As optimal axitinib exposure differs among patients, blood pressure monitoring and pharmacokinetics are among the factors that help to individualize axitinib dosage [19, 20].

Although generally we expect that data from clinical practice differ from those of the clinical trials, here treatment efficacy measured by PFS almost coincides with the values from AXIS. The incidence of toxicity, especially unacceptable or in the third degree (often related to laboratory abnormalities only), seems to be quite high as for palliative treatment, that is why the ability to manage side effects promptly is so important. It appears that many comorbidities, particularly of cardiovascular nature, contribute to increased treatment toxicity (especially life-threatening complications) and indirectly to reduced efficacy.

In majority of patients who remained on the initial dose of 2 × 5 mg, it was unclear why the clinician did not try to individualize the dose. This may raise the suspicion that he was not aware of how meaningful the attempts of dose escalation are. One can suspect that increasing the dose in patients not showing severe toxicity would lead to better treatment effect.

**Conclusions**

The results of the study confirm that axitinib have substantial antitumor effect against metastatic clear cell renal cell carcinoma. Management of side effects, adequate counseling, tailoring the dose and careful follow-up are crucial in maximizing the duration of disease control in second line setting.

Real-life data in terms of efficacy do not differ much from those from clinical trials, although only at the expense of increased toxicity. That is why meticulous monitoring of patients and proper side effects treatment should be required by trained and dedicated personnel.

The authors declare no conflict of interest.
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Submitted: 16.07.2016
Accepted: 30.09.2016