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REVIEW ARTICLE

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# Molecularly targeted therapies in advanced renal-cell carcinoma — optimisation of first-line therapy

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## ABSTRACT

Currently, systemic treatment of advanced renal-cell carcinoma is based on targeted therapy, mostly including tyrosine kinases inhibitors with anti-VEGF activity. The achieved effect is cytostatic. The systemic treatment is conducted in a sequential manner. The choice of the first-line treatment agent is crucial but may be problematic due to the lack of molecular predictors. Sunitinib and pazopanib are the tyrosine kinases inhibitors of choice in the first-line therapy. They differ in terms of their selectivity in cellular kinome inhibition. In effect, they also have a different toxicity profile and influence on the patient's quality of life during the therapy. These differences are important when choosing the optimal treatment. The superiority of the both drugs over one another has been discussed for years. The article is a review of this issue.

**Key words**: renal-cell carcinoma, molecularly targeted therapy, tyrosine kinase inhibitors, sunitinib, pazopanib

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## Introduction

Currently the therapy of locally advanced or metastatic renal-cell carcinoma (RCC) is based on molecularly targeted agents coming under the category of tyrosine kinase inhibitors (TKI). The mechanism of TKIs' activity is mostly based on the inhibition of the blood vessel formation within the neoplastic tumour (an antiangiogenic effect) by blocking the intracellular signalling pathways that depend on the activity of the vasoendothelial growth factor receptor (VEGFR) in the tumour's stroma. TKIs have a cytostatic effect. About 30% of patients have a primary resistant disease, while the secondary resistance occurs during the therapy in almost every treated person. The aforementioned agents must be administered sequentially. On this account, choosing the first-line therapy becomes a major issue. However, the choice is difficult due to the lack of molecular predictors of response in the renal-cell carcinoma.

Sunitinib and pazopanib the tyrosine kinase inhibitors with anti-VEGF activity represent the treatment of choice in the first-line systemic therapy of RCC. These drugs have a different selectivity in inhibiting the kinome of the cell, which results in diverse toxicity profiles and qualifies them for use of one of the presented agents. Comparison of the clinical value of sunitinib and pazopanib has been discussed for many years.

## Clinical studies — treatment efficacy

Sunitinib was one of the very first drugs registered in metastatic RCC (2007). In a multicentre, prospective, phase III clinical trial [1, 2] the drug was compared to interferon alpha (IFN-$\alpha$). Sunitinib had significantly higher activity measured by the overall response rate (ORR) as well as by progression-free survival (PFS). There was also a statistically non-significant trend (in the 'intent-to-treat' population) to the overall survival benefit (OS) in analysed population of patients.

The results of the registration study of pazopanib were published in 2010. It was a multicentre, prospective, phase III clinical study [3, 4]. The study revealed that pazopanib, as well as sunitinib, led to a clinically

and statistically significant improvement of the ORR and PFS with no significant impact on the median OS. The numeric values of ORR and PFS were comparable for sunitinib and pazopanib. However, there were some important differences concerning the design of both clinical studies.

First, there was a difference in study population number and type of patients' randomisation (in the sunitinib study 750 patients were randomly assigned in the ratio 1:1, while in the pazopanib trial 435 patient were randomised in the ratio 2:1 to each treatment arm). It is crucial that the registration study of sunitinib included only previously untreated patients, who were then randomly assigned to receive TKI or INF-$\alpha$. In the pazopanib study the patient population was nonhomogeneous (some patients had not received any previous systemic therapy and some had undergone immunotherapy with cytokines — INF-$\alpha$ and/or interleukin 2 (IL-2). Moreover, pazopanib was compared to placebo. The drug dosing regimen was also different. Pazopanib was administered in a continuous manner, while a cycle of sunitinib therapy consisted of four weeks on followed by two weeks off treatment. This divergence makes it difficult to compare the quality of life (QoL) because the grade of sunitinib side effects varied. The variable level of toxicity of sunitinib impedes the comparison of the patients' quality of life on both therapies.

A reliable comparison of the efficacy of the systemic therapy with sunitinib and pazopanib is difficult based on the results of the registration studies.

## Clinical studies — treatment toxicity

The prospective, randomised (randomisation in the ratio 1:1), double-blind, phase III PISCES study [5] compared the patients' choice and the treating physician's choice of therapy in the systemic treatment of metastatic RCC. The study had a specific construction and focused on comparison of the tolerance of sunitinib and pazopanib. A total of 169 patients enrolled for the study received pazopanib (10 weeks on therapy, the final response to treatment was evaluated according to RECIT criteria) and then sunitinib (four weeks on therapy followed by two weeks off the treatment and then another four weeks of therapy; final evaluation of the treatment efficacy by RECIST criteria) or in reverse order and in standard dosing. The reasons for choosing one or another drug were compared based on a questionnaire evaluating the treatment preferences, which was filled out by the patients at the end of therapy and before the final evaluation of the efficacy. The same evaluation was done by the treating physicians, who had access to the results of the laboratory studies of the treated patients. Pazopanib was preferred by 70% of patients and sunitinib by 22% of treated persons. The difference was statistically significant ($p < 0.001$) and indicated that the different toxicity profiles and their influence on the general quality of life are crucial for treated patients. Pazopanib was preferred by 61% of physicians, and 22% preferred sunitinib. The study was criticised for limited possibility of complete treatment preference assessment (complete evaluation feasible in 114 of 169 patients enrolled for the study) as well as for the time-points and system of the evaluation. The time of assessement is important and selecting of an optimal evaluation time difficult, if possible, when the dosing schedule and rhythm are substantially different (pazopanib administered in a continuous way and sunitinib 50 mg per day for four weeks with a subsequent two weeks off treatment). The evaluation is more reliable due to the study construction — a double-blind, randomised study with 'cross-over' possibility and evaluation of the preferences prior to the final analysis of the treatment efficacy. The analysis would be even more reliable if the evaluation of the drug preferences was done at several time-points over the treatment course.

## Clinical studies — comparative assessment of treatment efficacy

A COMPARZ study [6] was dedicated to comparative assessment of both drugs. In this prospective, randomised, phase III study (randomisation in the 1:1 ratio) 1110 patients with metastatic RCC (clear cell cancer or tumours containing a component of clear cell RCC) previously untreated and with no metastases to the central nervous system neither important cardiovascular comorbidities received pazopanib or sunitinib in standard doses and schedules. The primary end-point of this comparative assessment was to evaluate the influence of both drugs on the PFS — in the non-inferiority analysis. The evaluation of the response rate was done based on the blind study and according to the RECIST criteria (version 1.0) performed by an independent radiology board. Secondary end-points included the influence of the therapy on the OS, patients safety, and quality of life.

The study revealed that pazopanib has no lower efficacy than sunitinib concerning the PFS — the hazard ratio (HR) equalled 1.05 with 95% confidence interval (CI) of 0.9–1.22. The study met its primary end-point in terms of the comparability of the efficacy of both drugs. The influence of therapy on OS was similar (HR for pazopanib 0.91, 95% CI 0.76–1.08). Furthermore, the objective response rate was, in the independent assessment, significantly higher in the group receiving pazopanib compared to the group treated with sunitinib (31% and 25%, respectively, $p = 0.03$). Patients receiving sunitinib more frequently reported fatigue

(63% *vs.* 55% in the pazopanib treated population), and skin toxicity manifested as hand-foot reaction (50% and 29%, respectively) and haematological toxicities, mostly secondary thrombocytopaenia (78% *vs.* 41%). Pazopanib was characterised by a higher hepatotoxicity manifested by the increased alanine aminotransferase activity (60% compared to 43% on sunitinib). In the case of 11 of 14 evaluated quality-of-life domains related to health status, especially associated with fatigue and skin and gastrointestinal tract mucosa painfulness, the results indicated a better tolerance of treatment with pazopanib.

A major objection to the study concerned the protocol amendment extending the study population from the initial 927 to a final 1110 patients who had been previously enrolled into the concurrently ongoing Asian study, the construction of which was similar to the COMPARZ study except for the health related QoL evaluation. It was suggested that the tolerance of sunitinib may be worse in this group of patients, which could influence the final evaluation of the QoL in the general study population. Ignoring this part of analysis as well as the toxicity profile (analogous objections as in PISCES study) and focusing on the evaluation of the treatment efficacy, both drugs were found to be equivalent in first-line therapy of advanced RCC. A unique value of this analysis results from a rare (in the RCC field) head-to-head comparison of two drugs of choice administered as the first line treatment of advanced renal cancer, in a prospective, multicentre manner and on a large and diverse population of evaluated patients (in the years 2008–2011).

The real value of data coming from the controlled clinical studies and its potential implementation into everyday clinical practice remains a separate issue.

## Experience from the clinical practice

The results of the retrospective analysis of the first-line systemic treatment efficacy in patients with metastatic RCC were published in 2016. The treatment with sunitinib (6519) or pazopanib (919) was assessed. Between 2005 and 2015 the data was introduced into the International MRCC registry Database Consortium (IMDC) [7]. A population of 7438 persons included patients from 29 oncological centres in the United States, Australia, Denmark, Belgium, Greece, Italy, Poland, Japan, Singapore, South Korea, and New Zealand. The data was collected with a standardised template in order to get information allowing evaluation of the demography and initial characteristics of the study group, and the efficacy of therapy with molecularly targeted agents [including: OS, PFS, and the objective responses rate according to the RECIST criteria (version 1.1)]. The evaluation of the efficacy of the second-line therapy included into the registry was additionally evaluated (i.e. OS2 and PFS2). This was aimed to assess the influence of commonly used strategy of sequential therapy on main end-points of cancer treatment. The risk assessment was based on IMDC criteria, which include: the general performance status according to Karnofsky scale < 80%, anaemia, neutrophilia, thrombocytopaenia, hypercalcaemia, and time from diagnosis to the start of systemic treatment.

The evaluated group was representative for the RCC patient population in terms of demographic and clinical features. The median age was 62 years (range 56–69 years) in the sunitinib and 65 years (range 58–73 years) in the pazopanib group. The majority of patients were males (in both groups 71% and 70%, respectively) and had a previous surgical resection of the primary tumour (86% and 88%, respectively). Liver metastases were detected in 20% and 15% of patients, while distant metastases to the central nervous system were observed in 8% and 7% of patients, respectively, in each group. A higher tumor burden, defined as metastases in more than one localisation, concerned 75% of the study population. In 7–10% of patients the cancer had a different histological type than a clear cell renal cancer. In the assessed population, patients with favourable risk represented, respectively, 23% and 24%, with intermediate risk 57% and 58%, and with poor prognosis 20% and 18% of the sunitinib and pazopanib group.

The analysis was performed after a median follow-up of 40.4 months (95% CI 39.2–42.1 months). The median OS was 22.3 months in the sunitinib (95% CI 21.4–23.2 months) and 22.6 months in the pazopanib group (95% CI 21.1–24.7 months). The difference was not statistically significant ($p = 0.65$). The hazard ratio for cancer-related death, corrected by the IMDC risk scale, reached 1.03 (95% CI 0.92–1.17) in the pazopanib group. The differences of the relative risk of death were not significant in any of the analysed subgroups. There was also no significant difference between the median PFS in the populations receiving both evaluated TKIs ($p = 0.17$). The median PFS was 8.4 months in the sunitinib (95% CI 8.2–8.7 months) and 8.3 months in the pazopanib group (95% CI 7.2–8.9 months). The relative risk of progression corrected by the IMDC risk scale was 8% higher for pazopanib (HR 1.08; 95% CI 0.92–1.17). The efficacy of therapy measured by ORR was comparable in both subgroups (30% and 28% — for sunitinib and pazopanib, respectively). A higher proportion of patients treated with sunitinib in the first line (49% *vs.* 38%; $p < 0.0001$) received a subsequent second line of the systemic therapy. It is interesting that when the data were censored for analysis, the proportion of patients continuing therapy was higher in the pazopanib group, and the difference compared to the sunitinib group was statistically significant (39% *vs.* 21%; $p < 0.0001$).

Among the drugs used as subsequent treatment, the following were the most common: everolimus (45% and 53% in the sunitinib and pazopanib groups, respectively), sorafenib (22% and 2%, respectively), and axitinib (8% and 20%, respectively). Patients treated with sunitinib had a significantly higher frequency of receiving a third-line therapy (21% *vs*. 16%, respectively, p = 0.0007).

The above-cited study constitutes the biggest trial aimed at verifying the value of the data from controlled clinical studies in everyday clinical practice. Comparable to the COMPARZ values of ORR, median time of PFS and only slightly shorter OS were achieved in the group of patients with non-clear cell renal cancer histology, in a worse general performance status (13–14% of the group had KPS < 80%), prognostically unfavourable localisation of the metastases (central nervous system), or renal insufficiency. The authors suggest a possible important negative impact on the OS of the coexisting comorbidities which have no significant influence on cancer successfully controlled by TKIs. The efficacy of the systemic therapy in the metastatic renal-cell cancer in patients ineligible for clinical trials is lower and the prognosis worse, which has been previously documented (a relative death risk 55% higher compared to the population of patients enrolled to the experimental therapies) [8].

In the presented analysis, the therapy with pazopanib has a similar efficacy to that of sunitinib. The differences concerning the ORR and the median PFS and OS were not statistically and clinically significant. The choice of one of the discussed TKIs in the first-line therapy also has no impact on the efficacy of subsequent lines of therapy in the study population.

A reported statistically nonsignificant trend towards a better PFS2 in the pazopanib group has no major practical importance.

## Summary

Data concerning the toxicity and safety profile of each agent remains crucial because the TKI efficacy is comparable and no molecular predictors are defined. It is important to mention that in none of the cited publications the alternative dosing schedules of pazopanib and sunitinib were compared. Alternative dosing of sunitinib was proven to be equally effective but significantly less toxic.

The presented publication, even if retrospective and not evaluating the toxicity profile of the therapy, as well as being based on a heterogenic population primarily represents the reality of every day clinical practice. It is also another premise for an equivalent value of pazopanib and sunitinib as a systemic treatment option for metastatic renal-cell cancer.

Taking into consideration the initial data from the ongoing prospective clinical studies evaluating the use of drugs with a different mechanism of action, the assessement of the value of the discussed publication is constricted. The general recommendations concerning the first line treatment of metastatic renal-cell carcinoma may be updated in the near future.

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