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Outcomes of treatment, laboratory results, adverse effects, and tolerability of cancer treatment in patients with metastatic renal-cell carcinoma treated with sunitinib after cytoreductive nephrectomy

Maciej Michalak[1], Piotr Tomczak[2], Tomasz Milecki[1], Andrzej Antczak[1]

[1]*Department and Clinic of Urology and Oncological Urology, Poznan University of Medical Sciences, Poznan, Poland*
[2]*Department of Oncology, Poznan University of Medical Sciences, Poznan, Poland*

Introduction. This publication aims to present the results of a retrospective analysis of the treatment outcomes of patients with metastatic renal-cell carcinoma (RCC) who underwent cytoreductive nephrectomy (CN) followed by systemic treatment with sunitinib.

Material and methods. The retrospective analysis includes the results of 67 patients treated and followed up at the Institute of Oncology in Poznan University of Medical Sciences.

Results. Among the 67 patients included in the study, 24 were female (35.82%) and 43 were male (64.18%). The patients treated with sunitinib experienced several adverse effects, including weight loss, anaemia, neutropenia, hypokalemia, and thyroid dysfunction. For these reasons, some patients (n = 32, 47.76%) required a reduction in the dose of sunitinib. The most common reason for sunitinib discontinuation was disease progression (n = 52,77.61%).

Conclusions. Treatment with sunitinib requires regular clinical and laboratory monitoring to appropriately reduce the drug dose or increase the interval between drug cycles in the event of adverse effects.

Key words: sunitinib, metastatic renal-cell carcinoma, cytoreductive nephrectomy, CARMENA, SURTIME

Introduction

Renal-cell carcinoma (RCC) is a significant challenge in oncology. According to current literature, an estimated 30% of patients with RCC have metastases at the time of diagnosis [1]. In 2020, 4,770 cases of kidney cancer were recorded in Poland, and 2,522 people died from this cancer [27]. In recent years, significant progress has been made in understanding the molecular mechanisms underlying the development of this cancer. RCC is characterized by losing the *VHL* gene, leading to increased angiogenesis [2]. As our understanding of the biology of RCC deepens, innovative therapies that target specific molecules involved in cancer cell proliferation and angiogenesis processes emerge. One of the directions in treating RCC is sunitinib – an anti-angiogenic drug that represents a group of medicines known as tyrosine kinase inhibitors. Sunitinib can inhibit a number of key signaling pathways involved in the processes of cancer development and growth. It works by inhibiting angiogenesis – forming new blood vessels that supply blood and nutrients to the tumor – limiting tumor growth and inhibiting cancer cell proliferation. The U.S. Food

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and Drug Administration (FDA) approved the drug in 2006 as a first-line treatment for patients with advanced RCC. The approval of sunitinib in this indication was based on the results of a phase 3 study in which patients treated with sunitinib had a significantly longer median progression-free survival (PFS) – 11 months – than patients treated with interferon-α (INF-α) – 5 months – previously the leading systemic treatment for metastatic RCC [3]. Regarding secondary endpoints, 28% of patients showed significant tumor shrinkage with sunitinib compared to 5% of patients treated with IFN-α. At the end of the study, the primary endpoint of median PFS was still better with sunitinib (11 months *vs.* 5 months for IFN-α, $p < 0.000001$) [4].

In addition to treating RCC, sunitinib is also used to treat gastrointestinal stromal tumors and pancreatic neuroendocrine tumors [5]. What is more, reports suggest the use of sunitinib in treating thyroid cancer [6]. Although sunitinib has low toxicity compared to chemotherapy, it can cause systemic complications such as cardiotoxicity, heart failure, and hypertension [7]. The toxic effect of sunitinib on thyroid function, resulting in iatrogenic hypothyroidism, is also significant [8]. Other adverse effects include weakness, diarrhea, nausea, vomiting, skin lesions, mucositis, and hand–foot syndrome [9]. The classic treatment regimen for metastatic RCC is a daily dose of 50 mg of sunitinib for 4 consecutive weeks, followed by a 2-week interval, so one cycle lasts an average of 6 weeks. If adverse effects occur, the dose can be reduced to 37.5 mg or even 25 mg, but the cycle duration remains unchanged (4 weeks of drug administration, then 2 weeks off). In special situations, such as poor patient health or significant toxicity from sunitinib, the interval between cycles may be extended at the treating physician's discretion.

Sunitinib was part of two prospective randomized clinical trials, CARMENA and SURTIME, which evaluated the role of cytoreductive nephrectomy (CN) in patients with metastatic RCC treated with sunitinib [10, 11]. The CARMENA study enrolled 450 patients (an intermediate and poor prognosis group according to the Memorial Sloan Kettering Cancer Center – MSKCC) randomly assigned to an experimental arm (radical nephrectomy + sunitinib – 226 patients in total) and a control arm (sunitinib only, no surgical treatment – 224 patients in total). The study was designed to test whether sunitinib alone is not inferior (non-inferiority) to nephrectomy followed by sunitinib. The results were surprising – median overall survival was shorter in patients who received cytoreductive nephrectomy (CN) in combination with systemic treatment with sunitinib compared to patients who received systemic treatment alone without nephrectomy. Therefore, it was concluded that sunitinib alone is not worse than nephrectomy followed by sunitinib, thus questioning the validity of performing CN in patients with metastatic RCC, previously the gold standard of care until the above results were published. Therefore, it was concluded that patients in the poor and intermediate prognosis group, according to the MSKCC, should not undergo surgery but only receive systemic treatment.

In another clinical trial evaluating the role of CN in patients with metastatic RCC treated with sunitinib – SURTIME – patients were randomized into two groups: in the first group (experimental group), sunitinib treatment was started before CN and continued after the procedure. The second group of patients (the control group) did not receive the initial therapy with sunitinib but instead received CN followed by sunitinib. A total of 99 patients were enrolled in the SURTIME study, and their treatment outcomes were compared with respect to the assumed 28-week PFS. The primary objective of the SURTIME study was to determine whether pretreatment with sunitinib prior to CN improves prognosis. Another study objective was to identify patients refractory to systemic therapy who are unlikely to benefit clinically from CN. Previous single-arm phase 2 studies of delayed CN after preoperative sunitinib showed that this approach is safe and helps avoid CN in people with early resistance to tyrosine kinase inhibitors (VEGFR) [12, 13]. In addition, the approach of delayed CN after initiating preoperative treatment with sunitinib may reduce the size and vascularity of the primary tumor, thereby facilitating the procedure and reducing the perioperative risk [14, 15]. No differences in progression-free survival were observed between the two groups in the SURTIME study (experimental and control). However, there was a reduction in the relative risk of death in patients in the experimental group (patients treated with sunitinib prior to CN) compared to patients in the control group. Median overall survival was significantly longer in patients treated with sunitinib prior to nephrectomy – 32.4 months, compared to the control group, where median survival was 15 months. The SURTIME study also showed that delaying the initiation of systemic treatment by performing CN may put some patients at risk of not receiving systemic treatment. The results of the SURTIME study suggest that the delayed CN approach, in which patients are started on sunitinib and offered nephrectomy only if their disease does not progress, may be better than performing the procedure upfront in every patient and then including sunitinib.

Both the CARMENA and SURTIME studies had limitations and inconsistencies, so their results should be interpreted with great caution by urologists and oncologists. However, since the publication of the results of these two prospective randomized studies, the role of CN and the indications for its use in patients with metastatic RCC have become an integral part of discussions among physicians treating RCC.

Material and methods

In this study, we present the results of a retrospective analysis of the cancer treatment of patients with metastatic RCC who underwent CN and subsequently received systemic treatment with sunitinib. The retrospective analysis includes the results of 67 patients diagnosed with metastatic RCC who were

treated and followed up at the Institute of Oncology in Poznań University of Medical Sciences in 2022 and 2023.

The software used for statistical analysis was Dell Inc. (2016), Dell Statistica (data analysis software system) version 13. software.dell.com and Cytel Studio version 11.1.0. The normality of the distributions of the variables studied was tested using the Shapiro–Wilk test. Quantitative variables with a normal distribution were presented using the mean and standard deviation, and the remaining quantitative variables were presented using the median (minimum-maximum). Categorical parameters were described as n (%). The statistical significance of the relationships and differences studied was checked at the level of significance $\alpha = 0.05$.

Results

Among the 67 patients diagnosed with metastatic RCC, there were 24 women (35.82%) and 43 men (64.18%). The mean age of the patients at the initiation of sunitinib treatment was 63.16 years (ranging from 49 years to 84 years). The mean age of women and men was similar – the mean age of women was 63.25 years, and the mean age of men was 63.12 years. In most patients (n = 35, 52.24%), the tumor was located in the right kidney, while left-sided tumors were less common (n = 32, 47.76%). All patients included in the study (n = 67, 100%) underwent CN before initiating systemic treatment with sunitinib. The mean duration of sunitinib treatment was 23.00 months (ranging from 0.73 months to 113.67 months), with a mean duration of treatment of 16.18 months in women and 26.80 months in men (p = 0.083). The most common reasons for sunitinib discontinuation were disease progression (n = 52, 77.61%), less frequently cardiac complications (n = 6, 8.95%), poor tolerability (n = 3, 4.48%), death due to unrelated causes (n = 3, 4.48%), or other reasons (n = 3, 4.48%). Among all patients, 54 (80.60%) were qualified to continue treatment with another drug (including axitinib, nivolumab, cabozantinib). In the analyzed patient group, 3 patients (4.48%) discontinued sunitinib treatment during the first cycle. They were, therefore, excluded from the comparative analysis of laboratory test results at baseline and at the end of sunitinib treatment. The laboratory test results of the remaining patients (n = 64) at baseline and the end of treatment were subjected to statistical analysis; the collected results are presented in table I.

Among the patients included in the study, a statistically significant decrease in body weight was observed during systemic treatment with sunitinib (p = 0.001) (tab. I). Moreover, a statistically significant decrease in hemoglobin levels (p < 0.001), hematocrit levels (p < 0.001), platelet count (p = 0.001) and blood smear neutrophil count (p < 0.001) was also revealed in patients treated with sunitinib. A statistically significant decrease was also observed in serum albumin levels (p < 0.001). Importantly, a statistical increase in aspartate aminotransferase (AST) was found (p = 0.007). In addition, there was a statistical decrease in alkaline phosphatase (p < 0.001) and a statistical increase in lactate dehydrogenase (p < 0.001). Importantly, statistically significant potassium levels were also revealed during sunitinib treatment (p = 0.004). There were no statistical differences in creatinine levels at baseline and at the end of treatment, indicating that sunitinib did not cause statistically significant renal toxicity in the patient population analyzed. There were also no statistically significant changes in liver parameters such as alanine aminotransferase (ALT) or bilirubin; however, given the statistically significant increase in AST during sunitinib treatment, the effect of this drug on liver toxicity remains unclear. Importantly, short-term liver toxicity was observed in several patients during treatment, requiring a reduction in sunitinib dosage or an increase in the interval between cycles, which may indicate a negative effect of sunitinib on liver function. No statistically significant effect was found on serum sodium and calcium levels. Sunitinib treatment was associated with significant thyroid dysfunction manifested by iatrogenic hypothyroidism, most of which required thyroid hormone replacement. The TSH test was used as the reference parameter. At the start of sunitinib treatment, the mean TSH level was 1.89 (μlU/ml), while at the end of treatment, the mean TSH level was 6.27 (μlU/ml) – p < 0.001. It should be noted that most patients required thyroid hormone replacement during sunitinib treatment, so the final mean TSH appears to be significantly underestimated. Sunitinib-related adverse effects required dose reductions in 32 patients (47.76%). In addition to the above-mentioned laboratory abnormalities, the following adverse effects were observed in patients treated with sunitinib: weakness, hand–foot syndrome, diarrhea, decreased appetite, numbness of the upper and lower limbs, skin lesions, hypertension, oral mucosal lesions, musculoskeletal pain, and abdominal pain.

The study also analyzed factors that may have influenced the need to reduce the dose of sunitinib during treatment because of the adverse effects caused by the drug. The need to reduce the dose of sunitinib during treatment was observed to be correlated with patient age at the initiation of treatment – patients whose dose of sunitinib was reduced were older at the start of sunitinib treatment than patients whose dose of sunitinib was not reduced during the treatment (p = 0.038) (fig. 1).

The study also analyzed factors that may influence the presence or absence of cancer progression during sunitinib treatment. A correlation was found between patient age at the start of sunitinib treatment and the occurrence of disease progression – patients with disease progression during sunitinib treatment were younger at the start of sunitinib treatment. Therefore, the prognosis of younger patients treated with sunitinib is statistically worse than that of older patients (p = 0.004) (fig. 2).

Discussion

The retrospective analysis of the treatment outcomes of patients with metastatic RCC treated with sunitinib allowed us to identify the adverse effects of the drug that require special attention during the treatment process. A better understanding

Table I. The laboratory test results at baseline and sunitinib treatment's end

Laboratory test	n	Mean	Median	Minimum	Maximum	Stabilization of the disease	p-value
body weight (start of treatment) (kg)	64	82.82	83.50	45.00	124.00	17.56	0.001
body weight (end of treatment) (kg)	64	79.50	76.50	49.00	114.00	14.25	
hemoglobin (start of treatment) (mmol/l)	64	8.63	8.65	6.00	11.30	1.09	<0.001
hemoglobin (end of treatment) (mmol/l)	64	7.57	7.60	5.40	10.50	1.16	
hematocrit (start of treatment) (L/l)	64	0.41	0.41	0.27	0.55	0.05	<0.001
hematocrit (end of treatment) (L/l)	64	0.37	0.37	0.27	0.50	0.06	
platelets (start of treatment) (10^9/l)	64	265.38	249.00	126.00	508.00	74.63	0.001
platelets (end of treatment) (10^9/l)	64	231.25	211.50	72.00	533.00	81.73	
neutrophils (start of treatment) (10^9/l)	64	4.69	4.64	1.72	11.07	1.67	<0.001
neutrophils (end of treatment) (10^9/l)	64	2.82	2.39	0.58	14.98	1.99	
creatinine (start of treatment) (µmol/l)	64	107.45	106.00	60.00	247.00	29.17	0.521
creatinine (end of treatment) (µmol/l)	64	114.44	106.00	58.00	281.00	42.27	
albumin (start of treatment) (g/l)	64	38.85	39.30	25.50	49.00	4.15	<0.001
albumin (end of treatment) (g/l)	64	35.13	36.05	19.00	43.00	5.57	
ALT (start of treatment) (IU/l)	64	33.40	25.50	10.00	134.00	25.13	0.342
ALT (end of treatment) (IU/l)	64	31.23	25.00	8.00	113.00	21.05	
AST (start of treatment) (IU/l)	64	26.67	21.00	11.00	118.00	18.96	0.007
AST (end of treatment) (IU/l)	64	30.11	25.00	12.00	104.00	16.94	
bilirubin (start of treatment) (µmol/l)	64	10.71	10.10	4.00	23.00	4.09	0.946
bilirubin (end of treatment) (µmol/l)	64	10.87	9.00	4.40	30.00	5.59	
natrium (start of treatment) (mmol/l)	64	140.31	140.50	133.00	146.00	2.77	0.140
natrium (end of treatment) (mmoll)	64	140.81	141.00	130.00	146.00	3.17	
potassium (start of treatment) (mmol/l)	64	4.59	4.60	3.90	5.50	0.39	0.004
potassium (end of treatment) (mmol/l)	64	4.39	4.35	3.50	5.30	0.43	
alkaline phosphatase (start of treatment) (IU/l)	64	106.03	92.00	48.00	427.00	56.38	<0.001
alkaline phosphatase (end of treatment) (IU/l)	64	98.25	88.50	34.00	430.00	66.23	
lactate dehydrogenase (start of treatment) (IU/l)	64	187.11	184.00	106.00	280.00	37.04	<0.001
lactate dehydrogenase (end of treatment) (IU/l)	64	222.17	211.50	132.00	386.00	55.22	
calcium (start of treatment) (mmol/l)	64	2.42	2.42	2.14	2.75	0.15	0.954
calcium (end of treatment) (mmol/l)	64	2.42	2.41	2.12	2.92	0.16	
TSH (start of treatment) (µIU/ml)	64	1.89	1.64	0.01	6.44	1.35	<0.001
TSH (end of treatment) (µIU/ml)	64	6.27	2.87	0.01	88.08	11.80	

of the molecular mechanisms underlying sunitinib-related adverse effects helps physicians maximize the efficacy of sunitinib, and minimize the occurrence of adverse effects, thereby improving patients' quality of life. The analysis of the results collected allows us to conclude that, due to the adverse effects caused by sunitinib, appropriate qualification for treatment is necessary and that, when using sunitinib, it is absolutely essential to constantly monitor laboratory test results to reduce the dose of the drug or extend the interval between cycles in case of drug toxicity.

The adverse effects observed in the analyzed group of patients, such as weight loss, anemia, thrombocytopenia,

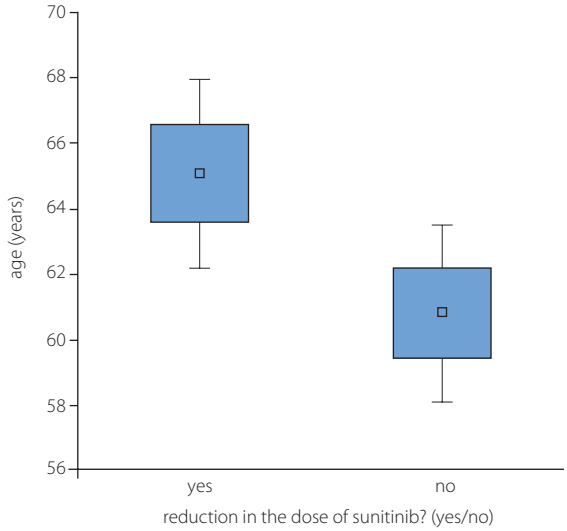

Figure 1. Correlation of the need to reduce the dose of sunitinib with a patient's age at the initiation of treatment

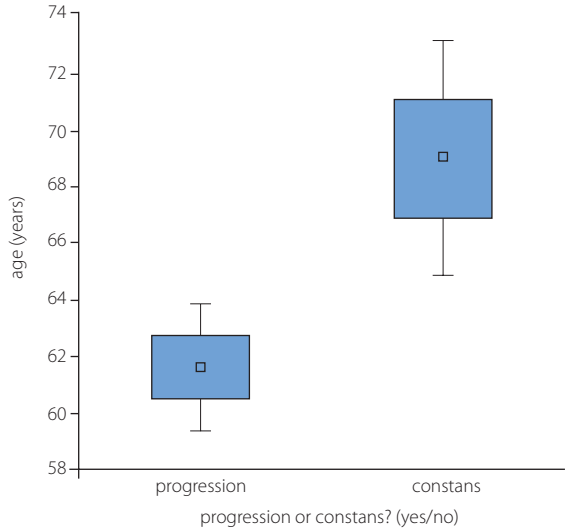

Figure 2. Correlation between a patient's age at the start of sunitinib treatment and the occurrence of disease progression

decreased neutrophil count, decreased albumin levels, increased liver function test values (ALT), electrolyte imbalance (hypokalemia), increased lactate dehydrogenase levels, or decreased alkaline phosphatase levels, may be related to the neoplastic process or its progression and not necessarily to the use of sunitinib. However, the adverse effects of sunitinib described in the study are consistent with reports in the literature regarding sunitinib [3, 4].

The thyroid toxicity of sunitinib is of particular interest in the results analyzed. The vast majority of patients developed iatrogenic hypothyroidism requiring thyroid hormone replacement. This observation is consistent with reports in the literature. Sunitinib causes iatrogenic hypothyroidism and even atrophy of the gland. The mechanism of this adverse effect is not fully understood. According to literature reports, the causes may include the antiangiogenic effect of sunitinib [16, 17], inhibition of iodine uptake [18], induction of destructive thyroid inflammation [19], inhibition of thyroid peroxidase activity [20], or reduced vascularization of thyroid cells due to regression or narrowing of blood vessels [16, 21]. Because of iatrogenic hypothyroidism in patients, screening for hypothyroidism is mandatory during sunitinib treatment, and any laboratory abnormalities or symptoms reported by patients suggesting hypothyroidism require levothyroxine supplementation [8].

The CheckMate 214 study compared nivolumab + ipilimumab with sunitinib in patients with metastatic RCC. A total of 1096 patients with metastatic RCC were enrolled between October 2014 and February 2016. The patients were randomized into two groups – those treated with nivolumab + ipilimumab (550 people) and those treated with sunitinib (546 people). The study showed that immunotherapy (nivolumab + ipilimumab) was significantly more effective than sunitinib in patients with intermediate and poor prognosis, according to the IMDC (International Metastatic RCC Database Consortium) scale in terms of overall survival, progression-free survival, and clinical response rate [22]. In addition, patients treated with the nivolumab + ipilimumab regimen had a statistically better quality of life compared to sunitinib [23].

Another phase 3 study – COMPARZ – compared sunitinib with another antiangiogenic drug – pazopanib [24]. Among the 1,110 patients with metastatic RCC enrolled in the study, 557 received pazopanib, and 553 received sunitinib. Pazopanib was shown to be non-significantly inferior to sunitinib in terms of progression-free survival and overall survival. However, pazopanib treatment was better tolerated, and fewer adverse effects were reported by pazopanib-treated patients compared to sunitinib-treated patients. Patients treated with sunitinib when compared to pazopanib, had a higher incidence of fatigue (63% *vs*. 55%), hand-foot syndrome (50% *vs*. 29%), and thrombocytopenia (78% *vs*. 41%), while patients treated with pazopanib had a higher incidence of ALT elevations (60% *vs*. 43% with sunitinib). The overall analysis of the COMPARZ study results concluded that pazopanib and sunitinib had similar efficacy. However, the safety profile, number of adverse effects, and patients' quality of life during treatment favored pazopanib.

Another clinical trial – CABOSUN – compared sunitinib with another antiangiogenic drug – cabozantinib, as initial therapy for advanced RCC of intermediate and poor prognosis according to the IMDC scale. A total of 157 patients were randomized 1:1 to cabozantinib (n = 79) or sunitinib (n = 78). In this trial, cabozantinib treatment significantly prolonged PFS compared with sunitinib as initial systemic therapy for advanced RCC of poor or intermediate risk [25].

Due to the emergence of drugs with higher efficacy and fewer adverse effects compared to sunitinib, the use of sunitinib

has been limited in recent years. However, this drug is still used in the following clinical situations:

- patients with advanced RCC in good and intermediate prognosis groups (I, A),
- patients with advanced RCC in intermediate prognosis group without access to cabozantinib, immunotherapy, or immunotherapy combined with kinase inhibitors (I, B) [26].

Tailored oncological treatment based on molecularly targeted therapies and immunotherapies (for example ipilimumab and nivolumab) play an increasing role in the multidisciplinary approach to patients with advanced RCC, so the use of sunitinib has recently been limited. The use of immune checkpoint inhibitors (ICI), i.e. ipilimumab and nivolumab, in the therapy of metastatic kidney cancer, has revolutionized treatment recommendations due to the high effectiveness of these drugs. Treatment personalization extends the scope of therapy and extends the survival of patients. Tremendous progress in molecular biology and the development of new molecularly targeted drugs allow treatment personalization for very narrow, genetically selected groups of cancer patients [28].

The study's main limitation is that it was conducted retrospectively, assessing the results of previous oncological treatments without the possibility of prospective assessment. There was no assessment of the quality of life in patients receiving sunitinib, which is clinically very important in the treatment of advanced cancer. Moreover, only patients who had previously undergone CN were included in the study. To increase the study's scientific value in the future, it seems reasonable to expand the experimental group to include additional patients with metastatic RCC treated with sunitinib who did not undergo CN, and to compare patients treated with sunitinib after CN and without CN in the past.

Conclusions

Since sunitinib was approved by the U.S. Food and Drug Administration (FDA) in 2006 as a first-line treatment for advanced RCC, the recommendations for its use have been modified several times in response to new clinical and literature data. Despite the emergence of immunomodulatory drugs, particularly ipilimumab and nivolumab, which are increasingly being introduced in the treatment of advanced RCC, sunitinib is still used with good results in patients with metastatic RCC in the aforementioned prognostic groups.

The complexity of the mechanisms associated with metastatic RCC forces researchers, oncologists, and urologists to constantly monitor the clinical effectiveness of the treatment regimens implemented. Since the introduction of sunitinib into widespread use, many studies have been published evaluating the efficacy of this drug. That said, all the reasons for the success or failure of the oncological treatment of patients with metastatic RCC receiving sunitinib still remain unknown. Therefore, the efficacy of sunitinib treatment in patients with metastatic RCC should continue to be evaluated and monitored, preferably using prospective randomized studies, the results of which are the most reliable from a scientific and clinical point of view.

Qualification to the correct prognostic group and the subsequent initiation of appropriate systemic treatment of metastatic renal-cell carcinoma requires a thorough analysis, which should be performed by a multidisciplinary oncology team (case conference). Treatment with sunitinib requires regular clinical and laboratory follow-ups, monitoring of the occurrence of adverse effects, and assessment of the patient's quality of life to appropriately reduce the dose of the drug or increase the interval between cycles in the event of adverse effects; this includes the possible implementation of the appropriate pharmacological treatment aimed at reversing the adverse effects of the drug.

Article information and declarations

Author contributions

Maciej Michalak – planning the study, collecting data, statistical analysis, writing an article.
Piotr Tomczak – planning the study, writing an article, content supervision.
Tomasz Milecki – planning the study, statistical analysis, writing an article.
Andrzej Antczak – planning the study, writing an article, content supervision.

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author, Maciej Michalak.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. The opinion of the Ethics Committee was obtained that there were no features of a medical experiment.

Conflict of interest

None declared

Maciej Michalak
Poznan University of Medical Sciences
Department and Clinic of Urology and Oncological Urology
ul. Szwajcarska 3
61-285 Poznań, Poland
e-mail: maciekmichalak@op.pl

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