

Pharmacotherapy is currently used mainly for palliative treatment of renal cell carcinoma and, less frequently, in locally advanced unresectable renal tumors.

The introduction of molecularly targeted therapeutics into clinical practice has improved the prognosis of patients with clear-cell histology tumors. Based on published data from prospective phase III clinical trials, several drugs have been registered for advanced renal-cell carcinoma. Indications for different agents vary, however some of them overlap. Although similar in their mechanism of action, the agents differ in toxicity profiles, which is important because of long duration of palliative treatment and possibility of sequential use. All the factors considered, there is no single drug ensuring optimal treatment of every patient with the disease.

In Poland, formal regulations reflecting a specific drug reimbursement policy lead to suboptimal treatment of some of the patients diagnosed with kidney cancer. The article presents a brief discussion of this issue.

**Key words:** renal cell carcinoma, molecular targeted therapy, non-standard chemotherapy, reimbursement.

# Pharmacotherapy of patients with metastatic renal-cell carcinoma – algorithm vs. Polish reality

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## Introduction

Pharmacological treatment of metastatic renal cell carcinoma (mRCC) is conducted with a palliative aim.

Neoadjuvant and adjuvant pharmacotherapy is investigated in ongoing clinical trials and, therefore, cannot be recognized as a standard of care or a recommended method of management.

Until recently, the only therapeutic option was based on cytokines such as interferon  $\alpha$  (IFN- $\alpha$ ) or interleukin 2 (IL-2). The introduction of molecularly targeted therapies into clinical practice has improved the prognosis of patients with advanced clear-cell histology tumours. During immunotherapy, the median overall survival (OS) in mRCC patients used to be ca. 12-14 months. At present, the above value corresponds to the expected median progression-free survival (PFS), while median OS has doubled. Consequently, new-generation drugs are now substituting or, less frequently, complementing immunotherapy. The latter, though undeniably beneficial in some clinical situations, is an older and thus less effective treatment method.

Sunitinib, pazopanib, sorafenib, bevacizumab, as well as temsirolimus and everolimus, have now been approved for the treatment of advanced RCC in the USA and in Europe.

The treatment algorithm for patients diagnosed with the disease is quite developed. Some of the drugs listed above are approved only for narrow indications, others – for much broader applications. What is more, indications for use of some of the agents may overlap to a smaller or greater degree.

It is not only vital to select optimal therapy but also take due account of efficacy parameters of the drug under consideration and its toxicity profile, also in the context of sequential therapy.

Another issue concerns the actual possibilities of using the drug in Poland in the light of Poland's specific drug reimbursement policy.

## Theoretical background

In 55-70% the development of clear-cell carcinoma is associated with the inactivation of the von Hippel-Lindau (VHL) tumour-suppressor gene [1]. This leads to overexpression of hypoxia-inducible factor (HIF) types 1a (HIF1a) and 2a (HIF2a), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). The factors play an essential role for RCC development and angiogenesis induced by activation of the PI3K/AKT/mTOR and Raf/MEK/ERK pathways [2]. Activation of the mTOR (mammalian target of rapamycin) pathway observed in the majority of patients causes increased proliferation and tumour progression [3]. Consequently, molecularly targeted drugs – which work by inhibiting pathways used for the transmission of signals inducing processes of nuclear expression of genes depending on membrane stimulation with the above-mentioned growth factors – play a major role in treating the underlying

**Table 1.** Prognostic factors and groups according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic system

1. Karnofsky performance status < 80%		
2. Serum haemoglobin < 10 g/dl		
3. Serum calcium (corrected) > 10 mg/dl		
4. Serum LDH activity > 1.5 × ULN		
5. Primary tumour <i>in situ</i> (no nephrectomy)		
prognosis	definition	median survival (months)
favourable	0 risk factors	20
intermediate	1-2 risk factors	10
adverse	≥ 2 risk factors	4

ing cause of this cancer type. Sunitinib, pazopanib, sorafenib, bevacizumab, as well as temsirolimus and everolimus, have already been approved for the treatment of advanced RCC in the USA and in Europe.

The prognosis of advanced cancer depends on several clinical and laboratory factors and concerns patients with multiple organ metastases [4]. The classification commonly used in clinical practice is the MSKCC (Memorial Sloan-Kettering Cancer Center) scale based on five risk criteria (low overall performance status, low haemoglobin, elevated lactate dehydrogenase, elevated calcium level and short time from diagnosis to recurrence). Depending on the number of factors, three prognostic categories can be distinguished (favourable, intermediate and adverse) [5] (Table 1). Therapeutic indications vary depending on whether the patient has had no previous pharmacological treatment (first-line treatment) or has previously undergone pharmacotherapy (Table 2). Optimum selection of first-line treatment is determined by MSKCC prognosis, while second-line treatment – by previous first-line therapy.

#### First-line treatment – favourable and intermediate prognosis

The first step should always be to assess the possibility of surgical removal of cancerous lesions. Systemic therapy should be reserved for patients with inoperable cancer. Diagnosis of metastatic renal cell carcinoma should not be the

sole and sufficient argument for pharmacotherapy, particularly in patients without adverse prognostic factors, who only developed metastases several years after primary tumour resection, and have documented slow disease dynamics. In this group, patient monitoring should be considered and treatment should only be undertaken once marked progression of the disease is noted. A prospective clinical trial is now under way to determine the optimum starting point for pharmacotherapy in this patient group.

In patients with intermediate prognosis, cancer advancement and dynamics usually result in immediate initiation of treatment.

Systemic treatment can be based on cytokines and molecularly targeted drugs: sunitinib, pazopanib, bevacizumab with interferon, or sorafenib.

The efficacy of immunotherapy (IL-2 and/or IFN- $\alpha$ ) is, however, limited [6]. High-dose i.v. interleukin-2 and s.c. interferon alpha produces objective response to treatment in ca. 6-15% of patients [7-9]. The drugs extend overall survival in patients compared to medroxyprogesterone therapy [10]. First-line cytokine therapy can be considered in patients diagnosed with clear-cell renal cell carcinoma following nephrectomy with primary tumour resection, with cancer metastases confined to the lungs and favourable prognosis according to the MSKCC scale. In other patients, however, immunotherapy yields poor results, while toxicity is high, especially for IL-2 given by i.v. bolus injections [11]. Toxicity manifests itself mainly by signs of the pseudo-flu syndrome, hypotension and low mood with psychomotor retardation. In extreme cases, IL-2 may cause acute cardiorespiratory failure requiring respiratory therapy.

Compared to interferon, sunitinib used in patient groups with favourable or intermediate prognosis prolongs median progression-free survival (11 vs. 5 months, HR 0.42) and significantly improves the quality of life (QoL) of patients, though without a clear effect on survival [12]. The analysis of survival times shows a significant superiority of sunitinib (26 and 22 months, respectively) after excluding from the assessment patients receiving sunitinib to treat disease progression occurring during interferon therapy [13, 14]. The most common adverse effects of therapy include fatigue, hypertension, mucosal and skin toxicity, and secondary haematological disorders.

Compared to interferon alone, bevacizumab used in conjunction with interferon extends progression-free survival (10 vs. 5 months and 8 vs. 5 months), unfortunately without

**Table 2.** Pharmacotherapy of patients with advanced renal-cell carcinoma

Indication	Group	Recommendation	Option
first-line	favourable prognosis	sunitinib pazopanib bevacizumab (+ IFN- $\alpha$ )	IFN- $\alpha$ IL-2 sorafenib
	intermediate prognosis	sunitinib pazopanib	bevacizumab (+ IFN- $\alpha$ ) sorafenib
	adverse prognosis	temsirolimus	sunitinib
second-line	after prior cytokine treatment	sorafenib pazopanib	sunitinib
	after prior TKI treatment	everolimus	clinical trial

prolonging survival times [15, 16]. Mortality risk reduction in groups of patients with favourable and intermediate prognosis according to MSKCC was comparable (31% and 26%, respectively). Toxicity of treatment is a quite significant problem, though. The most common adverse reactions are: general fatigue, muscle weakness and neutropenia, haemorrhagic and thromboembolic complications. Drug registration studies did not comprise an assessment of the effects of therapy on the QoL of patients. Interferon alpha dose reduction in patients with adverse reactions also resulted in improved treatment tolerance without compromising efficacy.

No differences in anti-cancer efficacy in terms of objective response rate (ORR) and progression-free survival (PFS) were observed between sorafenib and interferon in first-line treatment [17]. Disease stabilization rate combined with ORR was significantly higher for sorafenib. An assessment of QoL parameters also demonstrates the superiority of sorafenib.

Pazopanib, in turn, was found to extend progression-free survival (11.1 vs. 2.8 months), reducing the risk of disease progression by 60% ( $p < 0.001$ ) compared to placebo, without an effect on patient survival times (since patients could move from the control group to the pazopanib group if disease progression was observed, the issue could not be definitely resolved) [18]. Common adverse reactions caused by pazopanib were diarrhoea, nausea, appetite loss and hypertension. Elevated aminotransferase activity with simultaneous low haematological toxicity rates were also notable. Compared to placebo, therapy with the drug made it possible to maintain comparable QoL of patients.

In view of the above, sunitinib or pazopanib are recommended as drugs of choice for first-line therapy of patients with advanced RCC and intermediate prognosis. Used in intermediate prognosis patients, bevacizumab combined with interferon make it possible to achieve therapeutic effects similar to patients treated with kinase inhibitors. Since the effect of bevacizumab combined with interferon is based on antiangiogenic and immunomodulatory action [19], the method seems more justified in the group of patients with favourable prognosis. An additional factor limiting bevacizumab use in the intermediate prognosis group concerns adverse reactions caused by the drug.

Different toxicity profiles of sorafenib and pazopanib, relative to sunitinib, make the drugs a potentially valuable alternative for first-line treatment of the elderly or patients with moderate heart failure [18, 20, 21].

### First-line treatment – adverse prognosis

Since the median survival of untreated patients in the adverse prognosis group is barely around 4 months, indications for systemic treatment should always be assessed on a case-by-case basis. The only drug indicated for routine management is temsirolimus. Temsirolimus extends survival times compared to interferon and both drugs combined (11, 7 and 8 months, respectively) [22]. Furthermore, temsirolimus was found to induce disease stabilization in a considerably higher proportion of patients. Common adverse reactions identified during treatment included anorexia, skin rash, digestive mucosal damage and metabolic abnormalities (dyslipidaemias and hyperglycaemia). Immunosuppressive activity

of mTOR complex inhibitors should also be taken into account. Despite that, the QoL of temsirolimus-treated patients is significantly higher compared with patients receiving INF- $\alpha$  therapy [23].

### Second-line treatment

Second-line treatment can be given with multikinase inhibitors (sorafenib, pazopanib) and mTOR inhibitors (everolimus). Compared to placebo, sorafenib proved more effective in the group of patients previously treated with cytokines in terms of all parameters assessed (ORR, PFS), except for overall survival (OS) [24, 25]. Sorafenib is well-tolerated, also by patients aged over 70 years [26]. Adverse reactions commonly caused by the drug include dermatological toxicities (hand foot skin reaction, HFSR), diarrhoea and hypertension. The quality of life of patients in the sorafenib treatment group was similar to the QoL of placebo patients. Compared to placebo, pazopanib used in cytokine pretreated patients with disease progression was found to extend progression-free survival (7.4 vs. 4.2 months, HR 0.54,  $p < 0.001$ ), without impact on overall survival [18].

Compared to placebo, everolimus used in a group of patients pretreated with multikinase inhibitors, cytokines or bevacizumab [27] improves progression-free survival (4 months vs. 2 months), without extending overall survival. The drug was also found to double the disease stabilization rate. Common adverse reactions include: skin rashes, digestive mucosal damage, hypertension and metabolic abnormalities (dyslipidaemias, hyperglycaemia and diabetes). Similarly to temsirolimus, increased susceptibility to infection induced by the drug's immunosuppressive activity should be taken into account. The drug does not have a negative impact on the QoL of patients (relative to placebo), though objective clinical benefit from treatment defined as the objective response rate (ORR 2%) is limited.

### Sequential use of tyrosine kinase inhibitors

The currently observed longer overall survival of patients with metastatic renal carcinoma compared to historical data does not seem to be a consequence of introduction of any single pharmaceutical product into clinical practice. Most randomized prospective clinical trials investigating targeted drugs have failed to show with statistical power any clinically significant differences in median OS between these drugs and comparator treatments. Under the cautious approach, however, it would need to be assumed that even though no single targeted drug ensures a significant extension of overall survival, the differences between historical and currently reported OS rates can be attributed to the sequential use of these drugs, which justifies attempts to employ the strategy in clinical practice [28, 29].

Sequential therapy with molecularly targeted drugs has, in a way, become a clinical reality. The algorithm of pharmacological treatment applicable to patients diagnosed with the disease assumes, for example, that sorafenib and pazopanib treatment is initiated after previous cytokine therapy, while everolimus is introduced after prior treatment with tyrosine kinase inhibitors – if cancer progression is confirmed during prior therapy or if previous treatment is poorly toler-

ated. A separate and controversial problem is the sequential use of the TKIs sunitinib and sorafenib. No benefit has, as yet, been demonstrated for that management regimen in prospective clinical trials. Consequently, the treatment cannot be recognized as a standard of care. Although there have been reports of non-cross resistance between both drugs (particularly for the sorafenib–sunitinib sequence), evidence comes from the analysis of relatively small groups of patients receiving both inhibitors sequentially [29] or retrospective calculations of progression-free survival potentially associated with sequential treatment (total of medians obtained in various studies involving sunitinib and sorafenib [28]). The reports thus cannot form a basis for clinical decisions, even though they provide strong support for further prospective clinical trials.

### Polish reality

The reimbursement system of molecularly targeted drugs approved for the treatment of patients with advanced renal-cell carcinoma has been in place for several years now. It is regulated by the procedure of funding non-standard chemotherapy, i.e. an individual application requires the approval of the oncology consultant and a competent official from the regional NFZ (National Health Fund) branch. Leaving aside the fact that the competencies of Polish clinical oncology specialists are challenged by the health insurance system, since pharmacotherapy based on anti-VEGF drugs is costly, the procedure can be regarded as justified from the viewpoint of the system's finances.

In addition, for ca. two years the procedure regulating non-standard chemotherapy has incorporated a therapeutic programme for the treatment of advanced renal-cell carcinoma. Under the programme, only one of several molecularly targeted drugs approved for the indication, sunitinib, can be reimbursed. The availability (reimbursement) of other drugs is subject to approval of individually filed non-standard chemotherapy applications. In theoretical terms, reimbursement decisions often depend on factors other than strictly medical ones.

As previously described, sunitinib is a valuable therapeutic option ensuring a relatively high objective response rate (ORR), and clinically and statistically significant effect on extending progression-free survival (PFS) in cancer patients. Registration studies have also revealed a trend for longer overall survival. However, aside from drug efficacy defined as ORR, PFS and OS, treatment selection should also include therapeutic safety, specific drug toxicity profiles and QoL during therapy, all of which are briefly discussed above.

The therapeutic programme in place until now has ultimately resulted in sunitinib promotion and marginalization of other drugs approved for RCC therapy. Unfortunately, no detailed data are available that would make it possible to assess the effects of introduction of the one-drug therapeutic programme for the indication discussed – in terms of the number of patients that were deprived causal treatment due to non-medical reasons.

Attempts aimed, among other purposes, at evaluating the scale of the problem were undertaken by the Polish Kidney Cancer Group (PGRN) association which keeps the electronic Kidney Cancer register. Information gathered by the asso-

ciation to date (384 patients, unpublished data) shows that a considerable number of advanced kidney cancer patients do not receive any treatment in Poland. What is more, the tendency is not caused by typical ineligibility criteria such as poor general condition, coexisting medical problems, poor prognosis according to MSKCC, tumour histology other than clear-cell carcinoma, etc.

Also, an in-depth analysis of available data demonstrates that restricted access to molecularly targeted drugs in the treatment of renal cancer has resulted in a serious problem of inappropriate pharmacological treatment given to patients with the diagnosis. One example is interferon alpha which is used in clinically unjustified situations: immunotherapy is dedicated to a relatively narrow group of patients meeting specific eligibility criteria. Furthermore, the single-drug programme has phased out bevacizumab (used in conjunction with interferon alpha as an extended immunotherapy option) from clinical practice, and has markedly reduced the use of sorafenib and temsirolimus (drugs with specific indications and efficacy proven in prospective controlled clinical trials).

It should be noted, however, that the therapeutic programme, particularly in the aspect of verification of eligibility for therapy, has increased the discipline of assessing eligibility/ineligibility for sunitinib treatment.

In the light of the above, there is some hope for improvement in the form of draft of the new therapeutic programme “Kidney Cancer Treatment” [30]. As opposed to the current programme, the proposed scheme assumes reimbursement of more drugs, eliminating the protracted procedure based on applications for coverage of treatment costs. Another outcome of the current system of case-by-case applications for non-standard chemotherapy is, it seems, discouragement of clinicians from the generation of applications.

Despite that, the new draft also has several limitations that are worth discussing.

Contrary to previous assurances, the section on “Medical care recipients” fails to include eligibility/ineligibility criteria for interferon alpha (IFN- $\alpha$ ) treatment.

This is despite the fact that there is a group of patients who can derive tangible clinical benefits from cytokine treatment, total remission included (sometimes equivalent to recovery). Including this group in the programme (list of “Medical care recipients”) would sort out the treatment regimen for patients with the diagnosis, ensuring continuity of causal pharmacological treatment in a sequential pattern.

What is more, the “Medical care recipients” section misses eligibility/ineligibility criteria for pazopanib therapy. The efficacy and safety of the drug has been proven in a prospective randomized placebo-controlled clinical trial (VEG 105192). While assessing active substances used for the treatment of patients with advanced renal carcinoma, the Agency for Health Technology Assessment in Poland has not called into question medical data. It has, however, voiced objections regarding pharmaeconomic aspects. For pazopanib, the Agency has adopted a baffling (and harmful) requirement to demonstrate the superiority of pazopanib over previously approved and reimbursed sunitinib. Meanwhile, based on results of indirect efficacy comparisons of non-selective ty-



rosine kinase inhibitors (TKIs) [31, 32] and different toxicity/safety profiles of pazopanib and sunitinib, elimination of the former from the reimbursement system of the therapeutic programme would lead to suboptimal treatment of some renal carcinoma patients. Since the decision on the matter is likely to determine the fate of a relatively large group of kidney cancer patients, delay until the publication of results of the COMPARZ trial [33] is unsubstantiated.

Another harmful provision of the draft therapeutic programme, in the “Medical care recipients” section, item 3.1. “Eligibility criteria”, is that everolimus therapy is only acceptable after prior unsuccessful treatment with sunitinib or sorafenib. While it is true that the registration trial of everolimus (RECORD 1) did not involve patients previously treated with pazopanib, it was because the drug was not used in clinical practice during patient recruitment for the trial. Nevertheless, the drug’s mechanism of action as a non-selective TKI and, to a lesser degree, the above-mentioned indirect analyses comparing the efficacy of TKIs, seem sufficient reasons for the extrapolation of conclusions of RECORD 1 to pazopanib. Otherwise, the relatively large group of Polish patients treated with pazopanib as first-line therapy might lose the possibility of sequential treatment with an mTOR inhibitor. This will, naturally, make medical practitioners turn to sunitinib. Effects stemming from differences in toxicity profiles are discussed above.

It is also worthwhile to note that the draft therapeutic programme (information regarding everolimus dosage) suggests drug supply exclusively in the form of 5 mg tablets. Everolimus, however, is available as 5 mg and 10 mg tablets, while the price of 10 mg tablets is much more practical for the standard (i.e. most common) dosage regimen.

## Summary

Molecularly targeted drugs, mainly anti-VEGF, are commonly used worldwide for the treatment of patients with advanced renal carcinoma. Due to superior or at least non-inferior efficacy to cytokines, and better tolerance and favourable effects on the quality of life during therapy, the drugs have now marginalized immunotherapy. Clinical experience with already approved drugs is also growing exponentially, particularly in aspects concerning their use in single-drug and combined treatments (data from expanded access studies and daily clinical practice). New generation drugs have a cytostatic mechanism and the response they are expected to produce is usually stabilization of cancer progression with less frequent partial responses and occasional total remissions. An attempt to improve the efficacy of these drugs is their sequential use, i.e. introduction of another drug for disease progression during prior line of treatment in a specific patient. Access to approved drugs is of such essential importance because there are currently no predictors of response to a particular drug (biomarkers), while drug selection is based on vital clinical criteria including general condition, coexisting medical disorders and toxicity profile of the drug of choice. Access to drugs may become an even more important issue after establishing, on the basis of ongoing prospective trials, the optimum sequence in which molecularly targeted drugs should be used.

In view of the fact that treatment costs are considerable, on the one hand trials should be conducted to precisely identify the characteristics of patients who benefit from therapy. On the other hand, intensive price negotiations should be undertaken with manufacturers and efficient control mechanisms should be put into place to ensure the best possible expenditures of public funds. As preliminary observations show, a good way to exercise such control is reimbursement of treatment costs within the frames of the therapeutic programme. The strategy behind such control should be based predominantly on medical criteria rather than on the principle of restriction of drug access.

The restrictive approach causing all sorts of adverse consequences has sadly been in place in Poland for a number of months, with a negative impact on patients. Hopes for change in the *status quo* have emerged in the form of the new draft of a multi-drug therapeutic programme. Following modifications, the programme will make it possible to use advanced drugs in two or three lines of causal treatment.

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