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A systemic therapy of metastatic renal cancer. A review

Leczenie systemowe przerzutowego raka nerki. Przegląd piśmiennictwa

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S u m m a r y

For many years metastatic renal cancer was considered as a chemotherapy-refractory disease. The only two modestly active agents were interleukin 2 and interferon alpha but very few patients benefited from immunotherapy. In recent years, the advances in molecular biology of renal cancer and development of targeted agents have expanded the therapeutic armamentarium. The approved drugs include bevacizumab, sunitinib, sorafenib, temsirolimus, everolimus, and pazopanib. However, relatively many options of possible treatment may sometimes confuse a physician. This paper is a review of the most important clinical trials with the new drugs and an attempt to define the most evidence-based treatment approaches.

Key words: Carcinoma, Renal cell, Randomized Controlled Trials, Antineoplastic Agents, Humans

S t r e s z c z e n i e

Przez wiele lat przerzutowy rak nerki był uznawany za nowotwór oporny na chemioterapię. Jedynymi dwoma umiarkowanie aktywnymi lekami była interleukina 2 i interferon alfa ale korzyści z immunoterapii odnosili tylko nieliczni chorzy. W ostatnich latach postępy dokonane w poznawaniu biologii molekularnej raka nerki oraz opracowywanie związków ukierunkowanych molekularnie zwiększyły znacznie liczbę możliwych do zastosowania leków. Zarejestrowane są bewacyzumab, sunitynib, sorafenib, temsyrolimus, ewerolimus oraz pazopanib. Jednakże względnie duża liczba możliwości terapeutycznych może stanowić utrudnienie dla lekarza. Niniejsza praca jest przeglądem najważniejszych badań z użyciem nowych leków oraz próbą określenia, które ze strategii postępowania są najbardziej uzasadnione naukowo.

Słowa kluczowe: rak nerkowokomórkowy, badania kliniczne randomizowane, środki przeciwnowotworowe, ludzie

In Poland in 2007 nearly 4 000 of new cases of renal neoplasm and 2 500 deaths caused by this disease were observed (1). According to EUROCARE-4, a 5-year survival rate of patients diagnosed with kidney neoplasm in 1995-1999 in 23 European countries was 58.0% (2). At that time in Poland it was 53.8% but only 6% of all new cases were covered. A renal cell carcinoma (RCC) comprises of 90% of kidney neoplasms. The most common histopathologic type of RCC is clear cell renal carcinoma (CCRC) and it represents about 80-90% of all RCC. The treatment of choice is radical surgery, but this method is limited to early stages.

For many years metastatic RCC was considered as a chemotherapy-refractory disease. The only two modestly active agents were interleukin 2 and interferon alpha but very few patients benefited from immunotherapy. Moreover, treatment with interleukin 2 was related to serious toxicity. Thus, the most widely used form of immunotherapy was the treatment with interferon alpha. In recent years, the advances in molecular biology of renal cancer and development of targeted agents have expanded the therapeutic armamentarium.

A crucial molecular event in molecular biology of renal cancer seems to be inactivation of von Hippel-Lindau (*VHL*) gene (3). A VHL protein is mandatory for the process of hypoxia-inducible factor 1 (HIF-1) regulation (4). In a normal cell, the alpha subunits of HIF-1 are degraded by the proteasome, whereas in a hypoxic cell they are stabilized. In the absence of VHL protein, alpha subunits of HIF-1 are constitutively stabilized despite the normal oxygenation. In such case, HIF-1 promotes angiogenesis and other typical cellular responses for hypoxia. In the majority of CCRC there is a loss of *VHL* gene function. The mechanisms of such suppression include: deletion of one or both alleles, gene inactivation by mutations (commonly observed in sporadic tumors) or promoter hypermethylation (3, 5).

The two most important molecular targets for new drugs in renal cancer are vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways. HIF-1 induces expression of *VEGF* gene. VEGF protein is a potent proangiogenic factor that binds to its receptor on endothelial cells. mTOR is a cytoplasmic serine-threonine kinase that recognizes and mediates stress response signals from PI3K-AKT pathway. Its activation has been frequently observed in RCC (6). Several new agents targeting on VEGF or mTOR pathways have been developed. The approved drugs include bevacizumab, sunitinib, sorafenib, temsirolimus, everolimus, and pazopanib. Bevacizumab is a monoclonal antibody that binds to a VEGF protein. Sunitinib, sorafenib and pazopanib are small molecules that inhibit several protein kinases including tyrosine kinase of VEGF receptor. Temsirolimus and everolimus are mTOR inhibitors (7).

The possibility of having relatively many treatment options may sometimes confuse a physician. In this paper the most important clinical trials with the new drugs will be reviewed and the most evidence-based treatment approaches will be highlighted. These trials have been confined to patients with CCRC unless otherwise stated.

Interferon alpha

It has been demonstrated that interferon alpha prolongs both progression-free survival (PFS) and overall survival (OS) in patients with CCRC compared with medroxyprogesterone (8). There was a 28% reduction in a relative risk of death ($p = 0.017$) and an improvement in median survival by 2.5 months. However, very few patients really benefited from immunotherapy and such treatment was often related to significant toxicity, especially when high-doses of interleukin 2 were administered. As the survival gain for patients treated with interferon alpha was further confirmed in a meta-analysis, interferon alpha was regarded as a standard treatment of metastatic CCRC and a comparator in further clinical trials (9).

Some attempts have been made in order to identify possible predictive and prognostic factors in patients treated with interferon alpha. First of all, two prospective trials confirmed the role of nephrectomy. Cytoreductive nephrectomy prior to immunotherapy decreased a relative risk of death by 31% ($p = 0.002$) and prolonged median survival by 5.8 months (10). Motzer et al. proposed a prognostic model for patients treated with interferon alpha on prospective trials at the Memorial Sloan-Kettering Cancer Center (11). In this model five variables were included:

1. Poor Karnofsky performance status (≤ 70).
2. High serum lactate dehydrogenase level (> 1.5 x the upper limit of normal).
3. Anaemia.
4. High corrected serum calcium (> 10 mg/dl).
5. Short time (< 12 months) from the initial diagnosis to the beginning of interferon treatment.

Three risk categories (known as MSKCC or Motzer's risk categories) are presented in table 1.

Table 1. Risk categories in the prognostic model proposed by Motzer et al. at the Memorial Sloan-Kettering Cancer Center (11).

Number of risk factors	Risk category	% of patients	Median PFS (months)	Median OS (months)
0	Favorable	18	8	30
1-2	Intermediate	62	5	14
3-5	Poor	20	2.5	5

There are some data indicating that only patients at favorable risk may benefit from interferon alpha therapy. Negrier et al. have demonstrated that in the intermediate risk category immunotherapy provided no survival benefit (12).

Bevacizumab

Bevacizumab with interferon alpha was compared with interferon alone in the first-line therapy in two phase III trials: AVOREN in Europe and CALGB 90206 in the North America (13, 14). Patients enrolled in these trials had CCRC, a prior nephrectomy, and a favorable or intermediate risk category. Bevacizumab combined with interferon delayed disease progression and produced higher response rate. However, both trials failed to meet their primary endpoint, the prolongation of OS (15, 16). No group of patients benefited from adding bevacizumab to interferon alpha. This disappointing result could not be explained by the possible effect of a second-line treatment as there were no significant differences between treatment arms in the usage of active post-protocol therapies (15).

Sunitinib

Sunitinib has been compared with interferon alpha in the first-line treatment in one large, phase III trial including 750 patients with CCRC (17, 18). Almost all patients had a prior nephrectomy, were at a favorable or intermediate risk category, had performance status 0-1 according to ECOG and had no brain metastases. The results of this trial are presented in table 2. P value of an unstratified log-rank test was about 0.05 but it should be mentioned that 33% of patients randomly assigned to interferon had sunitinib as a second-line post-study therapy. This could affect the survival in a group treated with interferon. When data for 25 patients who had crossed over to sunitinib while still being on study were censored, the difference in OS reached statistical significance. Similarly, statistical significance was attained when stratified log-rank test was used. Noteworthy, the quality of life was significantly improved in a group treated with sunitinib.

Table 2. Results of a phase III trial comparing sunitinib with interferon alpha in the first-line treatment of CCRC (17, 18).

Response	Sunitinib	Interferon alpha	p
Objective response (%)	47	12	<0.001
Median PFS (months)	11	5	<0.001
Hazard ratio for progression	0.54		
Median OS (months)	26.4	21.8	0.051
Hazard ratio for death	0.82		

Sorafenib

A randomized phase II study did not show any improvement in PFS of patients treated with sorafenib when compared to interferon alpha in the first line treatment of CCRC (19).

A large phase III TARGET trial compared sorafenib to placebo in the second-line treatment of CCRC (21, 22). Most of 903 included patients had a prior nephrectomy, were cytokine-refractory (about 70% were pretreated with interferon), were at a favorable or intermediate risk category, had performance status 0-1 according to ECOG, had no brain metastases, and did not receive prior anti-VEGF therapy. The primary endpoint was OS. However, when the first pre-planned interim analysis of PFS was performed a clear difference in a relative risk of progression was observed (a reduction of a relative risk by 56%) the protocol was amended and a decision was made to reveal the study-group assignments and to offer sorafenib to patients receiving placebo. The first OS analysis made just before the cross-over revealed statistically significant reduction of a relative risk of death in patients treated with sorafenib (hazard ratio: 0.71; $p = 0.015$). The significant difference in OS was still maintained in the second interim analysis made 6 months after the cross-over but disappeared in the final analysis performed 16 month after the cross-over.

Temsirolimus

In one phase III trial temsirolimus monotherapy prolonged OS in patients with poor-prognosis RCC compared with interferon alpha or a combination of interferon alpha and temsirolimus (22). Neither a prior nephrectomy nor a clear-cell histology were mandatory for the inclusion. The patients enrolled in the trial had at least 3 of the following 6 negative predictors:

1. Karnofsky performance status 60 or 70.
2. High serum lactate dehydrogenase level (> 1.5 x the upper limit of normal).
3. Anaemia.
4. High corrected serum calcium (> 10 mg/dl).
5. Short time from the initial diagnosis (< 12 months).
6. Metastases to multiple organs.

Median OS of patients treated with temsirolimus was 10.9 months compared with 7.3 months in the interferon group (hazard ratio of death 0.73; $p = 0.008$). There was no difference in OS between patients treated with interferon alone and interferon with temsirolimus. A retrospective analysis of OS in subgroups suggested that patients with high serum lactate dehydrogenase level especially benefited from therapy with temsirolimus (median OS 6.9 v 4.2 months; hazard ratio 0.56; $p = 0.002$) (23). However, high serum lactate dehydrogenase level was a strong negative prognostic factor and survival in this group was approximately two times shorter compared with survival of patients with normal lactate dehydrogenase level (median OS 5.6 v 11.2 months, hazard ratio 1.97; $p < 0.001$).

Everolimus

Everolimus was compared to placebo in CCRC patients previously treated with VEGF receptor tyrosine kinase inhibitors (sunitinib, sorafenib) (24, 25). The majority of patients had a prior nephrectomy. The primary endpoint was PFS. This trial had a cross-over design i.e. patients who progressed on placebo received everolimus. After the second interim analysis the trial was halted early because the criteria for achieving the primary endpoint were already met. Median PFS of patients treated with everolimus was 4.9 months compared with 1.9 months in the placebo group (hazard ratio 0.33; $p < 0.001$). Despite this quite impressive result, the absolute benefit from everolimus was modest at best. Median duration of treatment was only 141 days for everolimus and 60 days for placebo. Moreover, virtually all patients progressed, regardless of treatment, within the first 12 months. Health-related quality of life was similar in both treatment groups. No significant difference in OS between the treatment groups was noted, but this could be affected by the trial design and by its premature termination.

Pazopanib

Pazopanib was compared to placebo in CCRC in a phase III trial (26). Of 435 patients enrolled, 54% were treatment-naive and the rest were cytokine-pretreated. Almost all patients were at favourable or intermediate risk category and had a prior nephrectomy. In a treatment-naive population pazopanib prolonged PFS compared with placebo (median PFS 11.1 v 2.8 months, hazard ratio 0.40; $p < 0.001$). This effect was also observed in the second-line treatment (median PFS 7.4 v 4.2 months, hazard ratio 0.54; $p < 0.001$). There was no significant difference in health-related quality of life between pazopanib and placebo groups. OS data are still immature.

Conclusion

Despite the apparent plurality of treatment choices in metastatic CCRC, the evidence-based approach seems to be quite simple. The first-line therapy is based on the assessment of risk category. Patients with a prior nephrectomy at a favorable or an intermediate risk category are candidates for sunitinib. Interferon al-

pha can also be used in a small group of patients at a favorable risk category, especially when metastases are confined to lungs. Bevacizumab failed to show an advantage over interferon alone and could not be recommended. Pazopanib is a promising drug but currently available data do not support its use instead of sunitinib (27). The phase III trial directly comparing pazopanib with sunitinib is under way and its results will define the role of pazopanib in the first-line treatment. For patients at a poor-risk category temsirolimus is the only choice and a prior nephrectomy or clear-cell histology are not mandatory. In cytokine-pretreated patients sorafenib is the drug of choice. The evidence for the use of pazopanib is considerably weaker. For patients who progress on VEGF receptor tyrosine kinase inhibitors everolimus is the only choice but absolute benefit is very modest.

BIBLIOGRAPHY

1. www.onkologia.org.pl
2. Sant M, Allemani C, Santaquilani M et al.: EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. Eur J Cancer 2009; 45: 931-91.
3. Kaelin WG Jr: The von Hippel-Lindau tumor suppressor protein and clear cell renal carcinoma. Clin Cancer Res 2007; 13 (2 Pt 2): 680-4.
4. Maxwell PH, Wiesener MS, Chang GW et al.: The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature 1999; 399: 271-5.
5. Nickerson ML, Jaeger E, Shi Y et al.: Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res 2008; 14: 4726-34.
6. Hanna SC, Heathcote SA, Kim WY: mTOR pathway in renal cell carcinoma. Expert Rev Anticancer Ther 2008; 8: 283-92.
7. Rini BI: Metastatic renal cell carcinoma: many treatment options, one patient. J Clin Oncol 2009; 27: 3225-34.
8. Medical Research Council Renal Cancer Collaborators: Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Lancet 1999; 353: 14-7.
9. Coppin C, Porzsolt F, Awa A et al.: Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev 2005; CD001425.
10. Flanigan RC, Mickisch G, Sylvester R et al.: Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004; 171: 1071-6.
11. Motzer RJ, Bacik J, Murphy BA et al.: Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002; 20: 289-96.
12. Negrier S, Perol D, Ravaud A et al.: Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. Cancer 2007; 110: 2468-77.
13. Escudier B, Pluzanska A, Koralewski P et al.: Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007; 370: 2103-11.
14. Rini BI, Halabi S, Rosenberg JE et al.: Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008; 26: 5422-8.
15. Escudier B, Bellmunt J, Négrier S et al.: Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010; 28: 2144-50.
16. Rini BI, Halabi S, Rosenberg JE et al.: Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol 2010; 28: 2137-43.
17. Motzer RJ, Hutson TE, Tomczak P et al.: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356: 115-24.
18. Motzer RJ, Hutson TE, Tomczak P et al.: Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 3584-90.
19. Escudier B, Szczylik C, Hutson TE et al.: Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 1280-9.
20. Escudier B, Eisen T, Stadler WM et al.: Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356: 125-34.
21. Escudier B, Eisen T, Stadler WM et al.: Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009; 27: 3312-8.
22. Hudes G, Carducci M, Tomczak P et al.: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356: 2271-81.
23. Armstrong AJ, George DJ, Halabi S: Serum lactate dehydrogenase (LDH) as a biomarker for survival with mTOR inhibition in patients with metastatic renal cell carcinoma (RCC). J Clin Oncol 2010; 28: 15s (suppl. abstr. 4631).
24. Motzer RJ, Escudier B, Oudard S et al.: Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372: 449-56.
25. Motzer RJ, Escudier B, Oudard S et al.: Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 2010; 116: 4256-65.
26. Sternberg CN, Davis ID, Mardiak J et al.: Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28: 1061-8.
27. Jeldres C, Sun M, Perrotte P et al.: Pazopanib trial data cannot support first-line use. Nat Rev Urol 2010; 7: 307-8.

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