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 EUROCA-RE-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. 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.

Streszczenie
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. Cyto-reductive 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>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Risk category</th>
<th>% of patients</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Favorable</td>
<td>18</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>1-2</td>
<td>Intermediate</td>
<td>62</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>3-5</td>
<td>Poor</td>
<td>20</td>
<td>2.5</td>
<td>5</td>
</tr>
</tbody>
</table>

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.
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 (17, 18).

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.

Temsirilimus

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 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-

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

<table>
<thead>
<tr>
<th>Response</th>
<th>Sunitinib</th>
<th>Interferon alpha</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response (%)</td>
<td>47</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hazard ratio for progression</td>
<td>0.54</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>26.4</td>
<td>21.8</td>
<td>0.051</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 temsiroliums 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

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