How to select amongst available options for the treatment of advanced RCC?

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The treatment of renal cell carcinoma has dramatically changed in the past 6 years with the approval of seven new drugs since 2006. Although treatment algorithms have been reported and updated every year since 2006, the choice of targeted therapy is not always easy. Selecting a targeted agent in metastatic renal cell carcinoma (mRCC) should take into account various parameters, including the status of the disease, the histology, the status of the patient and finally the availability of the drugs in each country. In addition, in front of every patient, the physician will need to raise important questions such as whether the patient should be treated, should receive surgery, and also what is his prognostic group. The different options are described in this manuscript.

Key words: antiangiogenic, mTOR inhibitor, renal cell carcinoma, sequential therapy, TKI

Treatment of metastatic renal cell carcinoma (mRCC) has dramatically changed in the past 6 years, with the approval of many targeted agents, either vascular endothelial growth factor (VEGF) inhibitors or mammalian target of rapamycin (mTOR) inhibitors. Successively, sorafenib [1] and sunitinib [2] in 2006, temsirolimus [3] and bevacizumab [in combination with interferon (IFN)] [4] in 2007, everolimus [5] in 2008 and pazopanib [6] have been approved by both Food and Drug Administration (FDA) and European Medical Agency (EMA). In addition, very recently, axitinib [7] was also approved by FDA. These drugs have now taken the lead over cytokines in most of the published guidelines. Based on pivotal phase III, recommendations can be summarized as follows (Table 1):

- Only clear-cell histology has been prospectively studied.
- First-line treatment should be different according to the risk group.
- Second-line treatment is slightly different in patients who received cytokines or VEGF-targeted therapy as first line.
- Third-line treatment will start to appear in guidelines.

Obviously however, these recommendations cannot help to perfectly select treatment amongst available options, since:

- Available drugs are not always reimbursed, and the differences between European countries are very wide.
- In some settings, different treatments are equally recommended, and there is no head-to-head study between these different options, such as first-line treatment, in good or intermediate-risk patients, or second-line treatment.
- Prognostic groups are evolving over time, and risk groups used to select patients for pivotal studies are not any more standard. In addition, prognostic factors have been described for the purpose of clinical trials, not for routine use.
- Tolerability of treatments is not taken into account in these recommendations, although tolerability concerns are important in elderly patients or in patients with comorbidities.
- Timing of treatment (i.e. when to start therapy), natural history of the disease (indolent versus rapidly progressive) as well as tumor burden are not defined, making treatment decision not always easy.
- Histology subtype is a key factor in recommendations. However, even clear-cell histology subtype, the most common one, is very heterogenous based, for example on histological grade or the presence of sarcomatoid cells.
- Finally, no biomarkers have been so far reported to help treatment decision.

We will try in this paper to provide decision tools for the physician in charge of patients with mRCC, based on the current guidelines but also on clinical experience from a large institution. For that purpose, we will review some important issues regarding treatment selection in the most common scenarios.

prognostic factors in mRCC

Prognostic models amalgamating multiple clinical factors are often used in clinical management. The most widely used is the Memorial Sloan Kettering Cancer Centre (MSKCC) model, which stratifies prognosis as good, intermediate or poor, based on high lactate dehydrogenase, low Karnofsky score, high corrected calcium, low hemoglobin and time from diagnosis to treatment [8]. This model is useful for identifying patients who
may benefit from immunotherapy, and has been further validated in patients receiving targeted therapies.

The most recent prognostic model for the targeted therapy era, developed by the International Kidney Cancer Working Group, uses nine factors: treatment, performance status (PS), number of metastatic sites, time from diagnosis to treatment, pretreatment hemoglobin, white cell count, lactate dehydrogenase, alkaline phosphatase and serum calcium [9]. In the database of 3748 patients used for its development, median overall survival (OS) times in the favorable-, intermediate- and poor-risk groups were 26.9, 11.5 and 4.2 months, respectively.

The MSKCC score has also been validated and updated for use in the current era of targeted therapies as the Heng criteria [10]. Patients are stratified according to the presence of six risk factors:

- Karnofsky PS <80%.
- Hemoglobin less than the lower limit of normal.
- Time from diagnosis to treatment of <1 year.
- Corrected calcium above the upper limit of normal.
- Platelets greater than the upper limit of normal.
- Neutrophils greater than the upper limit of normal.

This model allows good estimate of survival based upon the number of risk factors involved (Table 2).

In routine practice, risk assessment can alternatively be estimated based on the French classification. This model has been adapted from the French study previously reported [11]. This model uses three important risk factors (Table 3):

- PS
- Time from diagnosis to metastases (<1 or >1 year)
- Number of metastatic sites

Finally, the poor-risk group used for the pivotal study of temsirolimus [3] was based on six risk factors: high lactate dehydrogenase, low Karnofsky score, high corrected calcium, low hemoglobin, time from diagnosis to treatment and number of metastatic sites. Only patients with ≥3 of these poor-risk factors were included.

### Table 1. Recommendations for treatment of metastatic renal cell carcinoma (mRCC) based on pivotal phase III

<table>
<thead>
<tr>
<th>Histology and setting</th>
<th>Risk group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear-cell first line</td>
<td>Good or intermediate risk</td>
<td>Sunitinib, Bevacizumab + IFN</td>
</tr>
<tr>
<td>Clear-cell second line</td>
<td>Poor risk</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>Clear-cell third line</td>
<td>Post cytokines</td>
<td>Sorafenib, Pazopanib, Axitinib</td>
</tr>
<tr>
<td>Non-clear-cell histology</td>
<td>Post tyrosine kinase inhibitors (TKIs)</td>
<td>Everolimus, Axitinib</td>
</tr>
<tr>
<td></td>
<td>Post 2 anti VEGF treatment</td>
<td>Everolimus</td>
</tr>
</tbody>
</table>

### Table 2. Survival estimate based upon the risk factors [10]

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Risk group</th>
<th>Median overall survival</th>
<th>2-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Favorable</td>
<td>NR</td>
<td>75%</td>
</tr>
<tr>
<td>1–2</td>
<td>Intermediate</td>
<td>27 months</td>
<td>53%</td>
</tr>
<tr>
<td>3–6</td>
<td>Poor</td>
<td>8.8 months</td>
<td>7%</td>
</tr>
</tbody>
</table>

### Table 3. The French classification for metastatic renal cell carcinoma (mRCC) [11]

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Performance status (PS) 0 and 1 metastatic site</td>
</tr>
<tr>
<td>Intermediate</td>
<td>PS 1</td>
</tr>
<tr>
<td></td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td>PS 0 and &gt;1 metastatic site</td>
</tr>
<tr>
<td>Poor</td>
<td>PS 2</td>
</tr>
<tr>
<td></td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td>Any PS and liver metastases and &gt;1 metastatic site and interval &lt;1 year</td>
</tr>
</tbody>
</table>

Obviously, these different prognostic models are quite complex, and the French system is more friendly for routine practice.

### Natural history of the disease

mRCC is an heterogenous disease, with very different behaviors, including indolent diseases as well as very rapidly progressive diseases. As there is no clear definition of indolent disease, it is highly recommended, each time this is possible (especially in low tumor burden disease), to get two consecutive scans before starting systemic therapy. This attitude will allow a good estimate of tumor growth, and will avoid starting treatment in patients who could remain asymptomatic for a very long period of time without any treatment.

In indolent disease, starting treatment will depend on many factors, including sites of metastases, age and comorbidities.
and finally willingness of the patient to accept toxic treatment to prolong survival. Based on the results of the recently reported 'TORAVA' trial, indolent disease might be the best scenario to select bevacizumab plus IFN as first-line therapy [12].

**histology**

Histology subtype is a key factor to take into account when deciding which drug should be selected. Most available data are in patients with clear-cell renal cell carcinoma (RCC), which accounts for 70%–80% of cases. Papillary RCC (10%–15% of cases) is thought to have a prognosis comparable with that of clear-cell RCC, while chromophobe RCC (∼5% of cases) has a better prognosis, with 5-year survival approaching 90% [13]. However, owing to the lack of prospective trials in non-clear-cell histology, a general consensus is that non-clear-cell RCC should be treated as clear-cell RCC, although mTOR might have better efficacy in this subgroup. Ongoing phase II and III looking at mTOR inhibitors in non-clear-cell histology are expected to see whether this treatment might be better than TKIs (tyrosine kinase inhibitors) in this histological subtype. Similarly, some rare subtypes, such as translocation RCC, seem to behave like clear-cell carcinoma [14].

**first-line treatment**

**with primary tumor in place**

Cytoreductive nephrectomy is currently recommended in patients with good PS, following two randomized trials in the era of immunotherapy [15]. Whether this recommendation will remain with targeted therapies is currently investigated in two prospective trials. In routine practice, cytoreductive nephrectomy is recommended in patients with good PS and large primary tumors, whilst it is not recommended in patients with poor PS. Systemic treatment will then depend on the risk group:

- In patients with good or intermediate prognosis, TKIs (sunitinib or pazopanib) will be the preferred option after cytoreductive nephrectomy.
- In patients with poor-risk features, nephrectomy will not be recommended, and temsirolimus should be the best therapeutic choice.

**in nephrectomized patients with good or intermediate risk**

In this setting, three different options will be considered based on the recommendations: sunitinib, pazopanib and bevacizumab plus IFN. With all three agents, the median PFS ranged from 10.2 to 11.2 months in the pivotal phase III. The differences between sunitinib and pazopanib are unclear, although indirect comparisons suggest that tolerability of pazopanib might be better than tolerability of sunitinib. A large randomized phase III is currently comparing these two TKIs and should be reported shortly. Another randomized study looking at patient’s preference (PISCES study) suggests that more patients prefer pazopanib [16].

Whether TKIs or bevacizumab should be selected as a best option is unclear. As discussed above, indolent disease might be an ideal scenario to select bevacizumab instead of TKIs [12].

**in nephrectomized patients with poor-risk features**

The global ARCC trial compared the mTORi temsirolimus with IFN and with temsirolimus + IFN in 626 patients [3]. Patients all had a poor prognosis, by a non-standard definition that included ≥2 sites of metastasis rather than using MSKCC criteria. In terms of MSKCC criteria, 69% and 31% of the temsirolimus arm were classified as having poor or intermediate prognosis, respectively. The median PFS was 5.5, 3.1 and 4.7 months with temsirolimus, IFN and temsirolimus + IFN, respectively (temsirolimus versus IFN, P < 0.001) and the OS was 10.9, 7.3 and 8.4 months, respectively (temsirolimus versus IFN, P = 0.008). However, the patients most likely to benefit from temsirolimus are those with ECOG PS 2, non-clear-cell disease and no need for tumor shrinkage. In patients with good PS, sunitinib or pazopanib could be good options to consider.

Table 4. Suggestions for switching therapy [17]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow disease progression</td>
<td>Consider the possibility of switching very cautiously—a change in therapy may not be necessary</td>
</tr>
<tr>
<td>Rapid disease progression</td>
<td>Consider switching immediately. However, retrospective data suggest that patients with progressive disease as their best response on a vascular endothelial growth factor (VEGF)-targeted agent have poor outcomes on all current therapies, and that mTOR inhibitor therapy offers no benefit over a second VEGF-targeted agent</td>
</tr>
<tr>
<td>Mixed response to therapy (e.g. stable disease in one lesion and progression in another)</td>
<td>Also consider the possibility of treatments targeting isolated progressing lesions (e.g. surgery, radiosurgery, radiotherapy, etc.) while continuing systemic treatment</td>
</tr>
<tr>
<td>Discovery of new disease sites</td>
<td>Switch immediately if lesion is significant and definitely new, rather than simply previously undetected</td>
</tr>
<tr>
<td>Unacceptable toxicity</td>
<td>Any treatment strategy should aim at reducing as much as possible the number of patients with unacceptable toxicity. Toxicity is often higher with the second-line tyrosine kinase inhibitors (TKIs) compared with the first, and since many AEs (adverse event) (e.g. hypertension, diarrhea, stomatitis) can be managed effectively, there is no reason to switch immediately</td>
</tr>
</tbody>
</table>

AEs, adverse events.
second-line treatment

Although randomized trials have demonstrated that sequential treatments with TKIs (axitinib or sorafenib) or mTOR inhibitors (everolimus) have activity in second line, there are a number of factors which influence the decision to switch therapy and the time at which to switch. Table 4 gives some situations in which switching may be considered.

third-line treatment

There is no available randomized trial in third-line treatment. However, many patients from the RECORD 1 trial [5] were in fact in the third-line setting. Thus, in patients previously treated with two VEGF-targeted agents, everolimus should probably be recommended.

In conclusion, selection of the targeted therapy in mRCC remains a difficult choice. After raising the question of whether the patient should be treated or not, and whether surgery can be discussed, the decision will be made by taking into account the prognosis group of the patient, the current algorithm based on phase III pivotal trials and also the toxicity profile of the drug. In the future, hopefully, molecular biomarkers should be available to determine optimal treatment options according to tumor pathological and biological features [18]. Biomarkers such as carbonic anhydrase IX, plasmatic VEGF level, HIF (hypoxia inducible factor)-2α expression, phospho-S6 and phospho-AKT have been reported as possible predictive markers of efficacy of high-dose IL2, TKIs or mTOR inhibitors. Current prospective ongoing studies should be available in the near future.

disclosure

The authors have declared no conflicts of interest.

references