How to select targeted therapy in renal cell cancer

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Treatment of renal cell carcinoma has dramatically changed in the past 5 years, with the approval of six 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 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 prognosis. The different options are described here.

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

Introduction

Treatment of metastatic renal cell carcinoma (mRCC) has dramatically changed in the past 5 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, and everolimus [5] in 2008 have been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). In addition, very recently, pazopanib [6] has also been approved by the FDA and the EMEA. These drugs have now taken the lead over cytokines in most of the published guidelines.

Based on the results of large randomized phase III, these drugs should be used as described in Table 1.

Obviously, this algorithm raises many issues:

- Different standards of care are available for similar situations, such as good and intermediate risk groups, based on the MSKCC (Memorial Sloan-Kettering Cancer Center) prognostic factors [7]. However, this classification is not commonly used outside of clinical trials, and was established in the cytokine era. Recent studies have aimed to identify risk factors in patients receiving VEGF-targeted therapy [8, 9]. However, these classifications are rarely used in routine practice, and performance status (PS) remains the main prognostic factor for selecting a treatment for a given patient.

- Recent clinical studies form the basis of evidence-based recommendations for recently updated treatment guidelines for mRCC, helping to harmonize first- and second-line treatment approaches in patients with mRCC with different prognostic risk factors [10]. However, these guidelines have several limitations. In particular, recommended treatments for mRCC have not usually been evaluated specifically in elderly patients and/or those with comorbidites and who are receiving comedication [11]. Approximately one-third of patients enrolled in the recent phase III trials, on which recommendations for treatment with sunitinib, sorafenib, temsirolimus and bevacizumab + IFN-α were based, were >65 years of age: an under-representation of the number of elderly patients with mRCC.

- Most of the studies have only enrolled clear cell mRCC, leading to strong guidelines for this common histology, and very weak guidelines for non-clear cell histology.

- Finally, and very importantly, all published guidelines imply the broad availability of the approved drugs, which is currently not the case in many European countries.

Thus, selecting patients for targeted therapy will depend on many factors, and the decision will have to take into account:

(i) the status of the disease, i.e. primary tumor in place, extent of the disease (including the nature of metastatic sites), prognostic factors, line of treatment; (ii) the histological subtype; (iii) the status of the patient, i.e. age, comorbidities and comedictions; and (iv) obviously the availability of the drugs.

We will try in this paper to provide decision tools for the physician in charge of a patient with mRCC, based on the hypothesis that all the drugs approved are available. In this regard, we will advice the reader to ask the following questions in front of every patient with mRCC:

- Should we treat this patient?
- Is surgery a good therapeutic option?
- Is the histology going to change our decision?
- Which is the line of treatment?
- Finally, what is the prognosis of the patient?

Should we treat this patient?

Despite the efficacy of numerous new drugs, deciding not to treat a patient remains a valid option in two different situations: patients with very slow growing disease and patients...
with very limited life expectancy. The rationale for not treating some patients is (i) to avoid unuseful drugs in patients who were not progressing before therapy; (ii) to be able to evaluate the efficacy of a treatment (how to interpret stable disease in a non-progressive disease); and (iii) to avoid excessive costs and toxicities in patients with very short life expectancy.

mRCC is sometimes very slow growing, without any systemic treatment. There is no prognostic factor allowing the identification of such patients. However, patients with small tumor burden should be informed that waiting a few months before starting a systemic treatment has never proven to be harmful. The recommendation here is to await a confirmed progressive disease before embarking on a systemic treatment which can then continue until death. Good PS and small tumor burden, as well as a long interval between primary tumor and metastases, are strong arguments for not treating the patient immediately.

mRCC with poor prognostic features are good candidates for temsirolimus, which has been shown to be active, and has been approved in this group of patients [3]. However, one should remember that the pivotal phase III study was a clinical protocol with exclusion criteria, and that patients with very short life expectancy were not enrolled in the study. Thus, in end-of-life patients, based on common sense appreciation, mainly poor PS, starting with a weekly infusion of temsirolimus, instead of initiating good palliative care support, should be carefully discussed with both the patient and the family.

**is surgery a good therapeutic option?**

Surgery remains the best curative treatment in mRCC, and in every situation where surgery can be safely performed, such an approach should be considered through a multidisciplinary discussion. At any time during the course of the disease, and especially during targeted therapy, surgical resection should be considered, if it is possible to obtain complete surgical remission [12].

Another issue concerns the role of nephrectomy in metastatic patients. In patients presenting with mRCC and the primary tumor in place, nephrectomy is considered as the standard, at least in good PS patients, based on the results of two large randomized studies [13, 14]. These two studies were performed with IFN as systemic treatment, and whether this standard should remain with new targeted agents is questionable. However, due to the lack of randomized studies comparing the efficacy of targeted agents with or without nephrectomy, nephrectomy is recommended before systemic treatment in patients with good PS, especially when the primary tumor represents a large part of the tumor burden. In contrast, in patients with poor prognostic features [3], nephrectomy has not been shown to be beneficial, and should not be recommended.

**is the histology going to change our decision?**

Clear cell carcinoma represents, by far, the most common histology in mRCC. Most of the non-clear cell histologies are papillary or chromophobe tumors. There are no phase III data available to determine which should be the standard of care in these specific histologies.

As the temsirolimus phase III trial enrolled a significant number of patients with non-clear cell histology, this drug has sometimes been considered as the best therapeutic option in non-clear cell histology. However, retrospective analyses have demonstrated activity of sunitinib and sorafenib [15], and prospective studies are ongoing to determine whether mTOR inhibition is more active that VEGF inhibition in non-clear cell histologies. Until these data are available, one can recommend treatment of non-clear cell mRCC in the same way as for those with a clear cell histology.

**which is the line of treatment?**

The algorithm depicted in table 1 is based on pivotal studies, leading to registration of the drugs. Thus, for example, bevacizumab plus IFN has only been evaluated in first-line treatment, and there are no data available after other therapies. Similarly, temsirolimus was only evaluated in patients with at least three poor prognostic factors, based on MSKCC criteria [7], with the addition of the presence of more than one metastatic site [3].

Whether the active drugs could be given as a different line remains questionable. Surprising data have been reported, such as the disappointing activity of sorafenib in first-line treatment [16], or the better efficacy of temsirolimus in poor risk than in
good risk patients [17]. In contrast, sunitinib has been shown to be active in second-line treatment after cytokines [18] or after bevacizumab [19].

**what is the prognosis of the patient?**

The prognosis of patients with mRCC is usually assessed through the MSKCC criteria [7], taking into account the time between diagnosis and treatment, the PS and three laboratory values: hemoglobin, corrected calcium and lactate dehydrogenase level. This classification is not commonly used in routine practice, and PS is very often considered as the most important prognostic factor in mRCC (as it is in most cancers). The French classification, using only the number of metastatic sites and the PS, is a good alternative to the MSKCC classification [20].

Another issue regarding prognosis is whether the patient will be able to receive several lines of therapy. This issue might be important in the future, since recent reports suggest that sequential treatment is the best therapeutic option in mRCC, and that the choice of the sequence might be of interest [21, 22].

Based on the prognosis, current guidelines help us to decide between good and intermediate prognosis on one hand, and poor prognosis on the other hand. However, this applies only to first-line treatment and to clear cell carcinoma.

The most difficult choice is currently the patients with good and intermediate prognosis. In this population, both sunitinib and bevacizumab + IFN can be given, and very soon pazopanib will be another therapeutic option. To date, no comparative study of these two treatments is available. Based on our experience, we would recommend the following choices.

- In symptomatic patients, and in patients with large tumor burden, sunitinib will probably be preferred, due to the rapid tumor shrinkage often observed with this drug.
- In asymptomatic patients, especially in those with only or predominantly lung metastases, bevacizumab + IFN would be preferred, because this patient population is the most likely to benefit from IFN, and because bevacizumab will increase the efficacy.
- In the remaining patients, no strict recommendation could be made. The toxicity profile of each treatment should be discussed with each patient and, depending on the patient’s choice, treatment could be better decided.

In conclusion, selecting targeted therapy in mRCC remains a difficult decision. 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 to which the patient belongs, 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 [23]. Biomarkers such as carbonic anhydrase IX (CAIX), plasmatic VEGF level, hypoxia-inducible factor-2α (HIF-2α) expression, phospho-S6 and phospho-AKT have been reported as possible predictive markers of efficacy of high dose interleukin-2 (IL-2), thymidine kinase inhibitors (TKIs) or mTOR inhibitors. Current prospective ongoing studies should be available in the near future.

**disclosures**

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**references**


