New Treatment Options for Renal Cell Cancer—Critical Evaluation

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1. The birth of a new therapeutic era

Until the emergence of antiangiogenic drugs, systemic treatments in patients with metastatic renal cell carcinoma (mRCC) had proven largely ineffective. Only a very small percentage of patients were likely to develop long-term disease-free survival following therapy based on interferon-α (IFN-α) and/or interleukin-2 [1,2]. During the past 3 yr, we have witnessed a true revolution not only in the understanding of molecular pathways that are involved in RCC but also in the daily management of mRCC. Great hopes have been reached in prolonging survival of patients with mRCC. Although very effective in providing objective responses or delaying progression, new targeted therapies are still unable to cure patients. Therefore, intensive research is still needed to identify new drugs, assess increased drug dosage or drug associations, and determine the optimal place of surgery.
2. Four phase 3 clinical trials that changed the face of mRCC systemic treatment

Sorafenib (Nexavar®, Bayer Pharmaceuticals) is an oral tyrosine-kinase inhibitor (TKI) originally developed as an inhibitor of Raf kinases [3]. It was subsequently found to have activity against VEGF receptor (VEGFR), PDGF receptor (PDGFR), Fms-like tyrosine kinase-3, and stem-cell growth factor (c-KIT). A phase 3, placebo-controlled, randomized trial in 905 previously treated patients was recently published [4]. In patients treated with sorafenib (800 mg/d), progression-free survival (PFS) was doubled compared with the placebo arm (24 wk vs. 12 wk, \(p < 0.000001\)). This was the first randomized phase 3 study demonstrating that a TKI was able to prolong PFS in second-line therapy in mRCC.

Sunitinib (Sutent®, Pfizer Inc) is a selective inhibitor of certain protein tyrosine kinases including VEGFR and PDGFR. A phase 3 trial comparing sunitinib (50 mg/d for 4 wk followed by 2 wk off) versus IFN-α was recently reported with PFS as the primary end point [5]. The objective response rates were 31% versus 6%, respectively. The median PFS was more than twice as long in the sunitinib arm (11 mo vs. 5 mo, \(p < 0.000001\)). Reported side-effects were similar to those observed in the sorafenib studies, with grades 3/4 not exceeding 10% of patients. This was the first evidence that sunitinib was superior to conventional immuno-therapy in the first-line setting.

Temsirolimus (CCI-779, Torisel®, Wyeth Pharmaceuticals) has been shown to bind with high affinity to the immunophilin FKBP; this complex inhibits mammalian target of rapamycin (mTOR) kinase activity [6]. A phase 3 study was recently conducted in first-line therapy of 626 mRCC patients with poor-risk characteristics who received either IFN-α or temsirolimus alone or temsirolimus plus IFN-α [7]. Median overall survival (OS) was longer in only patients treated with temsirolimus alone compared with patients who received IFN-α or IFN-α plus temsirolimus (10.9 vs. 7.3 vs. 8.4 mo, \(p = 0.069\)). The most frequently occurring grade 3/4 adverse events were asthenia, anemia, and dyspnea. This was the first evidence that inhibiting mTOR in the first-line setting was able to prolong OS in mRCC patients with poor-risk characteristics.

Bevacizumab (Avastin®, Genentech, Roche) is a recombinant human monoclonal antibody directed against VEGF. The results of a phase 3 randomized trial comparing IFN-α alone (9 million UI, subcutaneous, three times weekly during 1 yr) or combined with bevacizumab (10 mg/kg, intravenous, every 15 d until disease progression) have recently been reported [8]. Six hundred forty-nine patients with clear-cell mRCC and previous nephrectomy were included in this study. Objective response rates were 30.6% and 12.4% in the combination and mono-therapy arms, respectively (\(p < 0.0001\)). Median PFS time in the bevacizumab plus IFN-α arm was 10.2 mo compared with 5.4 mo in the single-drug arm (\(p < 0.0001\)). The clinical trial was stopped because of toxicity twice as frequently in the bevacizumab plus IFN-α group (28%) than in the IFN-α group (12%). On the basis of these results, bevacizumab combined with IFN-α could represent a viable alternative to VEGF-R TKI in first-line treatment of mRCC.

Although the introduction of drugs targeting tumor angiogenesis features impressive progress compared with previous standard of care, we must be aware that mRCC is still an incurable disease. Therefore a number of questions still need to be addressed.

3. Have we identified predictive factors for antiangiogenic drugs response?

On the basis of the phase 3 trial comparing sunitinib and IFN-α in the first-line setting, prognostic factors for PFS with sunitinib have recently been evaluated [9]. It was shown that baseline factors that predicted longer PFS with sunitinib were haemoglobin = lower limit of normal, corrected calcium = 10 mg/dl (\(p = 0.001\)), Eastern Cooperative Oncology Group (ECOG) score = 0 (\(p = 0.0005\)), number of metastatic sites = zero or one (\(p = 0.0064\)), and time from diagnosis to treatment = 1 yr (\(p = 0.0002\)).

Similarly, on the basis of data from the TARGET trial, Bukowski et al [10] assessed the prognostic value of VEGF and soluble VEGFR2 (sVEGFR2). It was shown that, after sorafenib treatment, VEGF levels were increased and sVEGFR2 levels were decreased. With the use of a Cox proportional hazard model, it was shown that VEGF was an independent prognostic factor for PFS (\(p = 0.014\)) and OS. It was concluded that patients with high baseline VEGF levels have a poorer prognosis and are more likely to benefit from treatment with sorafenib.

The group of Choueiri et al [11] recently assessed prognostic factors in 120 patients with mRCC who had been treated with bevacizumab, sorafenib, sunitinib, or axitinib. Multivariate analysis identified the following independent adverse prognostic factors for PFS: time from diagnosis to current treatment < 2 yr, baseline platelet count > 300 K/μl, baseline neutrophil count > 4.5 K/μl, baseline corrected serum calcium < 8.5 or > 10.0 mg/dl, and initial ECOG performance status > 0. With the
use of these adverse prognostic factors, three risk groups were formed on the basis of the number of prognostic factors present for PFS: a favourable risk group possessing zero to one prognostic factors, an intermediate-risk group possessing two prognostic factors, and a poor-risk group possessing three to five prognostic factors.

In another study, Choueiri et al [12] evaluated whether von-Hippel Lindau (VHL) mutation status could predict an objective response to VEGF-targeted therapy. A retrospective study in 123 patients with mRCC treated with sunitinib, sorafenib, axitinib, or bevacizumab was performed. VHL mutation was found in 48% of patients. Patients with loss of function mutations had a response rate of 51% compared with 41% in patients with wild-type VHL. In multivariate analyses the presence of a loss of function mutation was an independent prognostic factor associated with an improved objective response rate ($p = 0.03$), even after correcting for ECOG performance, haemoglobin, corrected calcium, lactate dehydrogenase, prior radiation, prior therapy, and number of metastatic sites.

It is clear that we now have to reassess all prognostic systems that have been designed in the era of immunotherapy. Although a certain number of prognostic factors may be common between immunotherapy and TKIs, more specific factors involved in the tumor angiogenesis pathway need to be identified and validated.

4. What is the role for nephrectomy in the era of targeted therapies?

Although it remains reasonable to remove huge tumors that are likely to cause local complications under treatment, the question of nephrectomy needs to be addressed in organ-confined primary tumors. In contrast with cytokine-based therapy, TKIs are indeed able to drive significant responses within the primary kidney tumor. As a means to answer this question, a phase 3 randomized study that compares nephrectomy followed by antiangiogenic treatment with angiogenic treatment alone in synchronous metastatic RCC is currently being designed in France. Furthermore, adjuvant and neoadjuvant studies are on the way that could result in earlier introduction of antiangiogenic drugs in high-risk localized or advanced RCCs [13,14]. Finally, it is increasingly clear that the emergence of antiangiogenic drugs is going to change not only medical management but also surgical strategy in mRCC [15].

5. Is there a dose effect with antiangiogenic drugs?

Amato et al [16] have recently reported their experience in dose escalation with sorafenib. Forty-four patients were included in this study; 41 and 32 patients reached the 1200 and 1600 mg levels, respectively. Complete, partial, and 6-mo stable disease rates were 16%, 39%, and 20%, respectively. Median PFS and OS times were 8.4 and 11.4 mo, respectively. In another study [17], sorafenib dose escalation from 800 to 1200 mg resulted in an additional 3.6 mo of PFS time after progression. Finally, a third study [18] recently demonstrated a correlation between sunitinib pharmacokinetics and clinical benefit. Further studies are required for validating that plausible relationship between TKI dosage and clinical efficacy, especially regarding sorafenib.

6. Are non–clear-cell RCCs sensitive to antiangiogenic drugs?

Most series analysing results of antiangiogenic drugs in mRCC predominantly included clear-cell RCCs. Cytokine-based therapy was poorly effective in non–clear-cell RCCs [19]. To what extent antiangiogenic drugs are facing the same resistance in papillary or chromophobe metastatic carcinomas remains unclear. Two reports from the 2007 American Society of Clinical Oncology meeting addressed this issue. Plantade et al [20] retrospectively assessed sorafenib ($n = 20$) and sunitinib ($n = 33$) efficacies in non–clear-cell RCCs. Overall response rate in 12 patients with chromophobe carcinomas was 25% compared with only 4.8 in 41 papillary carcinomas ($p = 0.07$). Median PFS was also slightly different in chromophobe and papillary carcinomas (9.3 vs. 6.6 mo, $p = 0.07$). These findings might suggest that chromophobe carcinomas are better TKI responders than their papillary counterparts.

A second study [7] analysed the influence of histological subtype regarding temsirolimus efficacy in first-line therapy. Among tumors from patients who were included in the phase 3 trial comparing temsirolimus and IFN-α, 18% were non–clear-cell RCCs including 75% papillary carcinomas. All histological subtypes appeared to benefit from temsirolimus treatment. There was even a trend for a greater benefit in non–clear-cell RCCs [21]. These findings might suggest that different histologies driven by different molecular pathways could require more-specific targeted therapies.
7. Conclusion

Four phase 3 trials have recently changed the therapeutic landscape in mRCC. In first-line therapy, sunitinib, bevacizumab plus IFN-α, and temsirolimus have proven effective in prolonging PFS or OS depending on risk group selection criteria. In second-line therapy, sorafenib has been proven able to double PFS compared with placebo. Despite outstanding progress, many pending questions will need to be solved for improving antiangiogenic drug strategy and obtaining curative responses. Predictive factors for response, drug combination efficacy and toxicity, sequence of drug administration, drug dosing, and timing of surgery constitute an inexhaustible list of issues that will need to be addressed in further clinical trials.

Conflicts of interest

Dr Patard is a consultant for Pfizer, Bayer, and Wyeth Pharmaceuticals.

References