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ICUD-EAU International Consultation on Kidney Cancer 2010: Treatment of Metastatic Disease

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Abstract

Context: Until the development of novel targeted agents directed against angiogenesis and tumour growth, few treatment options have been available for the treatment of metastatic renal-cell carcinoma (mRCC).
Objective: This review discusses current targeted therapies for mRCC and provides consensus statements regarding treatment algorithms.
Evidence acquisition: Medical literature was retrieved from PubMed up to April 2011. Additional relevant articles and abstract reviews were included from the bibliographies of the retrieved literature.
Evidence synthesis: Targeted treatment for mRCC can be categorized for the following patient groups: previously untreated patients, those refractory to immunotherapy, and those refractory to vascular endothelial growth factor (VEGF)–targeted therapy. Sunitinib and bevacizumab combined with interferon alpha are generally considered first-line treatment options in patients with favourable or intermediate prognoses. Temsirolimus is considered a first-line treatment option for poor-risk patients. Either sorafenib or sunitinib may be valid second-line treatments for patients who have failed prior cytokine-based therapies. For patients refractory to treatment with VEGF-targeted therapy, everolimus is now recommended. Pazopanib is a new treatment option in the first- and second-line setting (after cytokine failure). Sequential and combination approaches, and the roles of nephrectomy and tumour metastasectomy will also be discussed.
Conclusions: Increasing clinical evidence is clarifying appropriate first- and second-line treatments with targeted agents for patients with mRCC. Based on phase 2 and 3 trials, a sequential approach is most promising, while combination therapy is still investigational. The role of nephrectomy in mRCC is being evaluated in ongoing phase 3 clinical trials.

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1. Introduction

Renal-cell carcinoma (RCC) accounts for 2% of all cancers. In Europe, 40 000 patients are diagnosed with RCC each year, leading to 20 000 deaths [1].

One-third of patients are initially diagnosed with locally invasive or stage IV disease. Recurrence occurs in about 25% of patients having surgical resection for localized disease even though it was considered as curative. The prognosis for patients with distant disease was generally poor, with a 5-yr survival rate not >10% [2]. Until the past 4 yr, systemic treatments in patients with metastatic RCC (mRCC) have proven largely ineffective. Regarding chemotherapy or hormonal therapy, no single agent has been reported to achieve a consistent response rate in >10% of patients. Only a very small percentage of patients are likely to develop long-term disease-free survival following interferon-α (IFN-α)–and/or interleukin-2 (IL-2)–based therapy [3,4]. At Memorial Sloan-Kettering Cancer Center (MSKCC), the overall median survival in 670 patients who were treated with chemotherapy or immunotherapy in 24 consecutive clinical trials from 1975 to 1996 was 10 mo [5].

Two key pathways are essential to the pathophysiology of the clear-cell RCC subtype: the hypoxia response pathway associated with inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene and the mammalian target of rapamycin (mTOR) signalling pathway [6]. Several therapies targeting these two pathways, including sunitinib, sorafenib, temsirolimus, bevacizumab, and everolimus, are available for clinical use and have revolutionized the treatment of mRCC [7]. This article reviews current targeted treatment approaches in the first- and second-line mRCC settings, as well as modifications to existing treatment algorithms, based on recently available data.

2. Evidence acquisition

Medical literature was retrieved from PubMed up to April 2011. Additional relevant articles and abstract reviews were included from the bibliographies of the retrieved literature. All data were reviewed and final statements were approved by experts in the field.

3. Evidence synthesis

3.1. Current treatment approaches utilizing novel targeted agents

At present, treatment for metastatic clear-cell RCC with molecularly targeted agents can be broadly divided into the following categories: previously untreated patients, those refractory or intolerant to immunotherapy, and those who have failed treatment with VEGF-targeted therapy [2]. An important consideration that influences treatment decisions is the MSKCC prognostic risk-stratification system, which is widely used to define patient profiles and provides an indication of overall survival (OS) [5]. In this system, derived from patients treated with IFN-based therapy in six prospective clinical trials at a single centre in the United States, five prognostic factors are used to categorize patients with mRCC into three risk groups: favourable (no risk factors), intermediate (one to two risk factors), and poor (three or more risk factors). Median OS times for patients with good risk is 30 mo, intermediate risk is 14 mo, and poor risk is 5 mo [7].

3.2. Treatment-naïve patients

3.2.1. Treatment-naïve patients with favourable or intermediate prognosis

Sunitinib is a multi–tyrosine kinase inhibitor (TKI) that acts mainly on the VEGF receptor (VEGFR) and platelet-derived growth-factor receptor (PDGFR). In a phase 3 trial of sunitinib versus IFN-α in untreated patients with mRCC, sunitinib demonstrated significant improvements in objective response rate (ORR; independent review: 31% vs 6%; $p < 0.000001$), median progression-free survival (PFS; 11 mo vs 5 mo; $p < 0.001$), and OS (26.4 mo vs 21.8 mo; hazard ratio [HR]: 0.821; $p = 0.051$) [8,9]. These data have led to sunitinib being recommended as a first-line therapy for patients with mRCC [10] (Fig. 1).

Bevacizumab, a monoclonal antibody targeting the VEGF ligand directly, in combination with IFN-α, has shown efficacy in two phase 3 trials in patients with previously untreated mRCC [11–14]. In the first of these studies, median PFS was 10.4 mo for bevacizumab plus IFN-α

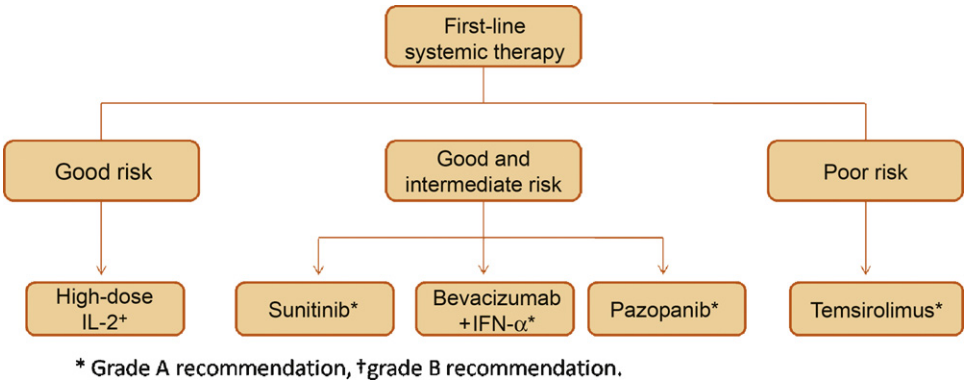

Fig. 1 – Treatment schematic for patients with metastatic clear-cell renal cell carcinoma in the first-line setting. IL-2 = interleukin-2; IFN-α = interferon-α.

compared with 5.5 mo for IFN-α alone ($p < 0.0001$) [11]. No significant difference in OS was observed (23.3 mo vs 21.3 mo; $p = 0.1291$) [13]. Consistent results were seen in the second study, performed by the Cancer and Leukemia Group B, with median PFS of 8.4 mo and 4.9 mo, respectively ($p < 0.0001$) [12]. Again, no significant difference in OS was observed (18.3 mo vs 17.4 mo; $p = 0.069$) [14]. The PFS benefits seen in these trials are similar to those obtained with sunitinib in therapy-naïve patients with advanced RCC [8], and support bevacizumab plus IFN-α as another acceptable and effective therapy in the first-line setting [10] (Fig. 1).

Pazopanib has a similar broad spectrum of kinase inhibition, including VEGFR1-3, PDGFR-A and -B, and c-Kit. The results of a phase 3 trial versus placebo in patients who either received no prior therapy or who failed one prior therapy with cytokines or bevacizumab has recently been reported [15,16]. Four hundred thirty-five therapy-naïve and cytokine-pretreated mRCC patients were randomised to oral pazopanib or placebo (randomisation 2:1 for pazopanib), with PFS as the primary end point. In both treatment-naïve and pretreated patients there was a significant benefit in PFS. The median PFS for pazopanib compared with placebo was 9.2 vs 4.2 mo and in treatment-naïve patients, 11.1 vs 2.8 mo, respectively ($p < 0.0000001$) [15]. With regards to final OS results, no significant difference in OS was observed (22.9 mo vs 20.5 mo; $p = 0.224$), but 54% of placebo patients were crossed over and some of them with very early crossover [16]. These data have led to pazopanib receiving US Food and Drug Administration (FDA) approval and, more recently, conditional approval by the European Medicines Agency (EMEA) (Fig. 1).

3.2.2. *Treatment-naïve patients with poor prognosis*

Temsirolimus is an intravenously administered inhibitor of mTOR. A randomised, phase 3 trial compared monotherapy with temsirolimus versus IFN-α versus temsirolimus plus IFN-α as first-line treatment in patients with mRCC and poor prognosis [17]. Patients were required to have at least three of six predictors of a poor prognosis and survival according to a prognostic factor scheme modified from the MSKCC model. Patients who received temsirolimus alone compared with those who received IFN-α alone or the combination had greater PFS (5.5 vs 3.1 vs 4.7 mo, respectively), OS (10.9 vs 7.3 vs 8.4 mo), and ORR (8.6% vs 4.8% vs 8.1%). The results of this trial justify mTOR as a target for renal cancer treatment and recent European guidelines recommend that temsirolimus be considered as first-line treatment in poor-risk patients [10] (Fig. 1).

3.3. *Cytokine-refractory patients*

Sorafenib is a small-molecule multikinase inhibitor of VEGFR and related receptors, and also inhibits the intracellular signalling of Raf kinase. In a placebo-controlled phase 3 trial involving patients with mRCC who had failed previous cytokine therapy, a PFS advantage for sorafenib of 5.5 mo versus 2.8 mo ($p < 0.001$) was observed [18,19]. Partial responses were reported as the best response in 10% of patients receiving sorafenib and in 2% of placebo recipients ($p < 0.001$). The disease-control rate was higher for sorafenib than placebo (62% vs 37%; $p < 0.001$) [18]. An improved OS with sorafenib was observed after censoring placebo patients who had crossed over to sorafenib (17.8 mo vs 14.3 mo; $p = 0.0287$) [19]. Based on the results of this trial, sorafenib is recommended as a second-line agent in cytokine-refractory or cytokine-unsuitable patients [10] (Fig. 2).

The efficacy of sunitinib in a total of 169 patients with mRCC who progressed on prior cytokine therapy was demonstrated in two phase 2 trials [20,21]. Across the two trials, partial responses were reported in 34–40% of patients and a median PFS of 8.3–8.7 mo was observed.

Taken together, these data indicate that either sorafenib or sunitinib may be valid second-line treatment options for patients who have failed prior cytokine-based therapies.

Pazopanib, in the recently reported phase 3 trial comparing its efficacy over placebo in naïve and cytokine-refractory

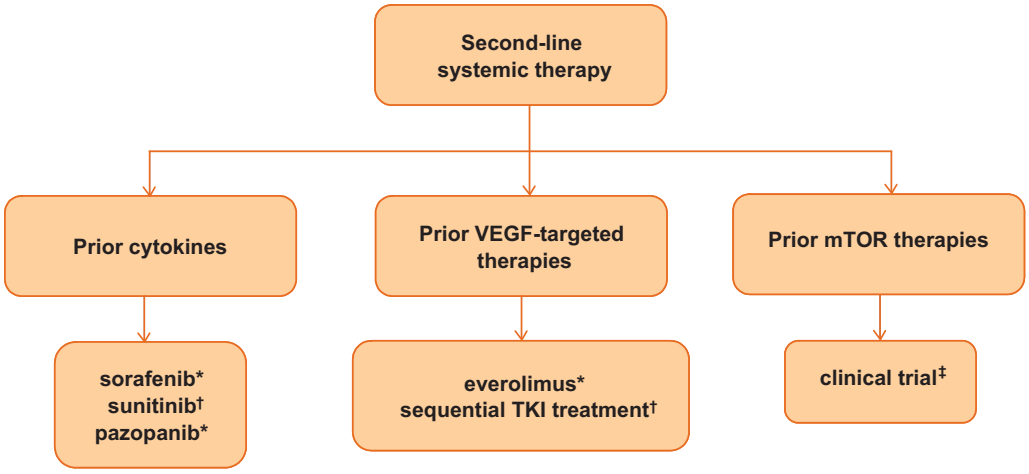

Fig. 2 – Treatment schematic for patients with metastatic clear-cell renal cell carcinoma in the second-line setting.
VEGF = vascular endothelial growth factor; mTOR = mammalian target of rapamycin; TKI = multi–tyrosine kinase inhibitor.

patients, also demonstrated a PFS advantage in the latest group (median PFS 7.4 vs 4.2 mo; $p < 0.001$) [15]. This has led to pazopanib's approval by the FDA and conditional approval by the EMEA in the second-line setting after cytokine failure (Fig. 2).

3.4. Vascular endothelial growth factor-targeted therapy-refractory patients and the sequential therapy concept

Retrospective or phase 2 trials have shown substantial clinical benefit from novel TKIs, including sunitinib, sorafenib, and axitinib, in patients with mRCC failing prior VEGF-targeted therapy [22–25]. The RECORD-1 trial has explored the possibility of switching to an agent with a different mechanism of action and molecular target, that is, an mTOR inhibitor such as everolimus [26,27]. In this phase 3 trial, patients receiving everolimus (10 mg once daily; $n = 272$) had significantly prolonged PFS versus those on placebo ($n = 138$; 4.0 mo vs 1.9 mo; HR: 0.30; $p < 0.0001$). The end of the double-blind analysis from this trial indicated a further improvement in PFS with everolimus treatment (4.90 mo [$n = 277$] vs 1.87 mo [$n = 139$]; HR: 0.33; $p < 0.001$). The PFS benefit following treatment with everolimus was maintained across patients with favourable ($n = 120$), intermediate ($n = 235$), or poor ($n = 61$) MSKCC prognosis. At the end of the double-blind analysis, median OS was 14.78 mo in the everolimus group and 14.39 mo in the placebo group. Crossover from placebo to the active treatment arm was allowed after disease progression, potentially confounding OS; 81% of placebo recipients who progressed crossed over to everolimus treatment.

Two other randomised phase 3 trials are currently recruiting to look at temsirolimus and axitinib as second-line options. The AXIS trial is testing axitinib versus sorafenib in patients failing any of the first-line regimens such as sunitinib, bevacizumab plus interferon, temsirolimus, or cytokines. The second trial is a prospective, randomised, phase 3 trial of temsirolimus versus sorafenib as second-line therapy in patients who have failed only first-line sunitinib option. In both trials, PFS is the primary end point. Results of this trial are awaited.

Other trials are ongoing to determine the optimal TKIs/TKIs or TKIs/mTOR inhibitors drug sequence. Based on several retrospective reports showing that the sequence of sorafenib given prior to sunitinib may be superior when compared to the reverse sequence, an ongoing phase 3 trial (SWITCH trial) has been designed to define the best sequence of TKIs. Another trial is the RECORD-3 study. This is an open-label, multicentre, phase 2 study to compare first-line everolimus followed by second-line sunitinib versus the opposite sequence (first-line sunitinib followed by second-line everolimus) in the treatment of patients with mRCC (ClinicalTrials.gov identifier NCT00903175).

3.5. Drug combination

The concept of an antiangiogenic drug combination is to enhance drug monotherapy efficacy by vertical or horizontal blockade. The inhibition of several steps of the same pathway (hypoxia-inducible factor [HIF]-VEGF-VEGFR) is a *vertical* blockade, while targeting in parallel two separate pathways with different functions (PDGFR, VEGFR, EGFR) is considered a *horizontal* blockade [28].

The combination of bevacizumab and sunitinib has been explored in a phase 1 study [29]. Nineteen patients with mRCC received escalating doses of sunitinib from 25 to 50 mg daily with fixed-dose bevacizumab (10 mg/kg intravenously [IV]). Dose-limiting toxicity (DLT) was grade 4 haemorrhage in one patient at each of the higher doses and one fatal myocardial infarction at the highest dose. All levels of treatment induced a 37% partial response (PR). The toxicity seen with these two agents precluded further development of the combination.

The combination of bevacizumab and sorafenib has been explored in a phase 1 trial [30]. Sixteen patients were included for a dose escalation. Grade 3 proteinuria and uncontrolled grade 3 hypertension were the DLTs at the highest level, corresponding to the maximum tolerated dose (MTD). The recommended dose was sorafenib at 200 mg twice daily and bevacizumab at 5 mg/kg. Interesting synergistic antitumour activity was observed with this combination.

Other phase 1 trials have explored the combination of TKIs inhibitors with IFN. In these trials, patients received sunitinib or sorafenib and IFN-α-2b with DLTs that included fatigue and myelosuppression. Only inferior dosages of both sunitinib or sorafenib and IFN-α-2b, compared to optimal dosages in monotherapy, were manageable. Phase 2 studies have evaluated the combination of sorafenib and IFN-α at standard or low dose without clear superior benefit for the combination [31,32].

Temsirolimus and bevacizumab were combined in a phase 1 study during which the recommended weekly dose of temsirolimus (25 mg/kg IV) and bevacizumab (10 mg/kg per 2 wk) were used. DLTs encountered were grade 3 stomatitis and hypertryglyceridemia. Among 12 evaluable patients, eight PRs were reported. Based on the preliminary results reported, a randomised phase 3 trial (INTORACT) is ongoing comparing temsirolimus/bevacizumab with bevacizumab/IFN.

The TORAVA trial is a randomised phase 2 trial comparing bevacizumab/temsirolimus versus bevacizumab/interferon versus sunitinib in 170 patients. The toxicity profile of the bevacizumab/temsirolimus combination was higher than expected and no evidence of a synergistic or additive efficacy was observed in terms of PFS (8.2 mo [bevacizumab/temsirolimus] vs 16.8 mo [bevacizumab/interferon] vs 8.2 mo [sunitinib]) [33].

The temsirolimus and sorafenib combination has also been evaluated [34]. Patients were treated with escalating continuous oral doses of sorafenib (200 and 400 mg twice daily) and weekly temsirolimus IV (15 mg, 25 mg). Thirty-three evaluable patients showed DLTs including grade 3 hand-foot syndrome, mucositis, rash, thrombocytopenia, neutropenia, and creatinine elevation. The full recommended dose of both drugs appeared unachievable mainly due to mucositis.

Bevacizumab in combination with the oral mTOR inhibitor everolimus is a promising combination in first- and second-line settings [35]. A randomised phase 2 trial is ongoing comparing bevacizumab/everolimus with bevacizumab/IFN (RECORD-2).

Other randomised phase 2 or 3 trials are being conducted. The BeST trial is a four-arm, randomised, Eastern Cooperative Oncology Group phase 2 trial (E2804) examining frontline therapy with bevacizumab versus temsirolimus and bevacizumab versus sorafenib and bevacizumab versus temsirolimus and sorafenib.

The current opinion of most investigators regarding combination therapy is that until it has clearly been shown superior to monotherapy, it should not be used outside the context of clinical trials. Results of ongoing trials are eagerly awaited.

3.6. The role for nephrectomy in the era of targeted therapies

Two randomised studies have demonstrated that nephrectomy is associated with a survival advantage in selected IFN-treated mRCC patients [36,37]. Based on these results, primary tumour removal is currently part of the standard of care in mRCC. However, no equivalent evidence has been obtained with antiangiogenic drugs so far, even though it remains reasonable to remove large tumours that are likely to cause local complications under treatment. In contrast to cytokine-based therapy, TKIs are indeed able to cause significant responses within the primary kidney tumour [38]. Therefore, TKIs could be used in the neoadjuvant setting for selecting those good- and intermediate-risk patients who may benefit from nephrectomy [39]. In several phase 2 trials, presurgical sunitinib or bevacizumab has demonstrated sufficient safety and efficacy [40–42].

A subgroup analysis from the phase 3 trial comparing temsirolimus with IFN in poor-risk patients demonstrated similar survival benefit for temsirolimus regardless of patient nephrectomy status, thus suggesting that nephrectomy may have a limited role in poor-risk patients [43].

Two phase 3 randomised studies, addressing respectively the questions of the role of upfront therapy and of the timing of nephrectomy, are ongoing in Europe [44]. The CARMENA trial is a phase 3 randomised study comparing nephrectomy plus sunitinib versus sunitinib without nephrectomy in first-line mRCC. The primary end point is OS. The European Organisation for Research and Treatment of Cancer trial (SURTIME trial) is a randomised phase 3 trial comparing sunitinib followed by nephrectomy in case of nonprogressive metastases followed by sunitinib versus nephrectomy followed by sunitinib in patients with synchronous mRCC. The primary end point is PFS.

3.7. The role of metastasectomy

The 5-yr survival rate for patients undergoing RCC metastases resection ranges from 35% to 60% [45]. An interval from RCC diagnosis to occurrence of metastases >1 yr, a unique metastatic site, and age <60 yr have been identified as favourable survival predictive factors following RCC metastases resection [46]. In case of pulmonary resection, delay from RCC diagnosis to metastases occurrence, complete resection, number of nodules to remove, and metastatic nodule size appear as major prognostic factors [47,48]. The 5-yr survival rate seems to be superior in case of pulmonary resection (54%) than in case of brain resection (18%) [46]. Pancreatic metastases are likely to occur late in the natural history of the metastatic disease and seem to have a good prognosis when a surgical resection is feasible. Due to the emergence of effective targeted therapies, the concept of tumour metastasectomy needs to be revisited for potentially rendering patients free of disease following combined surgical and medical treatments [45–50].

4. Conclusions

Sunitinib monotherapy and bevacizumab in combination with IFN-α may be considered first-line treatment options in patients with metastatic or unresectable clear-cell RCC and favourable or intermediate prognosis according to MSKCC criteria (grade A). In the first-line setting, temsirolimus is recommended in patients with poor prognostic features, according to modified MSKCC criteria (grade A). Cytokines, including high-dose IL-2, remain an option for first-line treatment of highly selected patients with clear-cell mRCC and good prognosis (grade B).

In the second-line setting, sorafenib treatment is recommended for patients with mRCC refractory to cytokines (grade A) and everolimus treatment is recommended for patients refractory to VEGF-targeted therapy (grade A). Pazopanib is a new therapeutic option in the first-line setting or in cytokine-refractory patients (grade A).

Sunitinib is a possible alternative to temsirolimus as first-line treatment in patients with poor prognosis and also as an alternative to sorafenib as a second-line treatment after cytokines (grade B).

For patients refractory to mTOR inhibitors, enrolment in clinical trials is advised (grade C).

Antiangiogenic drug combinations are still investigational (grade B). The sequential therapy concept is validated by phase 2 and 3 trials. Further trials are needed to determine the optimal intra- or interdrug class sequencing (grade B).

Based on previous randomised studies with IFN, upfront nephrectomy is advised in appropriately selected patients. However, further phase 3 clinical trials should clarify its exact role in the current therapeutic era. Nephrectomy is not likely to be useful in poor-risk patients, according to MSKCC criteria (grade B).

Surgical resection of a unique metastasis should be considered as a valuable therapeutic option, particularly in cases of delay between RCC diagnosis and occurrence of metastasis >1 yr, young age, or favourable prognostic features, and when a complete resection is expected. The concept of tumour metastases resection should be revisited in the era of targeted therapy (grade C).

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Study concept and design: Patard, Pignot, Escudier, Eisen, Bex, Sternberg, Rini, Roigas, Choueiri, Bukowski, Motzer, Bellmunt.
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Analysis and interpretation of data: Patard, Pignot, Escudier, Eisen, Bex, Sternberg, Rini, Roigas, Choueiri, Bukowski, Motzer, Bellmunt.
Drafting of the manuscript: Patard, Pignot, Escudier, Eisen, Bex, Sternberg, Rini, Roigas, Choueiri, Bukowski, Motzer, Bellmunt.
Critical revision of the manuscript for important intellectual content: Patard, Bellmunt.
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