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Current and Future Treatment Options for Metastatic Renal Cell Carcinoma

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Abstract

Context: Metastatic renal cell carcinoma (mRCC) is associated with poor survival, and until recently, treatment options have been very limited. However, the advent of targeted therapies has radically improved the outlook for patients with mRCC. **Objective:** This review describes current treatment options for mRCC and summarizes the data on efficacy and safety of approved and newly emerging targeted therapies.

Evidence acquisition: Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.

Evidence synthesis: There continues to be a role for surgery and immunotherapy in mRCC, but this role is limited to specific patient subgroups. Several pivotal, phase 3 trials have established the efficacy and tolerability of agents targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways in various clinical settings. The benefit of everolimus after failure of VEGF-targeted therapy in the phase 3 RECORD-1 trial has demonstrated the value of sequential treatment for patients with mRCC. Other sequential regimens as well as the combination of targeted agents with each other or with immunotherapy are all promising approaches warranting further investigation. There may also be a potential role for targeted agents in both the neoadjuvant and adjuvant settings. **Conclusions:** The development of targeted therapies for mRCC has substantially improved the treatment options for patients. The results of further studies that will enable the optimal integration of targeted agents into treatment strategies for mRCC are awaited with interest.

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1. Introduction

Metastatic renal cell carcinoma (mRCC) is associated with poor overall survival (OS) [1]. Approximately 20–30% of patients who present with localised disease develop

metastases; the median time to relapse after nephrectomy is 15–18 mo [1]. Furthermore, 25–30% of patients with renal cell carcinoma (RCC) present with advanced disease at the time of diagnosis [2]. Although conventional systemic treatments such as immunotherapies have

curative potential for some patients [3], this approach is mainly associated with limited efficacy and modest success rates in the majority of mRCC cases [4].

The advent of targeted therapeutic approaches has radically improved the outlook for patients with mRCC, providing new, active options for the medical management of this aggressive tumour. This article reviews current approaches to treatment and summarises recent data for newly emergent targeted therapies.

2. Evidence acquisition

Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.

3. Evidence synthesis

3.1. Surgery

Surgery has a vital, albeit limited role in the treatment of mRCC, and its success is largely dependent on the stage of the disease [5–7]. Surgical interventions can be directed at palliation of symptoms or controlling metastasis [5,8]. However, although regression of metastatic disease following nephrectomy exists, it is a very infrequent event [7,9,10].

The survival benefit of nephrectomy prior to immunotherapy has been demonstrated in two independent, prospective, identically designed clinical trials in which patients with a good performance status (PS) were randomised to nephrectomy followed by treatment with interferon- α (IFN- α) versus IFN- α alone [11,12]. The results of the two trials were highly congruent: Nephrectomy increased median survival time from 8.1 mo to 11.1 mo and from 7 mo to 17 mo, respectively [11,12]. A combined analysis yielded a median survival of 13.6 mo for nephrectomy plus IFN- α versus 7.8 mo for IFN- α alone, representing a 31% decrease in the risk of mortality ($p = 0.002$) [13]. Based on these trials, the previous general inclination to perform a nephrectomy in this situation has become the standard of care in patients with a good PS.

Other surgical approaches are directed at decreasing the metastatic burden. The benefits of metastasectomy can lead to improvements in OS and quality of life (QoL) [14], but careful patient selection is required for this procedure.

3.2. Immunotherapy

Historically, the efficacy of nonsurgical treatment for RCC has been very limited. Advanced RCC is notoriously resistant to cytotoxic chemotherapy, with response rates generally <10% [15], and radiation therapy is only recommended for palliation of symptomatic metastases in nonresectable brain or painful bone lesions [16]. However, the immunogenic nature of RCC suggested by occasional spontaneous regression of RCC, especially when spread to the lungs, as well as the detection of tumour-infiltrating lymphocytes in RCC tissue have led to an immunological approach to treatment,

including the development of cytokine therapy, with interleukin-2 (IL-2) and IFN- α becoming the mainstay treatment of metastatic disease. In addition, cellular immunotherapy, including autologous lymphocyte therapy and dendritic cell-based vaccines, may be an option in the future [17,18]. Although still experimental, encouraging anti-tumour effects with dendritic cell vaccination have been observed in phase 1/2 studies [19].

A comprehensive analysis of the effect of IL-2 or IFN- α on survival in advanced RCC concluded that immunotherapy was more effective than its comparators [20]. Partial or complete remissions were induced in 12.4% of patients receiving immunotherapy compared with 2.4% in non-immunotherapy arms. Complete remission was seen in 28% of the remissions, and median survival was 13 mo. No evidence exists of a dose-response relationship or a correlation between response rate and OS. A small proportion of highly selected patients with mRCC also appear to be able to achieve long-lasting responses to cytokines, and this treatment can be considered curative in some patients [3,21,22]. However, patients with a poor prognosis have been shown to derive little benefit from cytokine treatment [23,24], while patients with an intermediate prognosis have demonstrated a lack of survival advantage [24,25].

Carbonic anhydrase IX (CAIX) expression has been identified as a potential independent prognostic marker of clinical outcome in patients with mRCC and is being investigated as a therapeutic target for patients with clear-cell RCC [26,27]. Overall expression of CAIX appears to decrease with development of metastasis, and decreased CAIX levels may be associated with poor survival [26,28]. Therefore, it is possible that levels of CAIX expression could be used to predict outcome and identify high-risk patients who may benefit from immunotherapy or CAIX-targeted therapies [26].

Toxicity occurs frequently in trials of cytokine therapy, and high-dose IL-2 in particular can be extremely toxic, requiring inpatient administration with intensive supportive care [20]. However, the toxicity of IL-2 can be significantly reduced by subcutaneous administration [29]. Only selected patients with a good prognosis are potential candidates for cytokine therapy, and the European Association of Urology guidelines recommend that IL-2 only be used for selected patients with a good risk profile and clear-cell subtype histology [16].

As discussed elsewhere in this supplement, numerous prognostic factors associated with clinical outcome in mRCC have been identified during trials with cytokines or chemotherapy [30]. The stratification of patients as having good, intermediate, or poor prognosis has proved useful in the design and interpretation of clinical trials and for the subsequent identification of those patients most likely to respond to treatment with specific targeted therapies.

3.3. Targeted therapy

The limitations of cytokine treatment have intensified research into targeted therapies, and a growing understanding of the underlying molecular biology of RCC has

established first the vascular endothelial growth factor (VEGF) pathway and subsequently the mammalian target of rapamycin (mTOR) pathway as relevant therapeutic targets. Several recently published, pivotal, phase 3 trials served to redefine the therapeutic management of RCC; the results of these are summarized below and in Table 1.

3.3.1. Sunitinib

Sunitinib is an orally administered tyrosine kinase inhibitor of the VEGF receptors (VEGFR)-1, -2, and -3 and platelet-derived growth factor receptor- α and β (PDGFR- α/β) [31]. Results from a pivotal phase 3 trial in patients with previously untreated mRCC and mainly favourable or intermediate prognostic risk showed that median progression-free survival (PFS) was significantly longer with sunitinib than IFN- α (Table 1) [31,32]. A higher objective response rate (ORR) was also reported with sunitinib versus IFN- α (independent review, 39% vs 8%; $p < 0.000001$) [33]. At the initial interim analysis, there was a trend towards improved OS with sunitinib (hazard ratio [HR] for death: 0.65; $p = 0.02$), although median survival had not been reached in either group [31]. Final analysis demonstrated an almost significant improvement in median OS in favour of sunitinib versus IFN- α (26.4 mo vs 21.8 mo; HR: 0.82; $p = 0.051$) [32]. However, a significantly greater OS was observed for sunitinib compared with IFN- α (26.4 mo vs 20.0 mo; HR: 0.81; $p = 0.036$) after IFN- α recipients ($n = 25$) who crossed over to sunitinib were censored. Sunitinib-treated patients also had a significantly better QoL than those receiving IFN- α ($p < 0.001$). The most common grade 3 and 4 adverse events reported in the trial are given in Table 1. Based on the data from this trial, sunitinib is now recommended as a first-line therapy for patients with mRCC.

3.3.2. Sorafenib

Sorafenib is a multikinase inhibitor targeting VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β , and Raf kinase, which demonstrated efficacy in the first-line setting in a phase 2 trial involving 189 patients with mRCC [34]. Patients received sorafenib (400 mg twice daily; $n = 97$) or IFN- α (9 million U three times weekly; $n = 92$), with an option to escalate dose to 600 mg twice daily sorafenib or cross over from IFN- α to sorafenib (400 mg twice daily) upon disease progression. There was little difference between median PFS reported for sorafenib (5.7 mo) versus IFN- α (5.6 mo) or response rate (5.2% vs 8.7%, respectively); consequently, sorafenib was not approved by the European Medicines Agency as a first-line treatment for mRCC. However, patients treated with sorafenib reported better QoL and fewer symptoms compared with those receiving IFN- α .

Sorafenib was evaluated in a pivotal phase 3 trial in patients with mRCC, the majority (>80%) of whom had failed prior cytokine-based therapy [35]. Median PFS and ORR were significantly improved in patients receiving sorafenib compared with those on placebo (Table 1). The first interim analysis of OS showed that sorafenib reduced the risk of death by 28% compared with placebo (HR: 0.72; $p = 0.02$), although this benefit was not considered

statistically significant [35]. However, final analysis demonstrated a significant improvement in OS for sorafenib versus placebo after censoring of crossover data (Table 1) [36,37]. The most common grade 3 and 4 events reported in the sorafenib and placebo groups are given in Table 1. Based on the results of this trial, sorafenib is recommended as a second-line agent in cytokine-refractory patients.

3.3.3. Bevacizumab

Bevacizumab is a monoclonal antibody that binds and neutralizes circulating VEGF. Findings from a phase 3 trial (CALGB 90206) showed that the combination of bevacizumab plus IFN- α had greater efficacy than IFN- α monotherapy in previously untreated patients with mRCC [38,39]. Bevacizumab plus IFN- α had a higher ORR and longer PFS compared with IFN- α alone, although there was no significant difference in OS (Table 1). Overall toxicity was greater for bevacizumab plus IFN- α compared with IFN- α alone (Table 1).

The efficacy of bevacizumab in combination with IFN- α as first-line treatment in mRCC was also reported in a similar phase 3 trial (AVOREN) [40]. Median PFS was significantly greater in the bevacizumab plus IFN- α group compared with the IFN- α plus placebo control group (Table 1). Although PFS was longer with bevacizumab plus IFN- α versus IFN- α plus placebo in favourable (12.9 mo vs 7.6 mo; HR: 0.60) and intermediate (10.2 mo vs 4.5 mo; HR: 0.55) Memorial Sloan-Kettering Cancer Centre (MSKCC) risk groups, a smaller difference was observed in those with poor risk (2.2 mo vs 2.1 mo; HR: 0.81). There was no significant difference between median OS reported for bevacizumab plus IFN- α versus IFN- α plus placebo (23.3 mo vs 21.3 mo; HR: 0.86; $p = 0.1291$) [41]. Bevacizumab received European approval in December 2007 for the first-line treatment of patients with advanced RCC when used in combination with IFN- α largely based on data from the AVOREN trial.

3.3.4. Temsirolimus

Temsirolimus is an intravenously (IV) administered mTOR inhibitor that has been evaluated in a phase 3 trial involving treatment-naïve patients (most of whom were classified according to MSKCC criteria as having poor risk [69–76%]) [42]. Patients received temsirolimus, IFN- α , or combination therapy (temsirolimus plus IFN- α). Patients who received temsirolimus alone had significantly longer median PFS and OS compared with those who received IFN- α alone (Table 1). The most common grade 3 and 4 adverse events in the temsirolimus group are given in Table 1. Based on positive survival and PFS results, temsirolimus is recognised in recent guidelines as a first-line treatment option for patients with mRCC who have poor MSKCC prognostic factors.

3.3.5. Everolimus

Everolimus (RAD001) is an orally administered inhibitor of mTOR. Results from the recent phase 3 RECORD-1 study help to extend the role of mTOR inhibitors beyond the first-line, poor-prognosis group setting [43]. In this double-blind,

Table 1 – Summary of phase 3 trials with targeted agents in metastatic renal cell carcinoma

Agent	Comparator	Trial design	Patients	ORR* (%)	PFS (mo)	OS (mo)	Most common AEs grade ≥ 3
Sunitinib (50 mg od; 4 wk on, 2 wk off) [27–29]	IFN- α (9 million U tiw)	Randomised	n = 750 Mainly good or intermediate risk	39 vs 8*; $p < 0.000001$	11.0 vs 5.0; HR: 0.42; $p < 0.001$	26.4 vs 21.8; HR: 0.82; $p = 0.051^{\#}$ 26.4 vs 20.0; HR: 0.81; $p = 0.036^{**}$	Sunitinib: hypertension (12%), fatigue (11%), diarrhoea (9%), hand-foot syndrome (9%) IFN- α : fatigue (13%), anorexia (2%)
Sorafenib (400 mg bid) [31–33]	Placebo	Randomised, placebo controlled	n = 903 Cytokine refractory	10 vs 2; $p < 0.001$	5.5 vs 2.8; HR: 0.44; $p < 0.01$	17.8 vs 15.2; HR: 0.88; $p = 0.15^{\#}$ 17.8 vs 14.3; HR: 0.78; $p = 0.0287^{**}$	Hand-foot syndrome (6% vs 0%), fatigue (5% vs 4%), dyspnoea (4% vs 2%), hypertension (4% vs <1%)
Bevacizumab (10 mg/kg every 2 wk) plus IFN- α (9 million U tiw) [36,37]	IFN- α (9 million U tiw)	Randomised	n = 649 Treatment naïve	31 vs 12; $p < 0.0001$	10.4 vs 5.5; $p < 0.0001$	23.3 vs 21.3; HR: 0.86; $p = 0.1291$	Fatigue (12% vs 8%), asthaenia (10% vs 7%), proteinuria (7% vs 0%), neutropaenia (4% vs 2%), hypertension (3% vs <1%)
Bevacizumab (10 mg/kg every 2 wk) plus IFN- α [34,35]	IFN- α (9 million U tiw)	Open label	n = 732 Treatment naïve	25.5 vs 13.1; $p = 0.0001$	8.4 vs 4.9; $p < 0.0001$	18.3 vs 17.4; HR: 0.86; $p = 0.069$	Hypertension (9% vs 0%), anorexia (17% vs 8%), fatigue (35% vs 28%), and proteinuria (13% vs 0%)
Temsirolimus (25 mg alone or 15 mg plus IFN- α 6 million U tiw) [38]	IFN- α (3 million U with an increase to 18 million U tiw)	Randomised	n = 626 Poor risk	8.6 vs 4.8 vs 8.1 ^{##}	5.5 vs 3.1 vs 4.7; $p < 0.001$ (tems vs IFN- α)	10.9 vs 7.3 vs 8.4; HR: 0.73; $p = 0.008$ (tems vs IFN- α) HR: 0.96; $p = 0.70$ (tems plus IFN- α vs IFN- α)	Anaemia (20% vs 22%), asthaenia (11% vs 26%), hyperglycaemia (11% vs 2%), pain (5% vs 2%), rash (4% vs 0%) (tems vs IFN- α)
Everolimus (10 mg od) [39–41]	Placebo	Randomised, placebo controlled	n = 416 VEGF-targeted therapy refractory	2 vs 0	4.0 vs 1.9; $p < 0.0001$ End of double blind: 4.9 vs 1.87; $p < 0.001$	14.78 vs 14.39; $p = 0.177^{\#}$	Lymphopenia (15% vs 5%), anaemia (9% vs 5%), hyperglycaemia (12% vs 1%), stomatitis (3% vs 0%), fatigue (3% vs <1%), infections (3% vs 0%), pneumonitis (3% vs 0%)

ORR = objective response rate; PFS = progression-free survival; OS = overall survival; AE = adverse event; od = once daily; IFN- α = interferon- α ; tiw = three times weekly; HR = hazard ratio; bid = twice daily; tems = temsirolimus; VEGF = vascular endothelial growth factor.

* Response Evaluation Criteria in Solid Tumours.

* Investigator assessment of ORR for this trial was 47% versus 12% ($p < 0.001$).

[#] The primary OS end point was confounded by required crossover after disease progression.

^{**} OS after data from patients who crossed over from comparator to active treatment were censored.

^{##} Temsirolimus versus IFN- α versus temsirolimus plus IFN- α .

multicentre trial, everolimus significantly prolonged PFS relative to placebo in patients with mRCC who had progressed on other targeted therapy (Table 1) [43,44]. PFS benefit following treatment with everolimus was maintained across patients with favourable ($n=120$), intermediate ($n=235$), or poor ($n=61$) MSKCC risk. Although there was no significant difference in median OS at the end of double-blind analysis (Table 1) [45], the results are likely to have been confounded by crossover upon disease progression; 81% of patients receiving placebo who progressed crossed over to everolimus. The most frequently reported adverse events in the RECORD-1 trial were mostly mild or moderate in severity; most common grade 3 and 4 adverse events are given in Table 1 [43]. Based on the data from this trial, everolimus is now the recommended therapy in patients who have progressed on prior VEGF-targeted therapy.

3.4. Sequential treatment and combinations

The availability of multiple active monotherapies has resulted in the use of sequential therapy as well as investigational studies of different therapy combinations. An option in patients with mRCC who have failed one prior VEGF-targeted therapy is to administer agents that target mTOR-signalling pathways, and this approach is supported by recent clinical evidence. The oral mTOR inhibitor everolimus has been evaluated in a phase 2 trial involving patients with mRCC who had failed prior sorafenib or sunitinib [46]. A partial response (PR) was observed in 16% ($n=3$) of patients and stable disease in 74% ($n=14$) of patients [46]. Median PFS was ≥ 5.5 mo. As discussed earlier, the large phase 3 RECORD-1 trial then demonstrated the PFS benefit of everolimus in >400 patients with mRCC refractory to prior VEGF-targeted therapy [43]. RECORD-1 is currently the only completed phase 3 trial in this particular treatment setting, and this clinical evidence supports the use of everolimus after VEGF-targeted therapy failure. Furthermore, everolimus is currently the only treatment recommended in this setting by international guidelines supported by level 1 clinical evidence [16,47–50].

Despite the lack of phase 3 prospective data, sequential treatment with a VEGF-targeted agent followed by a different VEGF-targeted agent is also used in mRCC. A number of small phase 2 studies have investigated the efficacy and tolerability of sequentially applied targeted agents.

A phase 2 study of sunitinib in 61 patients with Response Evaluation Criteria in Solid Tumours (RECIST)-defined disease progression during or within 3 mo of bevacizumab-based treatment demonstrated a median PFS of 30 wk and a PR in 23% of patients, with some degree of tumour burden reduction observed in 75% of patients [51].

Axitinib is another oral selective inhibitor of VEGFRs that has been shown to have promising antitumour activity and favourable tolerability in patients who have failed prior VEGF-targeted regimens. Results from an open-label phase 2 trial suggested an absence of cross-resistance between axitinib (starting dose 5 mg twice daily) and other VEGF-

targeted therapies in patients with mRCC refractory to sunitinib and sorafenib (group 1; $n=14$), cytokines and sorafenib (group 2; $n=29$), or sorafenib alone (group 3; $n=15$) [52]. For groups 1, 2, and 3, the ORRs were 7%, 28%, and 27%, respectively, with median PFS of 7.1 mo, 9.0 mo, and 7.7 mo, respectively [52]. Grade 3/4 treatment-related adverse events included fatigue (13%), hypertension (11%), and hand-foot syndrome (11%) [52]. A randomised phase 3 trial is under way to evaluate axitinib in patients with mRCC who have failed one prior systemic treatment regimen (NCT00678392) [53].

Pazopanib, an oral angiogenesis inhibitor that targets VEGFR, PDGFR, and c-Kit, has also shown activity in mRCC [54]. A phase 3 trial of pazopanib (800 mg once daily) in patients with mRCC with no prior treatment ($n=233$) or one prior cytokine-based treatment ($n=202$) demonstrated a significant improvement in median PFS for pazopanib compared with placebo (9.2 mo vs 4.2 mo; HR: 0.46; $p < 0.000001$) [54]. Objective responses occurred in 30% of patients treated with pazopanib compared with 3% of patients receiving placebo.

The activity and tolerability of sorafenib (400 mg twice daily) in patients with mRCC who had become refractory to prior bevacizumab ($n=13$) or sunitinib ($n=18$) after a median of 8.5 mo were assessed in a phase 2 trial [55]. Despite 58% of patients having grade 3 toxicity, administration of sorafenib was feasible in patients previously treated with these agents. Although no objective responses were observed, 52% of patients had some tumour shrinkage, with 14% of patients ($n=4$) achieving $\geq 20\%$ shrinkage. A reduction of tumour burden was observed in 33% and 41% of patients with prior bevacizumab or sunitinib, respectively. Median PFS was 3.8 mo.

The sequential use of sorafenib and sunitinib was reviewed retrospectively in a series of 90 patients with advanced RCC [56]. PRs were observed in 17.6% of patients receiving sorafenib, then sunitinib and in 22.7% of patients receiving sunitinib, then sorafenib. Only six patients had progressive disease with both drugs, and four patients had PR with both drugs. However, no definitive conclusions can be drawn on the basis of this retrospective study.

In another retrospective analysis of 30 patients, anti-tumour activity was observed when sorafenib or sunitinib were administered to patients who had failed at least one antiangiogenic therapy [57]. Of 16 patients treated with sunitinib after prior antiangiogenic therapy, 13 (81%) had some degree of tumour shrinkage, including 9 (56%) with a PR and 4 (25%) with disease stabilisation [57]. Of 14 patients treated with sorafenib after prior antiangiogenic therapy, 10 (71%) had some degree of tumour shrinkage, including 1 (7%) with a PR and 9 (64%) with disease stabilisation [57]. Further investigation of sequential VEGF-targeted agents is warranted in larger phase 3 trials to help define the clinical benefits associated with this approach.

Combination therapy is also emerging as a treatment option for mRCC: It may be more efficacious than individual therapies and may help overcome resistance of sequential single agents [58,59]. Combination therapy can involve either drugs that act on the same pathway at different levels

(eg, VEGF ligand and the VEGFR) or drugs targeting different pathways that have a major impact on tumour proliferation (eg, VEGF-targeted therapies and mTOR inhibitors). However, this approach is unlikely to be a viable option for all patients, and it will be vital to determine whether potential increases in toxicity associated with simultaneously applied therapies will permit the use of optimal doses for each drug in order to maximise clinical efficacy over the individual monotherapies. The current view is that combination therapies, if shown to be more efficient, will be reserved for patients in whom rapid tumour shrinkage is warranted or for treating patients so that they are macroscopically free of tumour before surgery.

In a phase 2 study of 40 patients with mRCC receiving a standard dose and schedule of IFN- α in addition to sorafenib 400 mg twice daily, a response rate of 33% was reported, including two complete responses (CR) and a median PFS of 10 mo [60]. A Southwest Oncology Group trial also reported a 19% response rate (better than that reported for either agent as monotherapy) and PFS of 7 mo for this combination [61]. The Italian phase 2 randomised RAPSODY study evaluated IFN- α at two doses (total weekly dose of 15 million U or 27 million U) plus sorafenib 400 mg twice daily [62]. A higher ORR (34.7% vs 17.6%; $p = 0.05$), longer median PFS (≥ 8.5 mo vs ≥ 7.9 mo), and better safety were observed for patients receiving the lower dose of IFN- α .

Inhibiting multiple points in a biologic pathway that mediates tumour growth by combining different VEGF-targeted agents may be an effective therapeutic strategy for mRCC. Accordingly, the combination of bevacizumab and sorafenib to inhibit the VEGF pathway at both the level of ligand and its receptor has shown preliminary efficacy in 48 patients with mRCC enrolled in a phase 1 study [63]. The combination provided encouraging antitumour activity, despite toxicities of bevacizumab and sorafenib leading to a lower maximum tolerated dose of each agent (bevacizumab 5 mg/kg every 2 wk plus sorafenib 200 mg daily) than would be used for monotherapy [63]. Twenty-one of 46 patients (46%) had a PR, and 23 (50%) had stable disease. Median time to progression was 11.2 mo, with 10 patients (21%) progression free at 18 mo. A multiarm phase 2 trial in mRCC is under way to further investigate this combination as well as each agent combined with temsirolimus (NCT00378703) [64].

Combining agents that target different tumourigenic pathways, such as VEGF and mTOR, represents another treatment approach for patients with mRCC. In a recent phase 2 study [65], 59 patients with advanced RCC were treated with standard doses of bevacizumab (10 mg/kg every 2 wk) plus everolimus (10 mg daily). Partial or minor responses were observed in 66% of sorafenib- and sunitinib-naïve patients and 39% of patients who had previously received sorafenib and/or sunitinib. Stable disease was also observed in 10% and 44%, respectively, and median PFS was 9 mo and 6 mo, respectively, in these patient groups. A phase 2 trial of everolimus in combination with bevacizumab as a first-line treatment in patients with mRCC is currently under way (NCT00719264) [66].

A phase 1 study investigated the combination of bevacizumab (either 5 mg/kg or 10 mg/kg every 2 wk) and temsirolimus (25 mg IV every wk) in 12 patients with mRCC who had received up to two previous treatment regimens [67]. This combination approach was generally well tolerated and had promising clinical antitumour activity; best responses included seven PRs and three disease stabilisations [67]. The phase 2 part of this study in mRCC patients refractory to VEGF-targeted therapy is under way to further assess the efficacy and safety of this combination as well as possible prognostic biomarkers [67].

These trials provide interesting hypotheses regarding the potential for combinations of cytokine therapy and anti-angiogenic agents to be incorporated into future clinical practice.

3.5. Adjuvant and neoadjuvant setting

Given the high rate of recurrence of RCC after nephrectomy, adjuvant approaches would be desirable, especially for patients with high-risk tumours, where there is a 35–65% recurrence rate [68]. Effective adjuvant therapy may reduce the risk of relapse in these patients. Conventional chemotherapy has not proved effective as an adjuvant therapy, however, and data on the use of cytokines in the adjuvant setting are scarce and largely negative. The efficacy of IFN- α and/or IL-2 as adjunctive therapies for patients with RCC after radical nephrectomy has been investigated in several studies [69–73]. However, none of these studies reported positive outcomes with adjuvant cytokine therapy in terms of extending survival or reducing the risk of disease progression [69–73]. Moreover, adjuvant cytokine therapy was associated with substantial side-effects [69,70].

Whereas cytokines induce immunologic responses, multitargeted agents directly inhibit receptor tyrosine kinases, such as VEGFRs and PDGFRs, which are important mediators of angiogenesis. A number of trials are currently evaluating the benefit of multitargeted therapies in the adjuvant setting. The S-TRAC trial (NCT00375674) will assess the effectiveness of 1 yr of adjuvant sunitinib therapy (cycles of 50 mg/d for 4 wk followed by 2 wk without therapy) compared with placebo in patients with high-risk RCC as defined by the University of California, Los Angeles Integrated Staging System (modified UISS) [74]. This trial aims to recruit 290 patients, and the end point is disease-free survival (DFS).

A second trial, ASSURE (NCT00326898) [75], will examine whether this treatment is effective across patients with a range of histologies, including clear-cell and non-clear-cell carcinomas. DFS at 5 yr is the primary end point; stratification relating to surgical techniques has also been incorporated and should detect differences in outcomes in patients who have open versus laparoscopic surgery. The study aims to accrue >1300 patients and will assess the effect of adjuvant sunitinib (50 mg/d for 4 wk followed by 2 wk without therapy for a total of nine cycles), sorafenib (400 mg twice daily for 6 wk for a total of nine cycles), or placebo in patients with nonmetastatic RCC.

A longer-term trial aims to identify the drug exposure necessary to achieve optimal reduction in the risk of recurrence with multitargeted therapy [76]. The SORCE trial (NCT00492258) is a three-arm study (primary end point is DFS) that will compare 3 yr of sorafenib therapy (400 mg twice daily), 1 yr of sorafenib therapy plus 2 yr of placebo therapy, and 3 yr of placebo therapy in patients with resected primary RCC and no residual disease but at intermediate or high risk of relapse (Leibovich score 3–11) [76].

Neoadjuvant approaches that integrate systemic therapy before surgical intervention may also hold promise as a treatment paradigm by inducing downstaging of primary tumours and facilitating patient selection for nephrectomy [77]. In the first case report of a complete histologic remission following neoadjuvant treatment with sunitinib, a significant objective response was observed for renal tumour size and vena cava thrombus [78]. Preliminary findings from a case series indicated that absence of progression at metastatic sites following treatment with IFN- α while the primary tumour is in place may be used as selection for palliative nephrectomy in patients with intermediate prognosis [79]. A randomised study is ongoing to assess the potential benefits of initial versus delayed nephrectomy in combination with IFN- α in terms of morbidity and survival. The timing of immunotherapy—either as neoadjuvant (prior to nephrectomy) or adjuvant (after nephrectomy) treatment—in treating mRCC remains controversial [80].

There is a rationale for investigating neoadjuvant VEGF-targeted therapy prior to nephrectomy in patients with RCC based on the potential of VEGF-targeted therapy to produce responses in the primary tumour and induce cytoreduction in tumours that are initially considered inappropriate for surgical removal [81,82]. In addition, the neoadjuvant setting provides an opportunity to evaluate the efficacy of VEGF-targeted therapy in patients with metastatic disease. Results from a case series of nine patients who received sorafenib or sunitinib before nephrectomy for mRCC indicated that neoadjuvant VEGF-targeted therapy can induce responses in the primary tumour and has the potential advantage of cytoreduction [81]. Administration of neoadjuvant sunitinib in patients with advanced RCC considered unsuitable for nephrectomy was shown to be feasible and lead to a reduction in tumour burden that can facilitate subsequent surgical resection [83]. Although none of the 19 patients experienced a CR, PRs and disease stabilisation of the primary tumour were observed in three (16%) and seven (37%) patients, respectively. At a median follow-up of 6 mo (range: 1–15 mo), four patients (21%) had undergone nephrectomy [83]. Sunitinib was associated with grade 3/4 toxicity in seven patients (37%) [83].

Well-designed trials are required to evaluate the potential benefits of neoadjuvant VEGF-targeted therapy and identify the optimal agent, timing of therapy, and disease stage that would derive the greatest benefit from preoperative therapy.

4. Conclusions

The efficacy of currently available targeted therapies in the treatment of mRCC is a significant advance on the limited effectiveness of historical treatments for this disease. Furthermore, several other targeted agents are currently under evaluation in mRCC clinical trials, including axitinib [52,84] and pazopanib [54].

Despite the progress that has been made in the treatment of mRCC, questions remain regarding the optimal sequencing of treatments. In the second-line setting, everolimus is now a recommended treatment for patients with mRCC after the first failure of a VEGF-targeted therapy. However, further questions remain regarding the appropriate use of combination therapy, activity in the adjuvant setting, and appropriate time for surgery, including nephrectomy and surgery for metastases. It is hoped that further advances will provide answers to at least some of these questions.

Conflicts of interest

Professor Bracarda has been an Advisory Board Member for Bayer-Schering Pharma, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth and has received honoraria from Novartis. Dr Ravaut is a member of the Global, European, and/or French Advisory boards for Bayer, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth for urologic tumours. Institutional funding support for research has been obtained from GlaxoSmithKline, Novartis, and Roche. The authors did not receive an honorarium or consultancy fee for writing this manuscript.

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