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Review

Recent advances in the treatment of renal cell carcinoma and the role of targeted therapies

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ARTICLE INFO

Article history:
Received 17 June 2008
Accepted 23 June 2008
Available online 29 September 2008

Keywords:
Metastatic renal carcinoma
Kinase inhibitor
Sorafenib
Sunitinib
Bevacizumab
Temsirolimus
Everolimus

ABSTRACT

Immunotherapy confers a small but significant overall survival advantage in metastatic renal cell carcinoma (RCC) but only for the minority of patients, i.e. the 20% with good prognostic features. Recent developments in the molecular biology of renal cell carcinoma have identified multiple pathways associated with the development of this cancer. Several strategies have been investigated targeting these pathways, with significant clinical benefits shown in early studies. New agents including the small molecule targeted inhibitors sunitinib, sorafenib and temsirolimus, and the monoclonal antibody bevacizumab have shown anti-tumour activity in randomised clinical trials and have become the standard of care for most patients. Sunitinib and temsirolimus have shown significant improvements in progression-free survival (sunitinib) and overall survival (temsirolimus) in separate phase III studies in the first-line setting when compared with interferon-α. Sorafenib has demonstrated prolonged progression-free survival in a phase III study in comparison with placebo in the second-line setting. More recently two phase III studies have compared bevacizumab and interferon-α with interferon-α alone. Both studies showed a statistically significant improvement in progression-free survival for the combination arm. Additional studies are needed to optimise the use of these agents by identifying those patients who most benefit and elucidating the best way of delivering them, either in combination or as sequential single agents.

1. Introduction

Renal cell carcinoma (RCC) affects 38,000 patients in the United States each year.[1] Localised disease is curable with surgery but a third of patients present with metastatic disease that is incurable and the aim of management is palliation although with the development of the novel targeted agents prolongation of life appears to be a real possibility with their sequential use. A third of patients treated surgically for localised disease also subsequently relapse with metastatic disease. The median survival for patients with metastatic RCC is 10–12 months.[2]

Renal cell carcinomas are classified histologically as clear cell (60–80%), papillary (10–15%), chromophobe (5–10%) and collecting duct (<1%). Clear-cell histology is associated with a better outcome than papillary or chromophobe histology in the metastatic setting[3] but the opposite is true for localised disease.[3,4]

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.06.028

Metastatic RCC generally is resistant to cytotoxic chemotherapy[5] and to hormonal therapy[6] with response rates generally less than 10%. Interferon therapy results in responses in 10–20% of patients with a median duration of 3–16 months[7] and a survival advantage for interferon over non-immunotherapy has been reported in randomised trials.[8,9] High dose immunotherapy with intravenous interleukin-2 results in generally durable complete responses in approximately 6% of patients,[10] but this treatment is associated with significant toxicity.

In summary, although renal cell carcinoma can be cured with surgery, metastatic disease is difficult to treat and is generally resistant to cytotoxic chemotherapy. A minority of patients with metastatic disease benefit from immunotherapy, but there is a need for more effective and less toxic systemic treatments.

2. RCC biology and the development of targeted agents

Inactivation of both Von Hippel Lindau (VHL) alleles via mutation or promoter hypermethylation[11] is found in 70–80% of sporadic clear-cell renal carcinomas. Von Hippel Lindau syndrome is also the commonest background for inherited clear-cell renal carcinoma and is associated with an increased incidence of haemangioblastomas of the central nervous system and retina.[12] The VHL protein has an important role in the cellular response to hypoxia. Under conditions of normal oxygen tension, the VHL protein is bound to hypoxia-inducible factors (HIFs) 1α and 2α, which become ubiquitinated and tagged for degradation in the proteasome.[13] Under hypoxic conditions (or in the absence of VHL), HIF-1α accumulates in the cell, stimulating the production of growth factors such as transforming growth factor α (TGFα), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which stimulate angiogenesis and cellular proliferation.

This improved understanding of the molecular biology underlying RCC has led to the development of several new drugs that specifically target these pathways and there is now convincing evidence that they are of benefit. The results of these trials and ongoing efforts to improve treatment of RCC are the focus of this review.

3. Kinase inhibitors in metastatic renal cell carcinoma

Kinase inhibitors are drugs that generally inhibit tyrosine kinases (TKs). Tyrosine kinases catalyse the transfer of phosphate groups from adenosine triphosphate (ATP) to tyrosine residues on proteins. This can be an activating event for proteins involved in signalling and leads to increased cellular proliferation and the promotion of angiogenesis and metastasis. Tyrosine kinases can be categorised as receptor- and non-receptor kinases. Receptor tyrosine kinases (RTKs) such as the epidermal growth factor receptor (EGFR) are located in the cell membrane and transduce signals from the extracellular environment to the cell interior. Numerous downstream signalling pathways[14] such as RAS/RAF/MEK/ERK and PI3K (phosphoinositol 3'-kinase)/Akt may be activated by ligand binding to a RTK. Non-receptor tyrosine kinases such as c-ABL are located intracellularly and can be activated by mechanisms such as phosphorylation. Tyrosine kinase inhibitors (TKIs) disrupt TK signalling by preventing the binding of either protein substrates or ATP. The kinase inhibitors sorafenib, sunitinib and axitinib have shown significant clinical activity in phase II and III trials in metastatic RCC and will be reviewed here.

4. Sunitinib (SU011248)

Sunitinib inhibits the RTKs VEGFR2, PDGFR, FLT-3 and c-KIT[15,16] (Table 1). A dose of 50 mg orally once a day for 4 weeks followed by a 2 week break was the recommended phase II dose based on two phase I studies.[17,18] There have been two independent multi-centre phase II trials of sunitinib in metastatic RCC. Sixty-three patients were treated in the first trial[19] and 106 in the second.[20] All patients had failed previous cytokine therapy. Partial responses were reported in 25 patients (40%) in the first trial; 24 of these patients had clear-cell histology (of 55 patients in the trial with clear-cell histology) and one had papillary histology (of four patients in the trial with non-clear-cell histology). Median time to progression overall was 8.7 months. Fatigue was the most common toxicity although only 11% of patients had grade 3 fatigue. The second study confirmed the results of the initial study. One hundred and six patients, all with clear cell RCC, were treated with a response rate of 34% and a median progression-free survival of 8.3 months. Again fatigue the commonest side-effect was seen in 30 patients (28%).

The unprecedented efficacy and manageable toxicity profile of sunitinib in the second-line setting in metastatic RCC led to a phase III trial of sunitinib versus interferon as first-line therapy[21] (Table 2). Seven hundred and fifty patients of ECOG performance status 0 or 1 were randomised to interferon or sunitinib. Interferon was given at a dose of 9MU three times a week and sunitinib at 50 mg for 28 d followed by 14 d of treatment. The primary end-point of the trial was progression-free survival (PFS) and all patients had clear-cell histology. Over 90% of patients were of favourable or intermediate prognosis and 90% had undergone prior nephrectomy. The response rate to sunitinib was 31% (103 partial responses) and to interferon it was 6% (20 partial responses, $p < 0.000001$) as assessed by independent central review. The median PFS was 11 months (95% confidence interval 10–12 months) for sunitinib and 5 months (95% CI 4–6 months) for interferon (hazard ratio 0.415, $p < 0.000001$); the median overall survival had not been reached for either drug at the time of reporting. Adverse events were similar in both groups except that 5–10% of patients in the sunitinib group had grade 3 or 4 diarrhoea, hypertension or hand–foot syndrome ($p < 0.05$ versus interferon). Grade 3 or 4 neutropenia and thrombocytopaenia were also more common in the sunitinib group, occurring in about 10% of patients ($p < 0.05$ versus interferon). Interestingly, grade 3 or 4 fatigue was seen in 7% of patients in the sunitinib group and 12% in the interferon group ($p < 0.05$). Of note patients in the sunitinib group reported a significant better quality of life than patients in the interferon group ($p < 0.001$). The

Table 1 – Selected targeted agents demonstrating activity in renal cell carcinoma

Agent	Target	Trial phase
Bevacizumab	VEGF	II,III
Sorafenib (BAY 43-9006)	VEGFR2, VEGFR3, PDGFR, FLT-3, c-KIT, CRAF, wtBRAF, V600E BRAF	II, III
Sunitinib (SU011248)	VEGFR2, PDGFR, FLT-3, c-KIT	II, III
Temsirolimus (CCI-779)	mTOR	II, III
Everolimus (RAD001)	mTOR	II
Axitinib (AG-013736)	VEGFR1, VEGFR2, PDGFR, c-KIT	II
Pazopanib (GW786034)	VEGFR 1, VEGFR2, VEGFR3, PDGFR	II

VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin.

Table 2 – Selected phase III studies of targeted therapy in metastatic renal cell carcinoma

Author	N	Regimen	Clinical setting	Efficacy
Escudier	903	Sorafenib versus placebo	Second-line (post cytokine)	Median PFS (months) 5.5 sorafenib versus 2.8 placebo ($p < 0.01$)
Motzer	750	IFN versus sunitinib	First-line	Median PFS (months) 5 IFN versus 11 sunitinib ($p < 0.000001$)
Hudes	626	Tem versus IFN versus Tem + IFN	First-line	OS (months) 10.9 Tem versus 7.3 IFN ($p = 0.008$)
Escudier	649	Bev + IFN versus IFN	First-line	Median PFS (months) 10.2 Bev + IFN versus 5.4 IFN ($p < 0.0001$)
Rini	732	Bev + IFN versus IFN	First-line	Median PFS (months) 8.5 Bev + IFN versus 5.2 IFN ($p < 0.0001$)
Motzer	410	Everolimus versus placebo	Second-line (post TKI)	Median PFS (months) 4.0 Ev versus 1.9 placebo

OS, overall survival; PFS, progression-free survival; IFN, interferon-α; Tem, temsirolimus; Bev, bevacizumab; Ev, everolimus.

authors conclude that sunitinib is a new reference standard for the first-line treatment of metastatic RCC.

An alternative dosing schedule for sunitinib has been investigated.[22] In this phase II study, 107 cytokine-refractory patients were treated with continuous daily sunitinib at 37.5 mg. A response rate of 20% was seen with stable disease for >3 months of 40%. The median PFS was 36 weeks and at this dose sunitinib was well tolerated with only a few patients requiring treatment breaks or dose reductions. Further investigation is required before this dosing regimen can be recommended for routine use and a randomised phase II study comparing the two dosing regimens of sunitinib is open to recruitment.

A dose finding study of sunitinib and interferon in patients with metastatic RCC has recently reported. Sunitinib at a dose of 37.5 mg (4 weeks on 2 weeks off schedule) in combination with interferon at 3MU (three times/week) was tolerated in this population. Higher doses were not tolerated with dose-limiting toxicities of myelosuppression and fatigue. The overall response rate was 12% (3 patients, all partial responses) and median time to progression of 11.9 months. It appears that this combination is poorly tolerated with no improvement in efficacy.

5. Sorafenib (BAY 43-9006)

Sorafenib inhibits the RTKs VEGFR2, VEGFR3, Flt-3, c-KIT and PDGFR and the non-receptor serine threonine kinases BRAF and CRAF[23] (Table 1). The BRAF and CRAF kinases are members of the RAF/MEK/ERK signalling cascade, which is involved in the survival and proliferation of tumour cells and is a therapeutic target in cancer[24] although it is not known to be important in RCC.

The recommended phase II dose of sorafenib was 400 mg orally twice daily on the basis of four phase I studies.[25–28] A multi-centre phase II randomised discontinuation trial of sorafenib in RCC has been conducted.[29] All histological subtypes were eligible, 90% of patients received sorafenib as second or third-line therapy and 56% of patients had undergone prior nephrectomy. Sixty-five patients with stable disease (between 25% tumour growth and 25% tumour reduction) after 12 weeks on sorafenib were randomised to sorafenib or placebo. After 24 weeks, 50% of patients on sorafenib were progression free in comparison with 18% of patients on placebo ($p = 0.0077$). This was the primary end-point of the trial. Median PFS after randomisation was greater with sorafenib than placebo (24 versus 6 weeks, $p = 0.0087$). Sorafenib was restarted in 28 patients who had progressed on placebo; median PFS after restarting sorafenib was 24 weeks. The most common adverse events were fatigue (73%), rash (66%) and hand–foot skin reaction (62%). It was concluded that sorafenib increases PFS in metastatic RCC with an acceptable toxicity profile.

On the basis of these results, a randomised phase III trial comparing sorafenib and placebo in RCC patients who had progressed on first-line therapy was initiated[30] (Table 2). Nine hundred and three patients with metastatic clear cell RCC of low or intermediate risk according to the Memorial Sloan-Kettering Cancer Centre (MSKCC) classification were randomised to sorafenib 400 mg twice daily or placebo. The majority of patients (>80%) had received cytokine-based therapy. The median PFS was 5.5 months for sorafenib and 2.8 months for placebo (hazard ratio for progression in the sorafenib group, 0.44; 95% confidence interval (CI); 0.35–0.55; $p < 0.01$). Partial responses were reported as the best response in 10% of patients receiving sorafenib and 2% of those receiving placebo

($p < 0.001$). The trial also helped to further characterise the side-effect profile of sorafenib. Discontinuation of treatment due to toxicity occurred in 10% of patients receiving sorafenib with 13% requiring dose reductions due to toxicity. The most important side-effects were diarrhoea (43%), skin rash (40%), hand–foot syndrome (30%) and hypertension (17%).

A randomised phase II study comparing sorafenib to interferon-α in 189 untreated patients with metastatic clear cell RCC has recently been reported.[31] Disappointingly, the response rate was only 5% in the sorafenib arm versus 9% in the interferon arm with no significant difference in PFS (5.7 months sorafenib versus 5.6 months interferon-α). Interestingly, on progression, patients in the sorafenib arm could have their dose escalated to 600 mg BD. This dose was well tolerated with a PFS of 4.1 months.

A recent phase II study in 44 patients with metastatic clear cell (or at least a component of clear cell on histology) has attempted intrapatient dose escalation (up to 1600 mg/d).[32] Forty three percent of patients had been treated with prior systemic therapy. Ninety one percent of patients were able to be escalated to 1200 mg or 1600 mg with acceptable toxicity. An impressive response rate of 55% was seen with 7 (16%) complete responses and 17 (39%) partial responses, stable disease for $\geqslant$6 months was seen in a further 9 (20%) patients. The median time to progression was 8.4 months. The potential increased efficacy of dose-escalated sorafenib, particularly the complete response rate, is extremely interesting and is being further investigated.

Sorafenib has been administered in combination with interferon in two phase II studies. Ryan and colleagues treated 62 patients with metastatic or unresectable RCC with a clear-cell component.[33] Sorafenib was administered at 400 mg twice daily and interferon at 10MU three times a week as a first-line treatment. Twelve (19%) of 62 patients achieved a confirmed response (1CR, 11 PR). The median PFS was 7 months. However, the combination of sorafenib and interferon was associated with significant toxicity with 77% of patients experiencing a grade 3 event. Forty nine (79%) patients had their interferon dose reduced and 22 (35%) had their sorafenib dose reduced. The most common adverse events were fatigue, anorexia and diarrhoea.

Gollob and colleagues treated 40 patients with metastatic or unresectable RCC.[34] Eighty-eight percent of patients had clear-cell histology and 37% of patients had received prior therapy (high dose IL-2 in the majority of patients). Again sorafenib was administered at 400 mg twice daily and interferon at 10MU three times a week. A response rate of 33% (13 of 40 patients) was seen (2 CR, 11 PR) and median PFS was 10 months. Grade 3 toxicities were lower in this study but dose reductions were required in 65% of patients, and 28% patients were eventually taken off the study due to toxicities.

The response rates from both of these trials suggest a favourable interaction between sorafenib and interferon as the expected response to either drug alone would not be above 10%. This apparent improvement should be balanced against the potential for increased toxicity. However, further investigation of this combination would appear to be warranted.

6. Axitinib (AG-013736)

Axitinib is an inhibitor of the receptor tyrosine kinases (RTKs) VEGFR1, VEGFR2, PDGFR and c-KIT (Table 1) with an acceptable side-effect profile consisting predominantly of hypertension and stomatitis.[35] A phase II study of axitinib in 52 patients with metastatic RCC, all of whom had failed at least one prior cytokine-based therapy has recently been reported.[36] A response rate of 44% was seen with two (4%) complete responses and 21 (40%) partial responses. Median time to progression was 15.7 months and median overall survival was 29.9 months. Treatment-related adverse events included nausea, fatigue, diarrhoea, hoarseness and anorexia or weight loss. Hypertension occurred in 30 patients but was successfully treated in 22 patients. Axitinib has also been studied in 62 patients with metastatic RCC who had progressed on sorafenib.[37] A response rate of 21% all of which were partial responses (13/62). Fifty-five percent of patients experienced some degree of tumour shrinkage. Fourteen patients had received both prior sorafenib and sunitinib of which nine achieved some degree of tumour shrinkage with one partial response. Axitinib is clearly an active drug in RCC, and a planned phase III trial of axitinib versus sorafenib in patients who have failed one prior therapy is due to open later this year.

7. Pazopanib

Pazopanib has broad spectrum of kinase inhibition including VEGFR 1–3, PDGFR αβ and c-Kit (Table 1).[38] It has been studied in a randomised phase II discontinuation study in patients with metastatic RCC, who were treatment naïve or who had failed one line of treatment not including a TKI.[39] An interim analysis of the first 60 patients showed a 40% response rate and randomisation was discontinued and patients on placebo were crossed over to pazopanib. The updated results from this study have recently been presented.[39] Of the 225 patients who were treated 154 patients had had no prior therapy and 71 patients had been treated previously (of which 56 patients had received cytokine therapy). A response rate of 27% (61/225) was seen all of which were partial responses. An additional 104 patients (46%) had stable disease at 12 weeks. The most common toxicities were liver enzyme elevation, hypertension and diarrhoea. A phase III placebo-controlled study in metastatic RCC has completed enrolment.

8. mTOR inhibitors

The mammalian target of rapamycin (mTOR) is a non-receptor TK in the PI3K-Akt pathway that controls the translation of specific messenger RNA; mTOR activation has multiple downstream effects including increasing HIF-1α gene expression.[40] Furthermore, reduced PTEN expression has been demonstrated in some renal cell carcinomas[41,42] and loss of PTEN function results in Akt phosphorylation with downstream effects on cell growth and proliferation that may be blocked using rapamycin derivatives.[43] This therefore provides a strong rationale for using mTOR inhibitors in RCC.

9. Temsirolimus (CCI-779)

Temsirolimus (CCI-779), a derivative of sirolimus (rapamycin), inhibits the mammalian target of rapamycin (mTOR) (Table 1). It was tested in metastatic RCC in a randomised phase II study in which 111 patients were treated with 25, 75 or 250 mg per week on the same schedule.[44] Almost all patients had received prior systemic therapy and many had poor-risk features. One complete response and 7 partial responses were reported (response rate = 7%) and 51% of patients had a response to treatment or stable disease for at least 24 weeks. Approximately 10–20% of patients had grade 3 or 4 anaemia, hyperglycaemia, hypophosphataemia or hypertriglyceridaemia. No dose response effect was seen and the lowest dose was chosen for the subsequent phase III study.

This three arm phase III study compared temsirolimus, interferon and the combination of the two agents as first-line therapy for poor-risk patients with metastatic RCC[45] (Table 2). Inclusion criteria for the study were Karnofsky performance status of 60 or greater and at least three of the following poor-risk features: time from diagnosis to first treatment of less than a year, corrected serum calcium >10 mg/dl (>2.50 mmol/l), LDH greater than 1.5 times the upper limit of normal, haemoglobin less than the lower limit of normal, Karnofsky performance status of 60–70 and multiple organ sites of metastases.

Six hundred and twenty six patients were treated, over 80% of whom had a Karnofsky performance status of 60–70 (ECOG 2). Two-thirds of participants had undergone prior nephrectomy and over 80% had predominantly clear-cell histology. Temsirolimus was given at 25 mg/m^2 once a week as a single agent and interferon at 18MU three times a week as a single agent. In the combination arm, temsirolimus was given at 15 mg/m^2 and interferon at 6MU on the same schedules. The primary end-point of the trial was overall survival and there were two planned interim analyses.

Temsirolimus was generally better tolerated than interferon or the combination: for example, fatigue was the commonest grade 3 or 4 toxicity and was seen in 12% of patients on temsirolimus, 27% on interferon and 30% on the combination. The commonest laboratory abnormality was anaemia with grade 3 or 4 seen in 21% of patients on temsirolimus, 24% on interferon and 39% on the combination. Sixty-nine percent of patients on temsirolimus had at least one grade 3 or 4 toxicity in comparison with 85% on interferon and 87% on the combination ($p < 0.001$ for both comparisons). Response rates were similar in all three arms and ranged between 7% and 11% but median overall survival was longer in the temsirolimus single agent arm in comparison with the other two arms (10.9 months for temsirolimus, 7.3 months for interferon and 8.4 months for the combination, hazard ratio 0.73, $p = 0.0069$ for single agent temsirolimus). The authors conclude that temsirolimus as a single agent significantly improves overall survival of patients with metastatic RCC and poor-risk features as compared with IFN, but the combination of the two drugs does not improve overall survival. Furthermore, temsirolimus was better tolerated than IFN and it is suggested that temsirolimus can be considered as first-line therapy for patients with poor-risk features. This study can be criticised inasmuch as IFN has been shown not to improve overall survival in comparison with hormonal therapy in patients with Karnofsky performance status of less than 80.[46] It could be argued therefore that the control arm in a trial of patients with intermediate prognosis should be the best supportive care rather than immunotherapy although this study did not show interferon to be detrimental in this patient group; it should also be noted that temsirolimus is the only kinase inhibitor active in renal cell carcinoma to date that is administered intravenously and as such is less convenient for patients. Nevertheless, this is an important study and the investigators should be congratulated on performing it in a group of patients who are traditionally underrepresented in clinical trials.

Further studies are needed to define the role of temsirolimus in first-line therapy for patients with a more favourable prognosis, combined with other targeted agents and as sequential therapy with sunitinib or sorafenib. A phase III first-line study of temsirolimus and bevacizumab versus bevacizumab and interferon is due to open later this year.

10. Everolimus (RAD001)

The importance of mTOR as a therapeutic target in RCC has been confirmed by the fact that a different mTOR inhibitor everolimus (RAD001) (Table 1) has activity in RCC.[47] Forty-one patients were treated with RAD001 in a single arm phase II trial at a dose of 10 mg daily orally of which 37 were evaluable for response. Partial responses were reported in 12 (32%) patients with 19 (51%) patients having stable disease for >3 months. Treatment was well tolerated, the commonest grade 3 toxicities being anaemia, thrombocytopaenia, hyperglycaemia and hypophosphataemia in 5–10% of patients.

A randomised phase III study of everolimus plus best supportive cares (BSC) versus BSC alone in patients with metastatic RCC who have progressed after treatment with sorafenib and/or sunitinib has recently been reported (Table 2).[48] Everolimus resulted in a statistically significant improvement in PFS (4.0 versus 1.9 months; $p < 0.0001$). The most common adverse events were stomatitis, anaemia and asthenia. Everolimus is the first agent to have shown clinical benefit post-TKI failure in a phase III study and should be considered the standard of care in this setting.

11. Bevacizumab

Bevacizumab is a humanised monoclonal antibody that is directed against VEGF (Table 1).[49] It has shown activity against metastatic RCC in a randomised phase II trial.[50] Bevacizumab was administered at two different doses (3 mg/kg and 10 mg/kg) every 2 weeks and compared with placebo in a three arm trial. The primary end-points were response rate and time to progression (TTP); an interim analysis after 110 patients showed a prolongation of TTP in the 10 mg/kg group (4.8 versus 2.5 months for placebo, hazard ratio 2.55, $p < 0.001$). The trial was stopped early on this basis although only four responses to treatment occurred (response rate 10%, all in the 10 mg/kg arm) and there was no survival benefit. Bevacizumab was, however, relatively well tolerated with asymp-

tomatic proteinuria and hypertension the main adverse effects. This was an extremely important trial as it was the first randomised trial to show that targeting angiogenesis could result in clinically relevant results.

In a attempt to improve its efficacy, bevacizumab has been combined with IFN-α in two separate phase III studies[51,52] (Table 2). Escudier and colleagues randomised 649 nephrectomised patients with untreated metastatic clear cell RCC to IFN-α (9MU subcutaneously 3 times/week) combined with either bevacizumab (10 mg/kg every 2 weeks) or placebo.[51] Median PFS was significantly improved in the bevacizumab plus IFN-α group compared to the control group (10.2 versus 5.4 months; HR 0.63, 95% CI 0.53–0.75; $p = 0.0001$). Response rates were also significantly improved in the bevacizumab and IFN-α groups (31% versus 13%; $p < 0.0001$). Subgroup analysis showed that benefit was maintained in both favourable and intermediate MSKCC risk groups, but not in poor-risk group although the numbers of patients were much smaller in this group. The treatments were well tolerated with no new toxicities seen outside of those already known for IFN-α and bevacizumab. The most common grade 3 toxicity was fatigue, 12% in the bevacizumab and interferon arm versus 8% in the control arm.

CALGB 90206 has recently been reported in abstract form.[52] Rini and colleagues randomised 732 previously untreated patients with metastatic clear cell RCC to IFN-α (9MU subcutaneously 3 times/week) alone or combined with either bevacizumab (10 mg/kg every 2 weeks). Median PFS was significantly improved in the bevacizumab plus IFN-α group compared to the control group (8.5 versus 5.2 months; $p < 0.0001$). Response rates were also significantly improved in the bevacizumab and IFN-α group (25.5% versus 13.1%; $p < 0.0001$). Toxicity was greater in the bevacizumab and IFN-α group, including significantly more grade 3 hypertension (9% versus 0%), anorexia (17% versus 8%), fatigue (35% versus 28%) and proteinuria (13% versus 0%). These studies show that the combination of bevacizumab plus IFN-α is a reasonable option in the first-line treatment of metastatic RCC.

12. EGFR kinase inhibitors

The over expression of EGFR in RCC is well recognised and EGFR signalling has been shown to be mitogenic for renal tubular cells.[53] The small molecule EGFR kinase inhibitors gefitinib and erlotinib have been tested in patients with metastatic RCC. Gefitinib was tested in a phase II study with stable disease seen in eight (38%) patients. Although all patients entered into this trial had evidence of progressive disease, the rate of progression was unknown and thus it is uncertain whether the stabilization of disease represents a treatment effect.[54]

In an attempt to improve upon its efficacy, bevacizumab has been combined with erlotinib. Fifty nine patients were treated in the initial phase II study with a response rate of 25%.[55] A subsequent randomised phase II study failed to demonstrate superiority in either progression-free survival (9.9 months bevacizumab + erlotinib versus 8.5 months bevacizumab: $p = 0.58$) or response rate (14% bevacizumab + erlotinib versus 13% bevacizumab: $p = 0.58$) for the combination over bevacizumab alone.[56]

Lapatinib, a dual EGFR/ErbB-2 kinase inhibitor, has been tested in a phase III study of 417 patients with EGFR-expressing RCC of any histology.[57] Patients had failed first-line cytokine therapy and were randomised to lapatinib or hormonal therapy. There was no significant difference between the 2 arms with respect to time to progression (TTP) or overall survival. However, a subgroup analysis of patients who strongly expressed EGFR had a longer TTP (15.1 weeks versus 10.9 weeks; $p = 0.06$) and survival (46.0 weeks versus 37.9 weeks; $p = 0.02$) in the lapatinib arm.

13. Areas of uncertainty

The rapid development and introduction of these targeted agents into clinical practice have highlighted many uncertainties regarding their use. These include questions with regard to biological and clinical markers of response, mechanisms of resistance, use in the neoadjuvant/adjuvant setting and in patients with non-clear-cell histology. Other important issues include toxicity, optimal dose and sequence as well as combination strategies. A number of these issues are the subject of ongoing or planned clinical trials, but we will try to clarify them in the following sections.

14. Toxicity

Although the targeted agents used in the treatment of RCC are reasonably well tolerated, their toxicity on a long-term basis is unknown. This will become increasingly important particularly if they are shown to have a role as adjuvant therapy. Thyroid dysfunction has been seen with both sunitinib and sorafenib[58,59] and left ventricular dysfunction has been seen with sunitinib.[21] It is important that these toxicities are recognised and monitored and treated accordingly.

15. Selection of patients for therapy

Given that a minority of patients with metastatic RCC benefit from immunotherapy (including durable complete responses in a small number) but that a larger proportion of patients benefit from treatment with kinase inhibitors (although complete responses are extremely rare), there is a need for markers in order to select patients suitable for either therapy. Carbonic anhydrase IX expression has been shown to predict outcome from interleukin-two-based immunotherapy[60] and it is conceivable that a (radiographic, pathological or molecular) marker of 'angiogenesis' could predict benefit from kinase inhibitors that act via anti-angiogenic pathways. Such markers are the subject of several ongoing clinical trials and will hopefully help to select those patients most likely to achieve the greatest clinical benefit.

16. Treatment of non-clear-cell RCC

The vast majority of patients treated on clinical trials of the new targeted agents had clear-cell histology. The activity of these agents in non-clear histology is therefore unknown.

Choueiri and colleagues evaluated 53 patients with metastatic papillary RCC (pRCC) or chromophobe RCC (chRCC) who received either sunitinib or sorafenib as their initial TKI treatment in five US and French cancer centres.[61] Three (25%) of 12 patients with chRCC achieved a partial response (two treated with sunitinib, one with sorafenib) with a PFS of 10.6 months. Two (4.8%) of 41 pRCC patients achieved a partial response (both treated with sunitinib). PFS for sunitinib-treated patients with pRCC was 11.9 months compared with 5.1 months for sorafenib-treated patients ($p < 0.001$). Further prospective studies of these agents are needed in non-clear-cell RCC to clarify their future role.

The randomised three arm phase III study comparing temsirolimus, interferon and the combination of the two agents as first-line therapy for poor-risk patients with metastatic RCC included a significant number of patients with non-clear-cell histology (124 (20%) patients out of 626).[45] A subset analysis has been performed to determine the effect of temsirolimus versus IFN-α on OS and PFS in patients with clear cell or other histologies.[62] For patients with non-clear-cell histologies, those in the temsirolimus group had a longer OS and PFS than those in the IFN-α group (OS: 11.6 versus 4.3 months, respectively, HR 0.49; PFS 7.0 versus 1.8 months, respectively, HR 0.38). Thus temsirolimus benefits patients irrespective of histology and warrants further study in this important patient group.

The familial form of papillary RCC is associated with germline activating mutations of MET (mesenchymal epithelial transition factor), while amplification and over expression of Met are also seen in the sporadic form. XL880 is a novel inhibitor of receptor tyrosine kinases targeting MET and VEGFR. In an ongoing phase I study, partial responses were noted in three out of four patients with pRCC.[63] This has led to the initiation of a phase II study of XL880 in patients with pRCC.[64] Preliminary results from three patients with at least one post baseline tumour assessment has shown one partial response and two patients with stable disease >3 months. Thus anti-tumour activity has been demonstrated for XL880, but further results are eagerly awaited and enrolment in this study continues.

17. Combination therapy

One way to potentially improve the activity of the targeted therapy to RCC would be to combine agents that target different points in the VHL-hypoxia-inducible gene pathway. For example, the combination of an mTOR inhibitor with an inhibitor of VEGFR. Bevacizumab has been combined with other targeted agents in phase I studies that have recommended dosing schedules for future studies. For example, it has been administered in combination with sorafenib in two phase I/II studies reported in abstract form.[65,66] The combination of the two drugs appears to increase the sorafenib-associated side-effects, generally limiting sorafenib dosing to 200 mg per day but despite this, preliminary evidence of efficacy was reported. A concern of combination therapy is that overlapping toxicities will result in dose reductions of agents that negate the benefit of combined therapy.

Several trials are evaluating combinations of new agents to try to elucidate the best combination. One such trial is ECOG E2804 that randomly assigns patients to bevacizumab, bevacizumab and sorafenib, bevacizumab and temsirolimus or sorafenib and temsirolimus. Until combination therapy is clearly shown to be superior to monotherapy, it should only be used in a clinical trial.

18. Sequential therapy

The development of several targeted agents means the clinician is now faced with the dilemma of which agent to give and in which order to provide optimal benefit. It also means that on progression after one targeted agent other similar drugs are now available. Tamaskar and colleagues reported a response rate of 20% in patients receiving sorafenib or sunitinib after therapy with a variety of anti-angiogenic agents.[67] Rini and colleagues have reported a response rate of 16% to sunitinib in patients who have become refractory to bevacizumab.[68] Axitinib has demonstrated promising activity in sorafenib-refractory patients with a response rate of 21% (13/62 patients) and some degree of tumour shrinkage in 55% of patients.[37]

Sablin and colleagues retrospectively reviewed 90 patients with advanced RCC who had been treated with sunitinib or sorafenib sequentially.[69] They showed that partial response or stable disease was possible irrespective of the sequence of drugs. These studies suggest that there is a degree of non-cross-resistance between anti-angiogenic agents and that these drugs can be used sequentially in metastatic RCC. Several trials are evaluating the sequence of new agents to try to elucidate activity and the optimal sequence.

19. Adjuvant therapy

The administration of adjuvant systemic therapy may reduce the risk of distant relapse and hence improve survival. No benefit has been demonstrated for adjuvant immunotherapy in renal cell carcinoma[70–72] and in fact outcomes may be worse in comparison with placebo.[73] No data are reported for the use of kinase inhibitors as adjuvant therapy and clinical trials are currently recruiting patients that will address this important issue. A large ongoing intergroup trial (ECOG-E2805) is randomising high-risk patients who have undergone nephrectomy to receive placebo, sunitinib or sorafenib for 1 year. Two other international adjuvant studies are also recruiting. SORCE is a trial of placebo versus 1-year versus 3-years of sorafenib in patients with resected renal cell carcinoma at high or intermediate risk of relapse. The STAR trial (sunitinib in advanced renal cancer) is randomising high-risk patients who have undergone nephrectomy to receive placebo or sunitinib for 1 year.

20. Neoadjuvant therapy

Neoadjuvant therapy with tumour biopsies both before and on treatment may allow insight into the mechanism of action and resistance to kinase inhibitors *in vivo* as well as possible tumour downstaging. This approach may also enable correlation of radiographic changes with pathological and molecular changes due to treatment and allow the identification of markers of response.

Table 3 – Proposed treatment algorithm for metastatic clear-cell renal cell carcinoma

	Setting	Treatment	Options	Evidence (treatment arm)
First-line	Good and intermediate risk MSKCC	Sunitinib Bevacizumab/IFN	HD IL-2 clinical trial	Level I
	Poor-risk Non-clear cell	Temsirolimus	TKI/ clinical trial	Level I
Second-line	Prior cytokines	Sorafenib	Sunitinib/clinical trial	Level I
	Prior TKI	Everolimus	Different TKI/clinical trial	Level I
	Prior bevacizumab	Sunitinib	Clinical trial	Level II

IFN, interferon-α; HD IL-2, high dose interleukin-2; TKI, tyrosine kinase inhibitor.

Several studies are investigating this novel approach using neoadjuvant sunitinib, sorafenib or bevacizumab. Initial results from the use of neoadjuvant sorafenib (400 mg twice daily 4–8 weeks until 24–48 h prior to nephrectomy) show that all patients had some reduction in size of the primary with a mean tumour reduction of 14.5% (range 1–54%).[74] Surgical technique, feasibility and complication rates were not affected by use of sorafenib suggesting that this represents a feasible approach for further investigation.

21. Which patients? which drug?

When possible, use of these new drugs should be limited to those subsets of patients in which the agent was studied. For example, a patient with poor-risk MSKCC prognostic features[2] should receive temsirolimus as there is level 1 evidence to support this choice. Table 3 suggests a proposed treatment scheme based on the best available evidence. It is obviously limited by the lack of data in certain settings, such as post-mTOR failure, but will evolve as such data become available.

22. Conclusions

Over the past few years there have been considerable advances in the understanding of renal cell carcinoma. These have been translated into the development of several drugs with improved efficacy, of which, the kinase inhibitors have demonstrated the most significant activity. Increasingly oncologists have choices regarding treatment options for patients with renal cell carcinoma. The advances in our understanding of the molecular mechanisms underlying disease progression have left us poised to individualise and optimise treatment based on the potential benefits and risks for a given patient. Studies to date raise many questions with regard to scheduling, dose, duration, potential combinations and toxicity of treatment. A deeper understanding of the relationship between the signalling pathways driving tumour growth and their inhibition is needed in order to optimise the use of these agents and should suggest strategies to delay or prevent resistance and identify appropriate therapeutic combinations. We are in an age of renewed hope with regard to treatment for renal cell carcinoma with increasing numbers of active agents. To realise these hopes, it is our challenge to match these agents with the biology of the tumours and their hosts.

Conflict of interest statement

Simon Chowdhury: Advisory boards for Novartis and Sanofi Aventis. James Larkin: Advisory boards for Novartis.

Martin Gore: Speaker Bureau, Research funding for trials and Advisory Boards for Schering Plough, Pfizer, Bayer, Centocor and Wyeth.

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