

For reprint orders, please contact reprints@expert-reviews.com

EXPERT
REVIEWS

Management of metastatic renal cell carcinoma: current trends

Expert Rev. Mol. Diagn. 9(1), 75–83 (2009)

Aza Mohammed[†],
Iqbal Shergill and
Brian Little

[†]Author for correspondence
19 Hilston Close, Ingleby
Barwick, Stockton on Tees,
TS17 5AG, UK
aza_bamerny@yahoo.com

Renal cell carcinoma is one of the common malignancies of the genitourinary tract. In approximately one third of patients, distant metastases are present at the time of initial diagnosis and in another third, the tumor will recur even after nephrectomy with a curative intent. Renal cell carcinoma is resistant to all conventional treatment modalities of cancer, including radiotherapy and chemotherapy. We review the management of patients with metastatic renal cell carcinoma in the era of the new targeted therapeutic agents.

KEYWORDS: cytokines • kidney cancer • management • metastasis • tyrosine kinase

Renal cell carcinoma (RCC) has a worldwide annual incidence of more than 200,000. It accounts for 90–95% of all kidney cancers and represents 3% of overall cancers. RCC represents the third leading cause of death among genitourinary malignancies and the 12th leading cause of overall cancer death in the USA. The highest incidence of this disease is found in well-developed countries such as North America, Europe and Australia and it has increased by 2–4% per year [1,2]. RCC is most commonly observed in the fifth and sixth decades of life and males are affected twice as much as females. Afro-Caribbeans have a higher likelihood of developing the disease while Asians appear to have the lowest incidence [3,4].

RCC is classified into five major histological subtypes based on the cell of origin, morphology and growth pattern (Box 1). These histological subtypes vary in their response to treatment and prognosis [5].

RCC runs an indolent course in 25–30% of cases and can only be incidentally diagnosed by abdominal imaging (ultrasound or CT scan). Symptoms vary from hematuria (40%), flank pain (40%) and palpable mass (25%). Only 10% of cases are detected by the classical triad of hematuria, loin pain and loin mass. It can also present with a variety of paraneoplastic syndromes such as polycythemia, hypercalcemia, hypertension and nonmetastatic hepatic dysfunction (known as Stauffer syndrome).

At initial presentation, 75% of patients will have a localized disease. In these cases, surgery can be offered as a curative measure. The 5-year survival for those with organ-confined disease is 90.4% but it drops to 61.7% in cases of regional spread. However, 20–25% of those patients have a local extension or metastatic disease at the time of initial diagnosis. The lung, bones, liver and brain are common sites for distant metastases in RCC. Even with curative treatment, almost a third of patients with RCC develop disease recurrence. Those patients will have a median survival of less than 13 months and a 5-year survival of rate of less than 10% [6].

Management of patients with metastatic renal cell carcinoma

The management of metastatic RCC (mRCC) is challenging for clinicians as it is resistant to all conventional cancer treatments such as radiotherapy and chemotherapy. The increased understanding of the molecular biology of RCC enabled the researchers to explore new horizons for treating mRCC, including targeting agents that interfere with the tumor growth and angiogenesis.

It is essential to stratify patients in terms of risk factors. These play an important role in patient selection for a particular type of treatment and prognosis. Motzer and coworkers from the Memorial Sloan Kettering Cancer Center (MSKCC) in the USA have defined

Box 1. Classification of renal cell carcinoma.

- Clear-cell renal cell carcinoma (75–85%)
- Papillary or chromophilic (12–14%)
- Chromophobic (4–6%)
- Oncocytic (2–4%)
- Collecting duct (Bellini's tumor; <1%)

five prognostic criteria that are used to predict survival in patients with mRCC receiving targeted therapy [7,8]. The factors are summarized in Box 2. Three risk categories are usually defined:

- Favorable risk groups: with no MSKCC risk factors (median survival: 20 months)
- Intermediate risk group: with up to two risk factors (median survival: 10 months)
- Poor risk group: with three or more risk factors (median survival: 4 months)

Treatment options**Radical nephrectomy**

This aims to remove the kidney and perinephric fat within Gerota's fascia and could be performed through an open or laparoscopic approach [9]. The subject of formal lymphadenectomy is controversial but nodes are often included within the specimen. Protocols for lymph node dissection include tumor necrosis and clinical T3 tumors [10]. The survival benefit for this is unclear but in some studies it was found to be associated with an increase in 5-year survival from 44 to 56% [11].

It is essential to carefully select patients for nephrectomy to optimize the clinical outcome. Suitable candidates include those exhibiting [10,11]:

- Good performance status
- Resectable primary tumor
- No evidence of brain metastases
- No evidence of rapidly growing extrarenal disease
- No prohibitive medical comorbidities

Two large randomized, controlled trials were conducted in the USA and Europe to assess the survival benefit of surgery in patients with mRCC. The Southwest Oncology Group (SWOG) and the European Organization for Research and Treatment of Cancer (EORTC trial) recruited 241 and 85 patients (with good performance status), respectively [12,13]. Those patients were randomized to either IFN- α alone or nephrectomy followed by IFN- α therapy. Both studies demonstrated a median survival benefit in the nephrectomy group over those who had IFN- α alone (8.1 to 11.1 months and 7 to 17 months, respectively). In addition, nephrectomy combined with IL-2 was found to improve survival in patients with mRCC as compared with those with nephrectomy alone [14].

In addition, resection of solitary metastases may lead to long-term survival in 30% of patients. Best results are obtained if the metastases are pulmonary; however, encouraging results have also been obtained from the excision of hepatic, adrenal, brain and pancreatic metastases and of isolated local recurrences in the nephrectomy bed [15].

Cytokine therapy

Cytokines are small proteins which regulate immunity, inflammation and hematopoiesis. They are produced *de novo* in response to immune stimuli and act over short distances and short time spans and at very low concentration. They exert their action by binding to specific membrane receptors, which then signal the cell via second messengers (usually tyrosine kinases) to alter the cellular function and behavior. Responses to cytokines include increasing or decreasing expression of membrane proteins (including cytokine receptors), proliferation and secretion of effector molecules.

Cytokines in the form of IFN- α and IL-2 have been used extensively in the treatment of mRCC. The rationale behind this was the fact that cytokines modify the ability of the body immune response mechanisms to regulate tumor growth. Rosenberg and coworkers were the first to study this concept on patients with metastatic cancer and observed objective regression in the size of the tumor (more than 50% reduction in the size) in 44% of patients who received cytokines [16].

Numerous studies followed to evaluate the effectiveness of cytokines in the treatment of mRCC either alone or in combination. Negrier and coworkers compared the use of cytokines as monotherapy and in combination [17]. In their multicenter, randomized, controlled trial, 425 patients with mRCC received either continuous intravenous infusion of IL-2, subcutaneous (SC) injections of IFN- α -2a, or both. Objective response rates (ORR) were found in 6.5, 7.5 and 18.6% ($p < 0.01$) for the groups receiving IL-2, IFN- α -2a and the combination therapy, respectively. At 1 year, progression-free survival (PFS) was found in 15, 12 and 20%, respectively. There was no significant difference in overall survival (OS) among the three groups. Toxic effects of therapy were more common in patients receiving IL-2 than the other groups. On the other hand, Yang and coworkers compared the efficacy of high dose (HD), low dose (LD) and SC IL-2 in the treatment of mRCC. Their study demonstrated higher response rates (both partial and

Box 2. Memorial Sloan Kettering Cancer Center risk criteria.

- Low Karnofsky performance status (<80%)
- Absence of prior nephrectomy
- Serum hemoglobin level less than the lower normal limit for the sex
- Corrected serum calcium more than 10 mg/dl
- Serum lactate dehydrogenase more than 1.5-times the normal value
- Time from initial diagnosis to treatment of less than 1 year was added later on, following retrospective analysis, as predictive factor for survival

complete) in patients receiving HD, but at the expense of higher incidence of side effects [18]. The efficacy of HD IL-2 was further supported by McDermott and coworkers from the Cytokines Working Group Study. In this trial, patients with mRCC were randomized to receive either HD IL-2 or combination of LD IL-2 plus IFN- α . Patients who received HD IL-2 showed higher response rates than those receiving a combination of LD IL-2 and IFN- α (23.2 vs 9.9%, respectively). However, none of the aforementioned studies demonstrated any survival benefit of HD IL-2 over LD or SC IL-2 [19]. Furthermore, Negrier and coworkers from the Percy Quattro trial concluded that cytokine therapy provided no survival benefit in intermediate-risk patients with mRCC [20].

In a systematic review by Cappins and coworkers IFN- α was found to provide a survival benefit compared with other commonly used treatments and the authors concluded that it should be considered as the control arm for future studies of systemic agents [21].

Both these agents have gained the US FDA approval for their use in the management of mRCC since the 1990s. Side effects of these agents are related to the activation of the immune system and include [22]:

- Flu-like illness;
- Vascular leak syndrome leading to severe hypotension;
- Exacerbation of underlying autoimmune diseases (e.g., thyroiditis, systemic lupus erythematosus, hematological disorders and insulin-dependent diabetes mellitus).

Targeted therapy

The discovery of the von Hippel–Lindau (*VHL*) gene in 1993 and its association with RCC has revolutionized the management of mRCC. The VHL syndrome was first identified by two ophthalmologists; Eugen von Hippel from Germany who reported the occurrence of hereditary retinal angiomas and Arvid Lindau from Sweden who determined that retinal angiomas and hemangioblastomas of the CNS belong to the same hereditary syndrome [23]. The association of RCC to VHL syndrome was first established in 1964 by Melmon and Rosen. Renal cancer in patients with VHL syndrome is typical of the clear-cell type and it is characterized by a germ-line mutation of chromosome 3p [24].

The *VHL* gene is a polyubiquitin complex that acts as a tumor-suppressor gene. The product of this gene forms a complex with other proteins, including elongin C/B and Cul2 and targets hypoxia-inducible factor (HIF) 1 α and 2 α for ubiquitin-mediated degradation. This process depends upon the oxygen status, because VHL can only bind to HIF- α 1 after hydroxylation of one of its prolyl residues. Under hypoxic conditions, hydroxylation of HIF- α 1 does not occur and hence preventing VHL from binding. Instead of being degraded, HIF- α 1 is then translocated to the nucleus and is attached to HIF- β 1 to form the active HIF-1 complex. In the nucleus, active HIF-1 acts as a transcription factor for several hypoxia-responsive genes, including VEGF, PDGF, the EGFR, glucose transporters (GLUT-1), TGF- α and erythropoietin. Many of these proteins are involved in angiogenesis, survival, pH regulation and glucose

metabolism, by acting as agonists for their respective tyrosine kinases receptors [25,26]. VEGF is essential for both normal and tumor-associated angiogenesis through interaction with receptors present on the cell surface. It mainly functions to:

- Stimulate endothelial cell division and migration
- Promote endothelial cell survival through protection from apoptosis
- Reverses endothelial cell aging

Conversely, PDGF stimulates the growth of pericytes which line these newly formed vessels and provide stabilization. The combined effects of these two genes lead to the hypervascular state which is characteristic of RCC. The vast majority of patients with clear-cell RCC have overexpression of VEGF in their tumor tissues, as demonstrated by the level of mRNA transcripts and VEGF protein identified in RCC tumor tissue. In patients with clear-cell RCC, VEGF expression results from the inactivation of the *VHL* gene. Noninherited clear-cell RCC is characterized by *VHL* gene inactivation. In addition, the HIF-1 activity is regulated by other growth factors and cell adhesion pathways, including the PI3K/AKT/mTOR pathway and the Ras/Raf/mitogen-activated protein kinase pathways [27,28].

Novel therapeutic agents have been developed that target these growth factors in an attempt to stop angiogenesis (TABLE 1). They also have antitumor activity and help to stop the growth of these cancers. Several agents are available and most of them have already completed Phase III clinical trials.

Targeted agents

Anti-VEGF antibody (bevacizumab)

This is a recombinant human IgG monoclonal antibody that is directed against VEGF. Bevacizumab was first included in a Phase I trial in 1997 by Gordon and coworkers who studied the safety and tolerability of this drug on solid tumors including RCC. It was found to be well-tolerated with only grade I and II side effects [29].

Yang and coworkers from the National Institute of Cancer (MA, USA) randomized 116 patients with clear-cell mRCC to receive placebo, LD (3 mg/kg) and HD (10 mg/kg) bevacizumab following failed treatment with IL-2. The study demonstrated a 10% ORR in the HD arm with the PFS for patients given HD, LD and placebo being 64, 39 and 20% respectively at 4 months and 30, 14 and 5% at 8 months [30].

Table 1. Novel targeted therapies in metastatic renal cell carcinoma.

Therapeutic agent	Action
Bevacizumab	Recombinant monoclonal antibody against VEGF
Sunitinib	Multi-tyrosine kinase inhibitor
Sorafenib	Multi-tyrosine kinase inhibitor
Temsirolimus	mTOR inhibitor
Everolimus	mTOR inhibitor

Bukowski and coworkers studied the effect of bevacizumab and erlotinib (which targets EGF receptors) given in combination to treat patients with mRCC. The study failed to demonstrate any survival benefit from this combination [31].

Escudier and coworkers started a first-line Phase III trial (AVERON) to compare bevacizumab plus IFN- α with IFN- α plus placebo in patients with clear-cell mRCC [32]. In their study, a large clear-cell component of more than 50% was required for inclusion. The ORR for those patients in the first arm was significantly higher than those in the second arm (31 and 13%, respectively). Median duration of response (DR) was comparable, with 13 and 11 months in both treatment arms. Tumor shrinkage was observed in 70 and 39% of patients receiving the combination and monotherapy, respectively. The median PFS time was doubled by the addition of bevacizumab (10.2 vs 5.4 months). A subgroup analysis, however, demonstrated that only patients with good and intermediate prognosis benefited from the combination therapy. A similar study by Rini and coworkers was recently presented in the Genitourinary Symposium 2008 Conference (Cancer and Leukaemia Group B [CALGB] study). Patients in this study were randomized to receive a combination of bevacizumab and IFN- α and IFN- α monotherapy. The median time to progression was 8.5 months in patients receiving combination therapy compared with 5.2 months in patients receiving IFN alone ($p < 0.0001$). In addition, the combination therapy arm had an improved ORR (25.5 vs 13.1%). This study further supported the use of this agent in combination with IFN- α [33].

The use of bevacizumab for the treatment of mRCC in the USA is still off-label and has not yet obtained US FDA approval. Conversely, it has gained FDA approval for its use in the treatment of metastatic colorectal cancer in combination with 5-fluorouracil. Side effects of this drug include:

- Hypertension: this might be attributed to reduced nitrous oxide production as a result of blocking VEGF. This subsequently leads to vasodilatation and reduced renal sodium excretion [34,35];
- Proteinuria: this can be found in 27–38% of patients receiving this treatment. It is usually transient and disappears after discontinuation of the drug. Proteinuria in patients receiving bevacizumab is not associated with renal parenchymal disease [36];
- Bleeding: this is mainly from the mucocutaneous membranes in the form of epistaxis, gingival bleeding and heavy periods in females. The incidence of grades III/IV bleeding is found in 3 and 9.4% of patients receiving LD and HD bevacizumab, respectively [37,38];
- Arterial thromboembolism: an increased incidence of thromboembolic events (such as cerebrovascular accident, myocardial infarction, unstable angina, transient ischemic attack, claudication or subarachnoid hemorrhage) has been noticed in patients receiving bevacizumab, compared with those receiving chemotherapy alone (4.5 vs 2%) [37,38];
- Delay in surgical wound healing and wound complication [39];

- Gastrointestinal (GI) perforation: it is a lethal complication and can be observed in up to 1.4–2.3% of patients receiving this treatment within the first 2 months. It is more commonly found in patients with pre-existing conditions like acute diverticulitis, bowel obstruction, previous radiotherapy, GI instrumentation and chronic use of nonsteroidal anti-inflammatory drugs [37,38];

- Reversible posterior leukoencephalopathy syndrome: this is a rare complication of this medicine and it includes symptoms like headache, visual disturbances, altered mental status, cortical blindness and seizures. The development of these side effects should alert the clinician to stop the treatment.

Tyrosine kinase inhibitors

Tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to the tyrosine residue of a protein. This phosphorylation is vital for signal transduction and enzymatic activity. They are classified into two main groups; receptor and nonreceptor tyrosine kinases. Receptor tyrosine kinases (RTKs) are composed of three main parts; an extracellular domain which binds a specific ligand, a transmembrane domain and an intracellular domain which binds and phosphorylates selected substrates. Binding of a ligand to the extracellular ligand leads to a series of structural changes in the RTK causing its enzymatic activation. This will subsequently activate a cascade of events through phosphorylation of intracellular proteins, that eventually leads to the transmission of the extracellular signal into the nucleus. Tyrosine kinase inhibitors (TKIs) block PDGF receptor, VEGF receptor 1 and 2, TKI and FLT3 (fms-related tyrosine kinase/Flk2/Stk-2) which are dependent on TK activity for their normal function and thus block the downstream signaling from these receptors. This approach might even be more powerful, since it offers the potential to block more than one ligand's function at a time, with the use of a single agent. This group comprises two main drugs, namely sunitinib and sorafenib, both of which have gained FDA approval for use in patients with mRCC.

Sunitinib

This is an oral multitarget TKI which has shown superior responses in patients with mRCC, compared with other available agents. Sunitinib exerts its antiangiogenic effect through inhibition of VEGF and PDGF receptors and its antitumor effects are a result of its actions on the FLT3 and c-KIT receptors, which promotes the proliferation and differentiation of hematopoietic progenitors.

Sunitinib undergoes a first-pass metabolism in the liver by the cytochrome P-450 (CYP) to produce the major active *N*-desethyl metabolite SU012662, which is as potent as sunitinib in inhibiting VEGF receptors, PDGF receptors and c-KIT *in vitro*. The half-life of sunitinib and its active metabolite ranges from 40–60 h and 80–110 h [40].

This drug has been studied extensively in clinical trials. Two sequential Phase II trials were conducted on patients who previously failed cytokine therapy. In the first study, Motzer and

coworkers recruited 63 patients to receive 50 mg/kg of sunitinib over 4 weeks with 2 weeks of no treatment. This drug was associated with partial response (PR) and stable disease (SD; lasting greater than 3 months) in 40 and 27% of patients, respectively. Median time to progression for the 63 patients was 8.7 months and the median survival was 16.4 months [41]. In the second study, only patients with prior history of nephrectomy and clear-cell carcinoma were recruited. PR was achieved in 34% of cases and SD for more than 3 months was found in 29% of cases. In addition, the median PFS was 8.8 months and an OS of 23.9 months was achieved by an independent central review [42].

Rosenberg and coworkers updated their pooled data from two similar second-line Phase II studies evaluating sunitinib in 169 patients with clear-cell mRCC who showed an ORR of 45%. Moreover, 32% achieved SD; the median DR, PFS and OS were 11.9, 8.4 and 19.9 months, respectively [43].

Harshman and Srinivas described the efficacy and safety of continuous 37.5 mg/day regimen of sunitinib. They recruited 107 patients who failed cytokine-based treatment and were randomized to receive sunitinib in the morning or in the evening. PR and SD were found in 20 and 40% of patients, respectively. In addition, 43% of patients had a clinical benefit (PR+SD) for at least 6 months. Interestingly, patients who received sunitinib in the evening suffered slightly more adverse events, which led to dose reductions in 51%, compared with 39% in patients who received an early morning dose [44].

In order to evaluate the effectiveness of sunitinib in patients who failed bevacizumab treatment, Rini and coworkers conducted a Phase II second-line study that evaluated the safety and activity of sunitinib in mRCC patients previously treated with the bevacizumab. A total of 61 patients were recruited who were previously treated with bevacizumab. The ORR was 23.0% while the median PFS was 30.4 weeks, the median DR was 44.1 weeks and the median OS was 47.1 weeks. These results suggested the usefulness of sunitinib in patients with bevacizumab-refractory mRCC [45].

In a multicenter, randomized, Phase III study, Motzer and coworkers compared the efficacy of sunitinib to IFN- α . The median PFS was significantly longer in the sunitinib arm (11 months) than in the comparison arm (5 months). Sunitinib was also associated with a higher ORR than was IFN- α (31 vs 6%, $p < 0.001$) [46]. Common side effects observed in patients treated with sunitinib include [47]:

- Fatigue: this is worse in the 4-week treatment course and less in the 2-weeks off. It is exacerbated by pain, stress, anemia and other comorbidities;
- Hand-foot syndrome: this includes a spectrum of disorders ranging from parasthesia, erythema, edema, hyperkeratosis and blister formation. This may progress to desquamation. This syndrome usually resolves after discontinuation of treatment. It is postulated that the inhibition of RTKs that are present in the skin lead to these symptoms [48];
- GI complications: such as stomatitis and diarrhea;

- Cardiovascular events: such as hypertension (various grades) and left ventricular dysfunction;
- Hypothyroidism: this occur in 7% of patients [49];
- Hematological abnormalities: such as grade 1–2 neutropenia, thrombocytopenia and anemia. Patients should be monitored for the development of myelosuppression.

Sorafenib

This is a multikinase receptor inhibitor that acts by blocking VEGF, PDGF and FLT3 receptors as well as the RAS family of receptors (RAF-1 and BRAF) which are involved in normal cell proliferation, differentiation and transformation.

Sorafenib undergoes a first-pass metabolism in the liver by the enzyme CYP3A4. Subsequently, it undergoes glucuronidation by UDP glucuronosyltransferase 1A9 [50].

After successful Phase I studies for sorafenib, Ratain and coworkers published the result of a first advanced Phase II discontinuation trial. They recruited 202 patients with cytokine-refractory mRCC who received oral sorafenib (400 mg twice daily) for 12 weeks. Most of the patients were in the low or moderate risk groups. Afterwards, the antitumor response of sorafenib was assessed using the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria and patients were divided into three main groups: patients with progressive disease (discontinued from the study); patients who responded to sorafenib (at least 25% shrinkage of the target lesions) who continued sorafenib in an open-label phase and a third group (who represented the true experimental arm) with SD (target lesions within 25% of the baseline measurement) who were then randomized to continue on sorafenib (400 mg twice daily) or receive placebo (discontinuation). The aim of the study was to determine whether the change observed in the tumor size in patients with SD who continued (after the initial treatment period of 12 weeks) on sorafenib was due to the effect of sorafenib or was it merely because of the slow rate of growth of the tumor. After 12 weeks of treatment, 50% of the patients in the sorafenib arm were progression-free compared with 18% in the placebo arm ($p = 0.0077$). The median PFS was significantly longer in the sorafenib arm (163 days) as compared with placebo arm (41 days; $p = 0.0001$). In addition, the median time to disease progression was 163 days for the sorafenib group versus 43 days for placebo ($p = 0.0002$) [51,52].

This was followed by the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) to further assess the efficacy of sorafenib in treating mRCC. In this trial, 903 patients with clear-cell mRCC were recruited from 117 centers scattered in 19 countries and it is regarded as the biggest trial in the history of mRCC. Patients were double-blinded to receive either sorafenib (400 mg twice daily) or placebo. The median PFS was 5.5 months in the sorafenib arm compared with 2.8 months in the placebo arm. Patients on placebo then were allowed to crossover into the sorafenib arm early as a result of the positive early results. The ORR were 10 versus 2% and disease control (OR+SD) for more than 3 months was 57 versus 34% [53].

Gollob and coworkers study the effect of combination therapy with sorafenib and IFN- α -2b as a first- or second-line therapy for patients with mRCC. In Phase II trial, 40 patients were recruited to receive eight cycles of oral sorafenib SC IFN- α -2b. The ORR was 33% including 28% PRs and 5% complete responses. Responses were similar as a first- and second-line treatment within the first two cycles. The median DR was 12 months. With a median follow-up time of 14 months, median PFS time was 10 months [54]. Sorafenib shares some of its side effects with sunitinib. However, some of its side effects are unique, such as:

- Hyperbilirubinemia: this occurs in the absence of hepatic or pancreatic toxicity;
- Grade 3–4 hypophosphatemia;
- Acute myocardial ischemia or infarction: this is particularly of concern in elderly patients receiving sorafenib [55].

mTOR inhibitors

The mTOR pathway links growth factor receptors to cell growth and proliferation via P13K. It also indirectly increases HIF expression. The mTOR inhibitors block the mTOR kinase, a component of intracellular signaling pathways involved in the growth and proliferation of cells and the response of those to hypoxic stress. They bind to an abundant intracellular protein, FKBP-12 and form a complex that inhibits mTOR signaling. This will subsequently suppress the production of proteins that regulate progression through the cell cycle (at late G₁) as well as angiogenesis (via HIF-1 α suppression) [56].

Temsirolimus

This is the most extensively studied drug in this group. Atkins and coworkers randomized 111 patients to receive different doses of temsirolimus (25, 75 or 250 mg intravenous weekly). The ORR and SD were 7 and 51%, respectively [57]. Retrospective analysis of risk criteria to patients in this study revealed that poor-risk patients who received temsirolimus had a median OS of 8.2 months compared with 4.9 months for first-line IFN- α -treated patients. This led to a large Phase III trial by Hudes and coworkers to observe the efficacy of temsirolimus in poor-risk patients with mRCC [58]. Both types of mRCC were included (clear and nonclear types) and a third of the patients had undergone prior nephrectomy. In this trial, 626 patients were randomized to receive either IFN- α monotherapy (up to 18 million units SC three-times weekly), temsirolimus monotherapy (intravenous 25 mg once weekly) or a combination of the two. Data showed that patients in the temsirolimus monotherapy arm had a statistically longer survival than those treated with IFN- α monotherapy (10.9 vs 7.3 months; $p < 0.0069$). OS in patients treated with IFN- α and temsirolimus plus IFN- α , however, was not statistically different (7.3 vs 8.4 months). Similarly, the ORR for each treatment arm was 7% for IFN- α , 9% for temsirolimus and 11% for the combination arm, while the median PFS was 3.1, 5.5 and 4.7 months for the IFN- α , temsirolimus and combination-therapy arms. This study may prove the efficacy of temsirolimus for treating patients with nonclear cell mRCC.

Temsirolimus was granted FDA approval in May 2007. The most common side effects associated with use of this agent include:

- Asthenia;
- Skin rash;
- Anemia;
- GI disturbances such as nausea and diarrhea;
- Dyspnea;
- Peripheral edema;
- Hyperglycemia, hypercholesterolemia and hyperlipidemia: this is related to the inhibition of mTOR-regulated glucose and lipid metabolism.

Everolimus

This is a new oral mTOR inhibitor that has been recently found to be effective in clinical trials. Jac and coworkers recruited 37 patients with mRCC to receive an oral dose of 10 mg of everolimus [59]. PR was found in 32% of treated patients whereas 51% of patients had a SD for more than 3 months. In a different study by Amato and coworkers, 22 patients who failed previous treatment for mRCC were recruited to receive a daily oral dose of 10 mg of everolimus for a median duration of 7 months treatment [60]. An ORR was observed in 33% of cases while 50% had a SD for more than 3 months. However, long-term results of these trials have not yet been published.

Integrated approach to the management of mRCC

The treatment of patients with mRCC should be tailored according to the MSKCC risk groups. Based on the clinical evidence mentioned previously, patients with favorable and intermediate risk are treated with sunitinib as the first line of treatment. The combination of bevacizumab and IFN- α appears to be a suitable alternative first-line treatment for the same groups. However, in patients with poor-risk mRCC, the first line of treatment is temsirolimus, based on the results of the Phase III Hudes trial [58]. Treatment with cytokines (IL-2) may be beneficial in patients with clear-cell type and good-risk group, but it is at the expense of greater toxicity.

In those patients who fail treatment with cytokines, sorafenib is the drug of choice. There is little evidence, however, to support the use of sorafenib in patients who failed targeted therapy. Other drugs are continuously being tested for their efficacy in treatment of mRCC, which may prove better effectiveness than the currently available ones [61].

Expert commentary

The current 5-year survival of mRCC is less than 10%. It remains a therapeutic challenge and the failure of standard chemotherapy and the modest success of immunotherapy using IL-2 and IFN- α has necessitated the requirement for other strategies to manage the disease. The discovery of the *VHL* gene and its effect on HIF

has revolutionized the management of those patients. The new targeted agents which block VEGF and PDGF were found to be effective in blocking angiogenesis in addition to their antitumor effect. Many of these agents were found in Phase III trials to be more effective than the conventional cytokine therapy, which has been the standard of care for the last two decades. Their introduction into the clinical setting is increasing and in some centers has quickly become the gold standard for care of mRCC. Widespread uptake, however, is limited by the cost–effectiveness issue, which remains a matter of hot debate, especially in the National Health Service. To address this issue, the National Institute of Clinical Excellence of the UK issued a recommendation, in August 2008, against the National Health Service funding for these targeted agents in the treatment of mRCC. This recommendation, based on cost–effectiveness, is likely to be overturned at the next review when more data from clinical studies become available.

Five-year view

Although the majority of targeted agents have gained FDA approval in the USA for their use in mRCC, uptake in UK and Europe is still patchy. Most of the concurrent trials are probing the effect of combining existing and new targeted agents on disease progression and survival (TABLE 2). Within the next 5 years, further trials assessing the use of these agents as primary, or adjuvant therapy are expected to report. In addition, further data on toxicity will also become available. Furthermore and probably of more interest, studies in the effectiveness of drug combinations on survival will be performed and published. These trials will eventually determine the future of novel targeted agents in treating patients with mRCC.

Table 2. Common terms used in clinical trials and their definitions.

Term	Abbreviation	Definition
Objective response rate	ORR	The size of measurable disease at the end of the study
Progression-free survival	PFS	Chances of staying free of disease progression after a particular treatment
Overall survival	OS	Chances of survival and cure in cancer
Partial response	PR	Decrease in size or number of the lesions by 30% or more at the end of the treatment period
Complete response	CR	Complete disappearance of the disease or lesion (negative examination, laboratory tests or imaging studies)
Stable disease	SD	The disease has remained unchanged in size and number of lesions (less than 50% decrease or a slight increase in size)

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Metastatic renal cell carcinoma is associated with low survival rates.
- The standard current treatment with cytokines (IL-2 or IFN- α) is associated with low survival rates and substantial toxicity.
- Novel targeted agents have emerged that inhibit VEGF and PDGF.
- These agents exhibit both antiangiogenic and antitumor effects.
- In the majority of trials, these agents proved to be superior to cytokines in terms of objective response rates and survival.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- Mancuso A, Sternberg CN. New treatment approaches in metastatic renal cell carcinoma. *Curr. Opin. Urol.* 16(5), 337–341 (2006).
- Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J. Clin.* 58(2), 71–96 (2008)
- Hutson TE, Figlin RA. Evolving role of novel targeted agents in renal cell carcinoma. *Oncology* (Williston Park, NY) 21(10), 1175–1180 (2007)
- Zisman A, Belldegrun AS, Figlin RA. Urinary tract cancers. In: *Manual of Clinical Oncology* (5th Edition). Casciato DA (Ed.). Lippincott Williams & Wilkins, PA, USA, 295–320 (2004).
- Motzer RJ, Russo P, Nanus DM, Berg WJ. Renal cell carcinoma. *Curr. Probl. Cancer* 21(4), 185–232 (1997).
- Escudier B. Advanced renal cell carcinoma: current and emerging management strategies. *Drugs* 67(9), 1257–1264 (2007).
- Motzer RJ, Bacik J, Mazumdar M. Prognostic factors for survival of patients with stage IV renal cell carcinoma: memorial Sloan–Kettering cancer center experience. *Clin. Cancer Res.* 10(18 Pt 2), 6302S–6303S (2004).
- Mekhail TM, Abou-Jawde RM, Boumerhi G *et al.* Validation and extension of the Memorial Sloan–Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J. Clin. Oncol.* 23(4), 832–841 (2005).
- Robson CJ. Radical nephrectomy for renal cell carcinoma. *J. Urol.* 89, 37–42 (1963).
- Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on

- outcome in patients with muscle invasive bladder cancer. *J. Urol.* 167(3), 1295–1298, (2002).
- 11 Schafhauser W, Ebert A, Brod J, Petsch S, Schrott KM. Lymph node involvement in renal cell carcinoma and survival chance by systematic lymphadenectomy. *Anticancer Res.* 19(2C), 1573–1578, (1999).
 - 12 Flanigan RC, Salmon SE, Blumenstein BA *et al.* Nephrectomy followed by interferon α -2b compared with interferon α -2b alone for metastatic renal-cell cancer. *N. Engl. J. Med.* 345(23), 1655–1659 (2001)
 - **One of two studies demonstrating the effectiveness of cytoreductive surgery in improving survival in patients with metastatic renal cell carcinoma (mRCC).**
 - 13 Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R; European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon- α -based immunotherapy compared with interferon α alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 358(9286), 966–970 (2001).
 - 14 Pantuck AJ, Belldegrun AS, Figlin RA. Nephrectomy and interleukin-2 for metastatic renal-cell carcinoma. *N. Engl. J. Med.* 345 (23), 1711–1712 (2001)
 - 15 Kavolius JP, Mastorakos DP, Pavlovich C, Russo P, Burt ME, Brady MS. Resection of metastatic renal cell carcinoma. *J. Clin. Oncol.* 16(6), 2261–2266 (1998).
 - 16 Rosenberg SA, Lotze MT, Muul LM *et al.* Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N. Engl. J. Med.* 313(23), 1485–1492 (1985).
 - 17 Negrier S, Escudier B, Lasset C *et al.* Recombinant human interleukin-2, recombinant human interferon α -2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. *N. Engl. J. Med.* 338(18), 1272–1278 (1998).
 - 18 Yang JC, Sherry RM, Steinberg SM *et al.* Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J. Clin. Oncol.* 21(16), 3127–3132 (2003).
 - 19 McDermott DF, Regan MM, Clark JI *et al.* Randomized Phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 23(1), 133–141 (2005).
 - **Trial demonstrating the efficacy of high-dose IL-2 on managing patients with mRCC compared to subcutaneous IL-2 and IFN- α .**
 - 20 Negrier S, Perol D, Ravaud A *et al.* Medroxyprogesterone, interferon α -2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer* 110(11), 2468–2477 (2007)
 - 21 Coppin C, Porzolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev.* (1), CD001425 (2005).
 - 22 Vial T, Descotes J. Immune-mediated side-effects of cytokines in humans. *Toxicology* 105(1), 31–57 (1995).
 - 23 Basche B. A new strategy in the war on renal cell cancer: hitting multiple targets with limited collateral damage. *JAMA* 295(21), 2537–2538 (2006).
 - 24 Melmon KL, Rosen SW. Lindau's disease. Review of the literature and study of a large kindred. *Am. J. Med.* 36, 595–617 (1964).
 - 25 Linehan WM, Vasselli J, Srinivasan R *et al.* Genetic basis of cancer of the kidney: disease-specific approaches to therapy. *Clin. Cancer Res.* 10(18 Pt 2), 6282S–6282S (2004).
 - **Provides an excellent review on the molecular biology of renal carcinoma and the rule of VHL gene mutation in the pathogenesis of renal cell carcinoma.**
 - 26 Izzedine H, Billefont B, Thibault F, Rixe O. New challenges in kidney cancer therapy: sunitinib. *Ann. Oncol.* 18(Suppl. 9), ix83–ix86 (2007).
 - 27 Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. *J. Clin. Oncol.* 23(5), 1028–1043 (2005).
 - 28 Kamura T, Sato S, Iwai K, Czyzyk-Krzaska M, Conaway RC, Conaway JW. Activation of HIF1 α ubiquitination by a reconstituted von Hippel–Lindau (VHL) tumor suppressor complex. *Proc. Natl Acad. Sci. USA* 97(19), 10430–10435 (2000).
 - 29 Gordon MS, Margolin K, Talpaz M *et al.* Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J. Clin. Oncol.* 19(3), 843–850 (2001).
 - 30 Yang JC, Haworth L, Sherry RM *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N. Engl. J. Med.* 349(5), 427–434 (2003).
 - 31 Bukowski RM, Kabbinavar FF, Figlin RA *et al.* Randomized Phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. *J. Clin. Oncol.* 25(29), 4536–4541 (2007)
 - 32 Escudier B, Pluzanska A, Koralewski P *et al.* Bevacizumab plus interferon α -2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind Phase III trial. *Lancet* 370(9605), 2103–2111 (2007).
 - 33 Rini BI, Halabi S, Rosenberg JE *et al.* Bevacizumab plus interferon α compared with interferon α monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J. Clin. Oncol.* (2008) (Epub ahead of print).
 - 34 Sane DC, Anton L, Brosnihan KB. Angiogenic growth factors and hypertension. *Angiogenesis* 7(3), 193–201 (2004).
 - 35 Granger JP, Alexander BT. Abnormal pressure-natriuresis in hypertension: role of nitric oxide. *Acta Physiol. Scand.* 168, 161–168 (2000).
 - 36 Ostendorf T, Kunter U, Eitner F. VEGF mediates glomerular endothelial repair. *J. Clin. Invest.* 104, 913–923 (1999)
 - 37 Hurwitz H, Fehrenbacher L, Novotny W. Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* 350, 2335–2342 (2004).
 - 38 Kabbinavar FF, Schulz J, McLeod M. Addition of bevacizumab to bolus 5FU/leucovorin in first-line metastatic colorectal cancer: results of a randomized Phase II trial. *J. Clin. Oncol.* 23, 3697–3705 (2005).
 - 39 Scappaticci FA, Fehrenbacher L, Cartwright T. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J. Surg. Oncol.* 91, 173–180 (2005).
 - 40 Faivre S, Delbaldo C, Vera K *et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J. Clin. Oncol.* 24(1), 25–35 (2006).
 - 41 Motzer RJ, Michaelson MD, Redman BG *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 24(1), 16–24 (2006).

- **One of two Phase II trials that showed the effectiveness of sunitinib in the management of mRCC.**
- 42 Motzer RJ, Rini BI, Bukowski RM *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 295(21), 2516–2524 (2006).
- 43 Rosenberg JE, Motzer RJ, Michaelson MD *et al.* Sunitinib therapy for patients with metastatic renal cell carcinoma (mRCC). Updated results of two Phase II trials and prognostic factor analysis for survival. *Proc. Am. Soc. Clin. Oncol.* 25, 5095 (2007)
- 44 Harshman L, Srinivas S. Continuous daily dosing of sunitinib in patients with metastatic renal cell cancer. *Onkologie* 31(8–9), 432–433 (2008).
- 45 Rini BI, Michaelson MD, Rosenberg JE *et al.* Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. *J. Clin. Oncol.* 26(22), 3743–3748 (2008).
- 46 Motzer RJ, Hutson TE, Tomczak P *et al.* Sunitinib versus interferon α in metastatic renal-cell carcinoma. *N. Engl. J. Med.* 356(2), 115–124 (2007).
- 47 Grünwald V, Heinzer H, Fiedler W. Managing side effects of angiogenesis inhibitors in renal cell carcinoma. *Onkologie* 30(10), 519–524 (2007)
- 48 Zuehlke RL. Erythematous eruption of the palms and soles associated with mitotane therapy. *Dermatologica* 148(2), 90–92 (1974).
- 49 Sutent. *Summary of product characteristics.* Pfizer Inc, NY, USA (2008).
- 50 Hiles JJ, Kolesar JM. Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. *Am. J. Health Syst. Pharm.* 65(2), 123–131 (2008)
- 51 Ratain MJ, Eisen T, Stadler WM *et al.* Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 24, 2505–2512 (2006).
- 52 Therasse P, Arbuuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J. Natl Cancer Inst.* 92(3), 205–216 (2000).
- 53 Escudier B, Eisen T, Stadler WM *et al.* Sorafenib in advanced clear-cell renal-cell carcinoma. *N. Engl. J. Med.* 356, 125–134 (2007).
- **Largest double-blinded study in the history of mRCC, which showed the effectiveness of sorafenib in the management of mRCC compared to the placebo.**
- 54 Gollob JA, Rathmell WK, Richmond TM *et al.* Phase II trial of sorafenib plus interferon α -2b as first- or second-line therapy in patients with metastatic renal cell cancer. *J. Clin. Oncol.* 25(22), 3288–3295 (2007).
- 55 Eisen T, Oudard S, Szczylik C *et al.* Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. *J. Natl Cancer Inst.* 100(20), 1454–1463 (2008).
- 56 Schrader AJ, Hofmann R. Metastatic renal cell carcinoma: recent advances and current therapeutic options. *Anticancer Drugs* 19(3), 235–245 (2008).
- 57 Atkins MB, Hidalgo M, Stadler WM *et al.* Randomized Phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J. Clin. Oncol.* 22(5), 909–918 (2004).
- 58 Hudes G, Carducci M, Tomczak P *et al.* Temsirolimus, interferon α , or both for advanced renal-cell carcinoma. *N. Engl. J. Med.* 356(22), 2271–2281 (2007).
- 59 Jac J, Giessinger S, Khan M, Willis J, Chiang S, Amato R. A Phase II trial of RAD001 in patients (pts) with metastatic renal cell carcinoma (MRCC). *J. Clin. Oncol.* 25 (2007) (Abstract 5107).
- 60 Amato RJ, Misellati A, Khan M, Chiang S. A Phase II trial of RAD001 in patients (Pts) with metastatic renal cell carcinoma (MRCC). *J. Clin. Oncol.* 24(Suppl.) (2006) (Abstract 4530).
- 61 Patard JJ. Tyrosine kinase inhibitors in clinical practice: patient selection. *Eur. Urol. Suppl.* 7(9) 601–609 (2008).

Affiliations

- Aza Mohammed
Registrar in Urology, The Ayr Hospital; 19 Hilston Close, Ingleby Warwick, Stockton on Tees, TS17 5AG, UK
- Iqbal Shergill, BSc (Hons), MRCS (Eng), FRCS (Urol)
Specialist Registrar in Urology, King George Hospital, Goodmayes, Essex IG3 8YB, UK
Tel.: +44 208 983 8000
Fax: +44 207 377 7292
iqbal.shergill@bhrhospitals.nhs.uk
- Brian Little, MD FRCS(Urol)
Consultant Urologic Surgeon, The Ayr Hospital, Dalmellington Road, Ayr KA6 6DX, UK
Tel.: +44 129 261 0555
Fax: +44 129 261 6451
brian.little@aaht.scot.nhs.uk