Vascular endothelial growth factor receptor tyrosine kinase inhibitors in metastatic renal cell cancer: latest results and clinical implications

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Abstract: Metastatic renal cell cancer (mRCC) accounts for 25–30% of patients with renal cell cancer at presentation. In addition to this, a significant proportion of patients with localized disease at presentation will develop metastatic disease. With the introduction of tyrosine kinase inhibitors (TKIs), the treatment of mRCC has been radically altered. Several newer generation vascular endothelial growth factor receptor TKIs have been tested in the clinical setting over recent years, resulting in the availability of more drugs. We review the latest results from clinical trials and the implications these have on the management of patients with mRCC.

Keywords: metastatic renal cell cancer, tyrosine kinase inhibitors, angiogenesis, vascular endothelial growth factor receptor

Introduction

Metastatic renal cell cancer (mRCC) accounts for 25–30% of patients with renal cell cancer (RCC) at presentation [Gupta *et al.* 2008]. Also, approximately 20–40% of patients who have had a nephrectomy for localized disease will develop mRCC [Janzen *et al.* 2003]. Since 2005, there have been major advances in the treatment of mRCC with the advent of tyrosine kinase inhibitors (TKIs) replacing immunotherapy as standard treatment in mRCC. Both first- and second-line targeted therapy is associated with clinical benefit in mRCC patients [Coppin *et al.* 2011]. Despite all of these improvements, these patients still have a poor prognosis with a 5-year survival rate of 23% [DeVita *et al.* 2008]. Since the introduction of TKIs to the management of mRCC, with sorafenib and sunitinib in 2005 and 2006, there have been several new agents tested. We review the latest results from clinical trials and the implications these have on the management of patients with mRCC.

The three multitargeted TKIs currently approved for use as first-line agents by the European Medicines Agency (EMA) in Europe and the

Food and Drug Administration (FDA) in the USA are sorafenib, sunitinib and pazopanib. In addition to these, there are now several TKIs being developed and tested in various cancers in order to fully exploit blockade of signalling pathways. The first TKIs include sunitinib, sorafenib and pazopanib, which are used as standard first-line therapy in treatment-naïve mRCC patients. Newer more potent and specific agents include axitinib and tivozanib. There are other agents currently under investigation, which include dovitinib, regorafenib and cabozantinib.

Although TKIs form the mainstay of treatment for mRCC, other therapeutic options are available and are associated with benefit in certain individuals. Cytokines can be used first line either as a single agent or in combination with high-dose interleukin [McDermott *et al.* 2005]. This is shown to be of benefit in a highly selected group of patients (less than 3% of the mRCC population).

Another group of drugs, the mammalian target of rapamycin (mTOR) inhibitors, are useful in mRCC. The options available are temsorilimus in

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the first-line setting and everolimus, which is known to be of benefit in the second-line and subsequent lines of treatment.

Temsirolimus is an inhibitor of the mTOR protein. The safety and efficacy of temsirolimus were demonstrated in a phase III, multicentre randomized Global Advanced Renal Cell Carcinoma (ARCC) trial [Hudes *et al.* 2007]. This looked at treatment-naïve patients with advanced RCC who had three or more unfavourable prognostic factors. There were 626 patients randomized equally to receive interferon (IFN)- α alone, or temsirolimus alone or both drugs. The group of patients who received temsirolimus alone showed a significant improvement in overall survival (OS) over those receiving IFN- α alone or both drugs: the median OS was 10.9 months for temsirolimus alone *versus* 7.3 months for those treated with IFN- α alone. The median progression-free survival (PFS) was increased from 3.1 months with IFN- α alone to 5.5 months with temsirolimus alone. The combination of temsirolimus and IFN- α showed an increase in toxicity without an improvement in OS or PFS.

In the RECORD 1 trial (a double-blind, randomized phase III trial), everolimus, an oral mTOR inhibitor, was compared with placebo for the treatment of mRCC in patients whose disease had progressed on treatment with sunitinib or sorafenib [Motzer *et al.* 2008]. A total of 410 patients were randomized to receive either everolimus or placebo. The median PFS was 4.9 months for everolimus *versus* 1.9 months (95% confidence interval [CI] 1.8–1.9) for placebo [Motzer *et al.* 2010].

These studies support the use of temsirolimus in the first-line setting and everolimus in the second and subsequent lines of treatment in subsets of patients.

Another treatment option is bevacizumab (a recombinant monoclonal antibody that binds VEGF-A), in combination with IFN- α . A multicentre phase III trial compared bevacizumab plus IFN- α with placebo plus IFN- α . The trial was a randomized, double-blind trial of 649 patients [Escudier *et al.* 2007b]. The addition of bevacizumab to IFN- α significantly increased PFS (10.2 *versus* 5.4 months) and objective tumour response rates (30.6% *versus* 12.4%). There was no statistically significant increase of adverse side effects with the combination treatment *versus*

IFN- α alone. Grade 3 fatigue occurred in 13% of patients in the bevacizumab plus IFN- α arm compared with 8% of patients in the IFN- α plus placebo arm. Similarly grade 3 asthenia affected 11% of patients in the bevacizumab plus IFN- α arm *versus* 7% of patients receiving IFN- α plus placebo. Proteinuria (8%) and hypertension (6%) were the most common grade 3 or 4 adverse events (AEs) associated with bevacizumab treatment. Bevacizumab or placebo was discontinued as a result of AEs in 23% of patients receiving bevacizumab plus IFN- α and 5% of patients receiving IFN- α plus placebo. IFN- α was discontinued as a result of AEs in 22% of patients in the combination arm and 12% of patients in the IFN- α plus placebo arm.

There was a trend towards improved OS (23.3 months with bevacizumab plus IFN- α *versus* 21.3 months for IFN- α), although the difference did not reach statistical significance [Escudier *et al.* 2010].

A further trial performed by the Cancer and Leukaemia Group B, looked at 732 treatment-naïve patients, who were randomized to either IFN- α or a combination of bevacizumab plus IFN- α . Bevacizumab plus IFN- α showed an improved PFS (8.5 months *versus* 5.2 months) and higher overall response rate (ORR; 25.5% *versus* 13.1%) *versus* IFN- α alone, but toxicity was higher with combination therapy. There was no significant difference in median survival between the two groups (18.3 *versus* 17.4 months for bevacizumab plus IFN- α *versus* IFN- α alone) [Rini *et al.* 2010].

The tyrosine kinase inhibitors

Recent advances in our understanding of the molecular pathogenesis underlying the development of RCC has enabled the development of targeted therapies. Vascular endothelial growth factor (VEGF) is probably the most important growth factor that is involved in tumour angiogenesis, and it has a substantial role in the growth and progression of RCC [Li and Kaelin, 2011]. Clarification of the downstream pathways from the VEGF receptor has defined a number of therapeutic targets involved with angiogenic signalling. Small-molecule TKIs such as sunitinib and pazopanib work by blocking the intracellular domain of the VEGFR and because of their response rates in terms of PFS have become established as the preferred treatment approach

for most patients with mRCC [Motzer *et al.* 2007b; Sternberg *et al.* 2010]. These approaches achieve disease control and PFS for between 8.4 and 11.1 months in the first line setting [Motzer *et al.* 2007a; Sternberg *et al.* 2010]. Highly potent and specific TKIs such as axitinib and tivozanib have been investigated and tivozanib has been the first drug to demonstrate a PFS of greater than 1 year in the first-line setting [Motzer *et al.* 2012c].

Sorafenib

Sorafenib is a potent small-molecule inhibitor of multiple tyrosine kinases including VEGFR-1, -2 and -3, FMS-like tyrosine kinase (FLT-3), intracellular serine/threonine kinase, Rapidly Accelerated Fibrosarcoma (RAF) platelet-derived growth factor receptor (PDGFR)- β , stem cell factor receptor (c-KIT), neurotrophic factor receptor (RET) and fibroblast growth factor receptor-1 (FGFR1) [Wilhelm *et al.* 2004].

The activity of sorafenib in advanced and mRCC was demonstrated in the phase III TARGET trial, in which 903 patients who had progressed with prior standard therapy with cytokines were randomly assigned to sorafenib (400 mg orally twice daily) or placebo [Escudier *et al.* 2007a, 2009a]. The median PFS was significantly longer in patients receiving sorafenib compared with placebo (5.5 *versus* 2.8 months). However, OS with sorafenib was not improved significantly compared with placebo (median 17.8 *versus* 15.2 months). The OS data results were confounded by the potential for crossover to the treatment arm on progression of disease [Escudier *et al.* 2009a].

In a separate analysis from this trial, sorafenib showed effectiveness in carefully selected older patients (≥ 70 years), as evidenced by a significant improvement in PFS (26 weeks *versus* 14 weeks with placebo) [Eisen *et al.* 2008]. This data showed the effectiveness of sorafenib in a clinical setting comprising primarily patients who progressed on prior cytokine therapy.

The role of sorafenib in previously untreated patients is less clear. In a phase II trial in good and intermediate-risk Memorial Sloan-Kettering Cancer Centre (MSKCC) group patients with previously untreated advanced RCC, patients were randomly assigned to sorafenib (400 mg orally twice a day) or IFN- α (9 million units three times a week). At disease progression, patients

originally given sorafenib were allowed to escalate the dose of sorafenib to 600 mg orally twice daily, while those who had been given IFN- α could be crossed over to sorafenib (400 mg twice daily). The results demonstrated a median PFS of 5.7 months for sorafenib *versus* 5.6 months for IFN- α . More patients treated with sorafenib had tumour regression compared with patients treated with IFN- α (68.2% *versus* 39%) [Escudier *et al.* 2009b]. Overall, the incidence of AEs was similar between both treatment arms, although skin toxicity (rash and hand-foot skin reaction) and diarrhoea occurred more frequently in patients treated with sorafenib, and flu-like syndrome occurred more frequently in the IFN- α group. The patients on sorafenib reported less symptoms and better quality of life (QoL).

Sunitinib

Sunitinib is a multikinase inhibitor targeting a number of receptor tyrosine kinases including PDGFR- α and - β , VEGFR-1, -2 and -3, c-KIT, FLT-3, colony stimulating factor (CSF-1R) and RET [Motzer *et al.* 2006, 2007b]. After promising phase I and II data, the efficacy of sunitinib in previously untreated patients with mRCC was studied in a large international phase III trial in which 750 patients with mRCC were randomized to receive either sunitinib or IFN- α [Motzer *et al.* 2007a]. The primary end point was PFS, and secondary end points were OS, response rate and safety. The majority of patients (90%) in the trial were in the favourable or intermediate MSKCC risk groups. The median PFS was 11 months *versus* 5 months for sunitinib and IFN- α , respectively. The independently assessed objective response rate was 31% for sunitinib *versus* 6% for IFN- α . Severe AEs (grade 3–4 toxicities) such as neutropenia, thrombocytopenia, diarrhoea, hand-foot syndrome and hypertension were within acceptable limits of between 5% and 12% with sunitinib. The results showed an OS advantage of sunitinib over IFN- α in the first-line setting (26.4 *versus* 21.8 months), which was statistically non-significant ($p = 0.051$).

The influence of baseline clinical features and previously identified pretreatment prognostic risk factors on OS was analyzed using a Cox proportional hazards model. The benefit of sunitinib over IFN- α was observed across nearly every subgroup except for the group of patients with a haemoglobin greater than or equal to the lower limit of normal.

Patients were grouped on the basis of baseline clinical features using the MSKCC criteria (favourable, intermediate and poor). In the intermediate-risk group (56% of sunitinib group *versus* 57% of IFN- α group), median OS was 20.7 months *versus* 15.4 months, respectively (hazard ratio [HR] = 0.787; 95% CI 0.617–1.004). In the poor-risk group (6% of sunitinib group *versus* 7% of IFN- α group), the median OS was 5.3 months compared with 4 months respectively (HR = 0.660; 95% CI 0.360–1.207). Median OS had not been reached with either treatment in the favourable-risk group (38% of sunitinib group *versus* 32% of IFN- α group); at 12 months, 91% of patients in the sunitinib group were alive compared with 92% of patients in the IFN- α group; and at 2 years, 72% *versus* 76%, respectively, were alive [Motzer *et al.* 2009].

A further exploratory analysis was performed in the subset of patients who did not receive any post-study cancer treatment (193 patients in the sunitinib group and 162 patients in the IFN- α group). These subgroups were well balanced in terms of baseline patient characteristics. Similar to the overall treatment groups, within the sunitinib and IFN- α subgroups, 37% *versus* 28% of patients were classified as favourable risk, 55% *versus* 56% were classified as intermediate risk and 8% *versus* 7% were classified as poor risk, respectively. Within this analysis, median OS with sunitinib was doubled compared with IFN- α (28.1 *versus* 14.1 months, respectively; HR = 0.647; 95% CI 0.483–0.870; p = 0.003) [Motzer *et al.* 2009].

The above data helped establish sunitinib as the mainstay for first-line treatment for mRCC.

In another randomized study, the schedule of sunitinib, 50 mg daily for 4 weeks with 2 weeks off as a 6-weekly schedule, was compared with continuous daily treatment (37.5 mg/day) in 292 patients with advanced RCC [Motzer *et al.* 2012a]. Preliminary results from this trial suggested that continuous dosing results in a shorter time to progression compared with the 6-week dosing schedule (median 7.1 *versus* 9.9 months, HR 0.77, 95% CI 0.57–1.04). OS and AE profiles were similar with the two schedules. It is difficult to say whether these clinical outcomes are due to a pharmacokinetic or a scheduling effect and further studies are needed to determine this.

Pazopanib

Pazopanib inhibits tyrosine kinases associated with VEGFR-1, -2 and -3, PDGFR- α and - β , and c-KIT. In a phase III trial, 435 patients, who were previously untreated or had received only cytokine therapy, were randomly assigned to pazopanib or placebo [Sternberg *et al.* 2010]. There was a significant increase in PFS with pazopanib compared with placebo (median PFS 9.2 *versus* 4.2 months), with improvement in PFS seen in both untreated patients and in those who had received cytokine therapy [Sternberg *et al.* 2010]. The treatment-naïve subpopulation of 233 patients had a median PFS of 11.1 months on pazopanib *versus* 2.8 months on placebo. The objective response rate was 30% with pazopanib and 3% with placebo. Common adverse reactions to pazopanib included diarrhoea (52%), hypertension (40%), hair colour changes, nausea (26%), anorexia (22%), vomiting (21%), fatigue (19%), weakness (14%), abdominal pain (11%) and headache (10%). A clinically important grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine transaminase (30%) and aspartate transaminase (21%). Therefore, it was noted that liver function must be carefully monitored before and during treatment with the drug. In the final analysis of the trial presented at the 2010 European Society of Medical Oncology meeting, there was a statistically nonsignificant improvement in OS (median 22.9 *versus* 20.5 months) [Sternberg *et al.* 2013]. Any potential effect on OS is likely to have been confounded by the high rate of crossover and other treatments after initial evidence of disease progression in patients receiving placebo. As a result of this trial, pazopanib was approved for patients with previously untreated advanced renal cell carcinoma and for patients who have progressed on cytokine therapy.

With the availability of different TKIs, it has become crucial to try and identify which drug gives the best outcome in the first-line setting in terms of efficacy as well as toxicity.

The COMPARZ study was designed to compare pazopanib and sunitinib in the first-line treatment of mRCC, looking at the efficacy, safety and QoL for these drugs in an international phase III trial which recruited 1100 patients [Motzer *et al.* 2012b].

Patients were randomized to either 800 mg pazopanib, given once daily, or 50 mg of once daily sunitinib given in 6-week cycles (4 weeks of

treatment followed by a 2-week off period). The primary end point was to establish noninferiority of PFS, and safety and QoL were evaluated as secondary end points. The results of this study were reported in the Presidential Symposium at the 2012 European Society of Medical Oncology conference and showed that pazopanib was non-inferior compared with sunitinib in first-line treatment of mRCC with a median PFS of 8.4 months for pazopanib compared with 9.5 months for sunitinib. There was similar median OS between the two agents at 28.4 months for pazopanib *versus* 29.3 months for sunitinib. ORRs were 31% and 25% for pazopanib and sunitinib, respectively. However, pazopanib was shown to have a better toxicity profile with less haematological toxicity, hand-foot syndrome, peripheral oedema, taste alteration, rash and fatigue, although patients did get more weight loss and worse hepatotoxicity as seen by raised transaminases (31% *versus* 18%, for pazopanib and sunitinib, respectively). Fatigue was noted to be slightly less prevalent in the pazopanib group (55%) compared with 63% of the sunitinib group.

The PISCES study, presented as an oral abstract at ASCO 2012, compared patient preference for pazopanib or sunitinib for first-line treatment of mRCC [Escudier *et al.* 2012].

A total of 169 patients with mRCC were randomly assigned to blinded treatment with pazopanib 800 mg daily for 10 weeks with a 2-week washout period followed by sunitinib (50 mg for four weeks on/two weeks off) for 10 weeks or vice versa.

Following the double-blind phase, patients were allowed to continue on treatment based on which agent they preferred. Significantly more patients preferred pazopanib compared with sunitinib (70% *versus* 22%, respectively). Pazopanib was associated with substantially better health-related QoL compared with sunitinib. This interesting study demonstrates a direct comparison of toxicities of the two drugs with a reasonable washout period between the drugs and highlights the benefits and tolerability of pazopanib.

Axitinib

Axitinib is an oral multitargeted kinase receptor inhibitor with antitumour activity inhibiting VEGFR-1, -2 and -3, PDGFR and c-KIT. In the AXIS trial, 723 patients with metastatic

clear cell RCC were randomly assigned to treatment with either axitinib (5 mg twice a day) or sorafenib (400 mg twice a day). All patients had received prior treatment with a cytokine or TKI or other molecularly targeted agent [Rini *et al.* 2011b]. The primary end point of the study was PFS and a median PFS of 6.7 months in patients on axitinib *versus* 4.7 months in patients on sorafenib was seen. The median PFS was almost doubled (12.1 *versus* 6.5 months for axitinib and sorafenib, respectively) in those previously treated with cytokines and was 4.8 *versus* 3.4 months (axitinib *versus* sorafenib, respectively) in those previously treated with sunitinib. Adverse effects that were higher in the axitinib arm compared with the sorafenib arm were hypertension (40%), diarrhoea (55%), dysphonia (31%) and nausea (32%). A higher incidence of hand-foot syndrome (51%), rash (32%) and alopecia (32%) were seen in the sorafenib arm.

A recent update on this trial reported no significant difference in median OS: 20.1 months (95% CI 16.7–23.4) with axitinib and 19.2 months (95% CI 17.5–22.3) with sorafenib (HR 0.969, 95% CI 0.800–1.174; one-sided $p = 0.37$) [Motzer *et al.* 2013b]. In a 12-week analysis, median OS was longer in patients with a diastolic blood pressure of 90 mmHg or greater than in those with a diastolic blood pressure of less than 90 mmHg: 20.7 months (95% CI 18.4–24.6) *versus* 12.9 months (95% CI 10.1–20.4) in the axitinib group ($p = 0.0116$), and 20.2 months (95% CI 17.1–32.0) *versus* 14.8 months (95% CI 12.0–17.7) in the sorafenib group (one-sided $p = 0.002$).

Although OS, a secondary end point for the study, did not differ between the two groups, PFS remained longer in the axitinib group compared with the sorafenib group. These results establish axitinib as a second-line treatment option for patients with mRCC and support hypertension as an on target effect of treatment [Motzer *et al.* 2013b].

The recent approval of axitinib in the USA and Europe increases the treatment options for patients who have progressed after one systemic treatment and it is useful in the second-line setting.

A further study compared axitinib *versus* sorafenib in treatment-naïve patients.

The study was designed to detect a 78% PFS improvement from 5.5 months with sorafenib to 9.8 months with axitinib (HR 0.561). Median PFS was 10.1 *versus* 6.5 months with axitinib *versus* sorafenib (HR adjusted for performance status [PS], 0.767; 95% CI 0.559–1.053; one-sided $p = 0.0377$). The benefit was much higher in patients with PS 0 with a median PFS for axitinib of 13.7 months *versus* 6.6 months for sorafenib (HR 0.644; 95% CI 0.419–0.991; one-sided $p = 0.022$). In patients who had PS 1, median PFS was 6.5 and 6.4 months for axitinib and sorafenib, respectively (HR 0.931; 95% CI 0.585–1.482; one-sided $p = 0.38$). Objective response rates (ORRs) with axitinib were 32.3% and 14.6% for sorafenib. The study demonstrated numerically longer median PFS but did not reach statistical significance [Hutson *et al.* 2013]. Hence, at present axitinib is licensed for second-line therapy in mRCC.

Tivozanib

Tivozanib is an active inhibitor of VEGFR-1, -2 and -3 [Nakamura *et al.* 2006]. At the 2012 ASCO annual meeting, the preliminary results of a phase III trial (TIVO-1 study) comparing tivozanib with sorafenib as first-line treatment in mRCC were presented [Motzer *et al.* 2012c]. In this trial, 517 patients were randomly assigned to treatment with tivozanib (1.5 mg/day on a 3 weeks on and 1 week off schedule) or to sorafenib (400 mg twice a day without a treatment break). Tivozanib compared with sorafenib resulted in a significant improvement in PFS (median PFS 11.9 *versus* 9.1 months for tivozanib and sorafenib, respectively) and a significantly higher ORR (33% *versus* 23%, respectively). In patients who were treatment-naïve for advanced RCC (70%), tivozanib demonstrated a statistically significant improvement in median PFS of 12.7 months compared with a median PFS of 9.1 months for sorafenib (HR 0.756, 95% CI 0.580–0.985; $p = 0.037$). This is the first drug to show such a substantial PFS in the first-line setting, compared with an active comparator. However, there was a higher incidence of serious (grade 3/4) hypertension (26% *versus* 17% for tivozanib *versus* sorafenib, respectively). Other toxicities that were more commonly encountered with tivozanib included dysphonia (21% *versus* 5%) and back pain (14% *versus* 7%). Tivozanib had less diarrhoea (24% *versus* 38%), palmar-plantar erythrodysesthesia (15% *versus* 71%) and alopecia (2% *versus* 21%) when compared with sorafenib.

Hence, this newer generation drug has good efficacy but also an extensive toxicity profile. The OS data from this study demonstrated mortality rates of 45.4% in the tivozanib group and 39.3% in the sorafenib group, corresponding to a stratified HR of 1.25 (95% CI 0.954–1.624; $p = 0.1$) trending in favour of sorafenib. Median OS was 28.8 months for tivozanib and 29.3 months for sorafenib [Motzer *et al.* 2013a]. As crossover was allowed, the antitumour activity of tivozanib may be a contributing factor towards the OS of patients randomized to sorafenib. The median PFS was 8.4 months after switching from sorafenib to tivozanib and tumour shrinkage occurred in 74% after changing to tivozanib.

However, due to concerns about the OS data, ODAC (the Oncology Drugs Advisory Committee) have not approved the use of tivozanib in mRCC. Unfortunately as a consequence of this, tivozanib is no longer being developed in RCC.

Other agents in development include cabozantinib, regorafenib and dovitinib.

A phase II trial of the MET and VEGFR2 inhibitor, cabozantinib, in patients with relapsed or refractory RCC was also presented at the 2012 ASCO annual meeting [Choueiri *et al.* 2012]. A total of 25 patients received cabozantinib at a dose of 140 mg daily. The majority of patients had been previously treated with a TKI (88%), an mTOR inhibitor (60%) or both (52%) and 20% had received prior cytokines. The preliminary results showed cabozantinib treatment led to a median PFS of 15 months and a partial response in seven patients (28%). Grade 3 or 4 toxicity associated with cabozantinib included electrolyte disturbances: hypophosphataemia (36%) and hyponatraemia (20%), fatigue (16%) and diarrhoea (12%). Grade 3 hypertension was observed in two patients (8%). This is extremely encouraging data but further studies are needed to establish the feasibility of this drug in advanced lines of treatment for mRCC.

Regorafenib has been shown to be active in the management of treatment-naïve unresectable RCC [Eisen *et al.* 2012]. Further assessment of regorafenib should exploit its ability to inhibit mechanisms of escape from anti-angiogenic treatment with a focus on biomarker-defined subsets of patients with evidence of angiopoietin or fibroblast growth factor (FGF) pathway upregulation.

Dovitinib is a potent oral angiogenesis inhibitor with a wide spectrum of therapeutic targets including FGFR-1 as well as the VEGFRs [Sarker *et al.* 2008]. It showed substantial activity in a recent phase II trial in mRCC patients previously treated with a VEGFR TKI and/or an mTOR inhibitor, with an ORR of 8%, a PFS of 6.1 months and an OS of 16 months [Angevin *et al.* 2011]. It is currently being evaluated in a randomized phase III trial as third-line treatment *versus* sorafenib in mRCC patients.

Clinical implications

With the development of newer generation VEGFR TKIS, we have a much larger armamentarium of drugs to choose from when deciding on treatment in patients with mRCC. The question then arises that with all of these drugs, how do we decide which drugs to use and in which order?

First-line treatment

Sunitinib has become established as the traditional standard TKI for first-line treatment. However, with the results of the recently reported COMPARZ study, pazopanib has been shown to be as efficacious with a different toxicity profile. In addition, the PISCES study has demonstrated patient preference for pazopanib as well, strengthening its position as a feasible first-line option for patients. Patients who may benefit from sorafenib in the first-line metastatic setting include the elderly (over 70 years), those with cardiovascular disease and other comorbidities [Bellmunt *et al.* 2010].

Second-line treatment

Axitinib has demonstrated benefit in the second-line setting and has been licensed for this indication in the United States and Europe. It is available in the UK via the Cancer Drugs Fund in England but has initially not been approved for NHS funding by NICE (National Institute for Health and Care Excellence). It is currently undergoing re-evaluation through an appeal process.

Third-line treatment

The choice of agent to use would be dictated by response to and toxicity of first-line and second-line therapy, as well as current performance status. The recommendation currently would be to

consider mTOR inhibitors in the first instance followed by trial enrolment if unsuitable for mTOR inhibitors or on progression.

Regorafenib, cabozantinib and dovitinib have shown promising results. Further studies are needed to establish their position and role in the management of mRCC.

Each of the TKIs has its own slightly different toxicity profile. By being able to tailor drug choice to the individual in the future, it is hoped that patients will be able to benefit maximally from treatment with limited effects from toxicity and minimal impact on QoL. Interestingly, in patients with mRCC, it has been demonstrated that sunitinib-associated hypertension (maximum systolic blood pressure [SBP] ≥ 140 mmHg or diastolic blood pressure [DBP] ≥ 90 mmHg) is associated with improved clinical outcomes without a clinically significant increase in hypertension-associated AEs [Rini *et al.* 2011a]. This data, in addition to data from the axitinib study, supports the role of hypertension as an efficacy biomarker in mRCC patients on TKIs.

In order to improve outcomes for patients with mRCC, we need to understand the mechanisms by which mRCC becomes resistant to the VEGF and mTOR inhibiting agents. Some data suggest that overexpression or upregulation of a variety of receptors and growth factors on the endothelial cells, such as interleukin 8 or basic fibroblast growth factor receptor, may play an important role [Huang *et al.* 2010]. Alternatively, the tumour cells themselves may adjust the growth factors they produce: an alteration in the complex cellular pathway. This leads to continued neovascularization and angiogenesis, even when the major factors, such as VEGF or PDGF, are blocked at the endothelial cell level [Rini, 2010]. These escape mechanisms are being addressed by newer drugs such as regorafenib but further studies are needed to exploit these pathways.

Conclusion

The treatment of mRCC has radically altered over the past 6 years since the introduction of small-molecule TKIs.

Sunitinib and pazopanib are both available for the first-line treatment of mRCC and the COMPARZ study has demonstrated the noninferiority of using pazopanib first line with a

suggestion of a better toxicity profile for some patients. Axitinib has demonstrated benefit and is licensed as a second-line agent with the potential for reserving mTOR inhibitors for further lines of treatment.

There are now, more treatment choices available and it would be better if possible, to tailor therapy to meet the needs of each individual RCC patient based on the biology of their disease [Porta *et al.* 2010].

The future

Despite the promising results with various VEGF pathway inhibitors in patients with advanced RCC, many questions remain regarding the optimal use of these agents, including which agent to use in a particular patient, when to start treatment and what is the optimal sequence of targeted agents and treatment approaches for an individual. The identification of predictive biomarkers for response to specific treatments is an important area of research. The use of targeted therapy may be altering the natural biology of the metastatic cancer and it is hoped that predictive biomarkers may help us identify therapeutic targets for individual patients to improve clinical outcomes. Another focus of current research is the evaluation of combination therapy with targeted agents and the effects of sequencing of drugs. As more information regarding mechanisms of disease and drug resistance becomes available, new targets, new targeted agents, and new combinations are being assessed in the clinical setting with the goal of providing maximal efficacy with minimal toxicity. Continued research is imperative to making small but significant steps towards improving progression free and OS in this group of patients.

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Conflict of interest statement

Tim Eisen has received honoraria in the past 5 years from Pfizer, Bayer, AstraZeneca, GSK, Amgen, Bristol-Myers, Aveo, Immatics, Astellas and Boehringer Ingelheim, has served on advisory boards for Pfizer, Bayer, Astra Zeneca, GSK, Amgen, Bristol-Myers, Aveo, Immatics, Astellas and Boehringer Ingelheim, and received research

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