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Overcoming resistance to tyrosine kinase inhibitors in renal cell carcinoma

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Article Outline

Abstract
Targeted agents have substantially improved patient outcomes in metastatic renal cell carcinoma (mRCC) and have now replaced cytokines as standard of care. Despite the clinical benefits observed, resistance to targeted agents has been shown to develop after a median of 5–11 months of treatment. Furthermore, a small subset of patients does not experience any clinical benefit from targeted therapy. Two general modes of resistance have been proposed: intrinsic (pre-existing) and evasive (adaptive). Evasive resistance is

thought to be the mechanism involved when patients progress after initial clinical benefit. It has been suggested that upregulation of alternative pro-angiogenic factors and/or downregulation of angiostatic factors may be involved. Several strategies have been shown to enable clinical benefit in patients who have experienced disease progression during prior therapy. These strategies include: adjusting the dose of the drug, combination therapy or switching to an alternative agent, with or without a different mechanism of action. Improvements in our understanding of the mechanisms of resistance associated with targeted agents and refinement of management strategies may help to improve patient outcomes further. In this article, we review the available evidence supporting mechanisms of resistance to targeted agents in mRCC, with a focus on tyrosine kinase inhibitors, and consider the potential management strategies which may allow further clinical benefit to be achieved.

Introduction

Targeted agents have significantly improved patient outcomes in metastatic renal cell carcinoma (mRCC) and have replaced cytokine therapy as the standard of care for these patients.[1 and 2] Currently licensed targeted agents include the multitargeted tyrosine kinase inhibitors, sunitinib (SUTENT®, Pfizer Inc.), sorafenib (Nexavar®, Bayer HealthCare/Onyx Pharmaceuticals) and pazopanib (Votrient®, GlaxoSmithKline); the mammalian target inhibitor of rapamycin (mTOR) kinase inhibitors temsirolimus (Torisel®, Pfizer Inc.) and everolimus (Afinitor®, Novartis Pharmaceuticals); and the vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (Avastin®, Genentech Inc.) given in combination with interferon (IFN) -α.[3, 4, 5, 6, 7, 8, and 9]

Current treatment guidelines for mRCC recommend that patients at favourable or intermediate prognostic risk receive first-line treatment with sunitinib, bevacizumab plus IFN-α or pazopanib. It is recommended that patients at poor prognostic risk receive temsirolimus first-line.[1 and 2] Based on phase III data, it is currently recommended that patients who have previously received therapy with VEGF receptor (VEGFR)-targeted therapy receive second-line therapy with everolimus.[1 and 2] Second-line options for patients who have progressed following VEGFR-targeted therapy are currently limited; however, agents in development may improve the situation.

Despite the clear clinical benefits observed with first-line targeted agents in renal cancer in terms of improved progression-free survival (PFS) and overall survival (OS), resistance has been observed. A subset of patients (approximately 25%) do not appear to experience any clinical benefit from targeted therapy, while, in many cases, patients respond to therapy initially but go onto experience disease progression.[10 and 11] Resistance to targeted agents has been shown to develop after a median of 5–11 months.[3, 5, 6, and 12]

Several management strategies have been shown to enable clinical benefit in patients who have experienced disease progression during prior therapy, including adjustments to dose[13] or switching to another agent.[14 and 15] This could be because the level of inhibition of targeted receptors by agents with similar mechanisms of action is not exactly the same and that a rotation of active drugs using a similar pathway may induce some benefit. Increased understanding of the mechanisms of resistance in mRCC and the refinement of management strategies to overcome resistance may help improve patient outcomes further. This article will provide an overview of potential mechanisms of resistance to targeted therapy in mRCC, with a focus on resistance associated with tyrosine kinase inhibitors, and will consider potential management strategies, including dose escalation and the pros and cons of switching to alternative agents, which may allow further clinical benefit to be achieved.

Biology of RCC

In the majority of clear cell RCC tumours, inactivation of the von Hippel Lindau tumour suppressor gene results in the accumulation of the transcription factor, hypoxia-inducible factor (HIF)-α.[16, 17, and 18] Accumulation of HIF-α results in the activation of several genes, including VEGF and platelet derived growth factor (PDGF),[16, 17, and 18] which play a role in tumour angiogenesis and growth, making these rational targets for the treatment of clear cell RCC.[19]

mTOR has also been implicated in the development of RCC as it is involved in the regulation of HIF-α levels.[20] Furthermore, mTOR activation results in the production of proteins involved in cell growth and proliferation.[21] mTOR is also involved in the AKT pathway, which has been shown to be dysregulated in several tumour types, including RCC.[21]

In non-clear cell RCC, which includes papillary RCC, chromophobe RCC and collecting duct RCC, the pathways involved are less well understood.[22] However, initial research indicates that the pathways may not be driven by accumulation of HIF-α or VEGF.

Mechanisms associated with resistance

Three patterns of resistance to VEGF-targeted therapy in patients with mRCC have been identified[10]: A subset of patients (25%) is resistant to therapy when they are initially assessed for response after 2–3 months of therapy.[10] A larger group experience tumour regression initially, followed by a short period of disease stability and then disease progression after 6–12 months of treatment.[10] A further subset of patients experience tumour regression during the first few months of therapy followed by a longer period of disease stability with no new lesions appearing.[10]

It has been suggested that there are two general modes of resistance to targeted therapy: intrinsic (pre-existing) and adaptive (evasive) resistance.[23]

Intrinsic resistance

In the subset of patients who experience no clinical benefit from VEGF targeted therapy, it has been hypothesised that tumours have an intrinsic resistance to targeted therapy.[23] Several underlying mechanisms

have been proposed, including the pre-existence of redundant pro-angiogenic signals. Late-stage breast cancers have been shown to express pro-angiogenic factors, such as fibroblast growth factor (FGF) 2, whereas earlier-stage tumours tended to express VEGF.[24] Pre-existence of pro-angiogenic factors in mRCC may compensate for the inhibition of VEGF signalling and thus allow angiogenesis to continue.[23] It has also been suggested that myeloid cells may have a role in intrinsic resistance to targeted therapy. In a preclinical study, tumours which were not responsive to an anti-VEGF antibody were associated with an increase in infiltrating CD11b + GR1 + myeloid cells, which expressed several pro-angiogenic factors.[25]

The poor outcome of these patients, even following treatment with available targeted agents, such as anti-angiogenic agents and mTOR inhibitors,[11] suggests that the level of resistance is wide and that to circumvent these mechanisms we should look at alternative pathways. Alternative pathways could include targeting of RAF and MEK. Another option currently under investigation in clinical trials is targeting of the PI3K/AKT pathway. For example, perifosine is an AKT inhibitor currently in clinical development.[26] Furthermore, there are several other PI3K inhibitors in early clinical development, such as PF0521384, GDC0980 and GSK2126458.[27] In clinical practice, we would recommend that patients who demonstrate primary resistance to VEGF-targeted therapy should be entered into clinical trials with agents that are investigating inhibition of these, and other, alternative pathways.

Evasive resistance

In patients who initially experience clinical benefit with targeted therapy but then experience disease progression, it is thought that the tumours adapt to inhibition of angiogenesis and acquire alternative means to evade therapeutic blockade (Fig. 1). It is as yet not clear why some patients have a longer period of clinical benefit than others. Data from animal models are providing some insights into possible mechanisms of evasive resistance. In RCC xenograft models, resistance to the tyrosine kinase inhibitor, sorafenib, has been shown to be reversed when the resistant xenografts were re-implanted in untreated mice. This suggests that acquired resistance is not due to genetic or epigenetic changes of the tumour cells, but instead may, in part, be related to changes in the microenvironment.[28] For example, changes in blood flow to the tumour may be involved. RCC xenograft models have shown that treatment with sorafenib resulted in a reduction of tumour blood flow. Increased blood flow was then observed prior to tumour growth, suggesting that the tumour cells are able to establish vasculature that is less dependent on VEGF signalling.[29 and 30]

Several mechanisms to explain how tumours may develop vasculature independent of VEGF-signalling have been proposed, including a change in the balance of angiogenesis through upregulation of pro-angiogenic factors or downregulation of angiostatic factors.
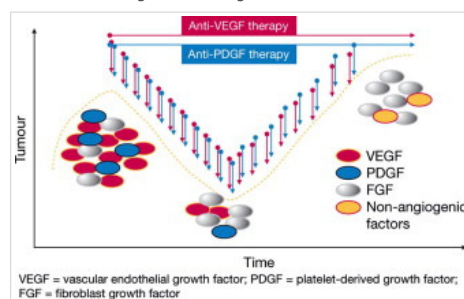

VEGF = vascular endothelial growth factor; PDGF = platelet-derived growth factor; FGF = fibroblast growth factor

Fig. 1

Tumour evolution and proposed mechanism of resistance development.[38] Anti-VEGF and anti-PDGF therapy initially reduces tumour size. However, as the tumour becomes less reliant on VEGF and PDGF, by using other pathways, such as FGF, and non-angiogenic pathways, resistance occurs and the tumour does not respond to treatment.

Upregulation of alternative pro-angiogenic factors

Preclinical studies have identified a number of pro-angiogenic proteins which may be involved in the development of resistance to targeted therapy (Table 1). In a mouse model of pancreatic neuroendocrine cancer, tumours which were resistant to an antibody blocking VEGF signalling expressed higher levels of FGF 1 and 2, ephrin A1 and A2 and angiopoietin 1.[31]

Table 1

Proposed changes in the balance of angiogenesis, through upregulation of pro-angiogenic factors or downregulation of angiostatic factors, may result in tumours becoming less dependent on VEGF-signalling.

Upregulation of pro-angiogenic factors	Downregulation of angiostatic factors
↑Levels of IL-8[32]	↓Expression of IFN-γ[36]
↑Levels of plasma angiopoietin 2[33]	↓IFN-γ plasma levels[36]
↑Expression of sphingosine kinase[35]	↓CXCL-10 levels[36]
↑Levels of sphingosine 1-phosphate[35]	

Results from RCC model studies with tyrosine kinase inhibitors also support this hypothesis. Recent data from a xenograft model of clear cell RCC, showed that microvessel density was significantly higher in

tumours which were resistant to sunitinib than those which were sensitive.[32] Furthermore, mice with sunitinib-resistant tumours had higher plasma levels of human IL-8, a potent pro-angiogenic chemokine, than those with sunitinib-sensitive tumours.[32] It was also shown that administration of an IL-8 neutralising antibody resulted in the tumour cells becoming sensitive to sunitinib treatment again.[32]

Plasma angiopoietin 2 (Ang2), a glycoprotein that has been implicated in angiogenesis and cancer neovascularisation, may also be important in the development of resistance to tyrosine kinase inhibitors.[33] Plasma levels of Ang2 were shown to decrease in patients with mRCC following initiation of sunitinib treatment. Following the development of resistance to sunitinib, an increase in Ang2 plasma levels was observed.[33]

Sphingosine kinase is an enzyme that catalyses the formation of sphingosine 1-phosphate (S1P). S1P is associated with cell proliferation, survival and angiogenesis.[34] Expression of sphingosine kinase has been shown to increase with the development of resistance to sunitinib. Furthermore, levels of plasma S1P were shown to decrease during sunitinib treatment, and there was a trend towards an increase in S1P levels as resistance developed.[35] A neutralising antibody against S1P delayed the growth of sunitinib-resistant tumours in mice.[35]

Downregulation of angiostatic factors

Downregulation of the IFN signalling pathway has also been implicated in the development of resistance to tyrosine kinase inhibitors (Table 1). RCC xenograft models showed that treatment with sorafenib and sunitinib resulted in the increased expression of several IFN-inducible genes, including the angiostatic chemokines CXCL 10 and CXCL 11 and the tumour suppressor IFITM1.[36] Following the development of resistance, the expression of IFN-γ and several of these IFN-inducible genes was reduced. Furthermore, plasma levels of human IFN-γ and CXCL-10 in mice with treatment-resistant xenografts were reduced compared with levels in untreated mice.[36] Treatment with sunitinib and sorafenib led to the down regulation of IFN-γ-R1, suggesting that downregulation of key components of the IFN signalling pathway and reduced expression of some IFN-inducible genes is associated with the development of resistance to sunitinib and sorafenib.[36]

Recruitment of bone marrow-derived cells

Other mechanisms of resistance to targeted therapy that have been suggested include the recruitment of bone marrow-derived cells, which can result in the development of new blood vessels.[23] As described earlier, a preclinical study has shown that resistance to VEGF treatment has been associated with recruitment of CD11b + GR1 + cells. There is also evidence to suggest that tumour vasculature may be protected by increased pericyte coverage allowing tumour blood vessels to survive and function during anti-angiogenic therapy.[23]

Development of an invasion without angiogenesis

Finally, invasion and metastasis of tumour cells into normal tissue and recruitment of normal tissue vasculature may enable tumours to become resistant to anti-angiogenic therapy.[23] It has been reported that the tumour of a patient experiencing disease progression during antiangiogenic therapy had invaded the surrounding tissue and there had been an increase of the vascularisation of the centre of the tumour.[37 and 38] Pathology showed a sarcomatoid transformation, invasion of surrounding tissue and an epithelial to mesenchymal transition (decrease of cytokeratin markers and expression of vimentin on tumour cells).[37 and 38]

How can we manage resistance?

Several options have been investigated to try to overcome resistance to tyrosine kinase inhibitors: adjusting dose[13] and switching to an alternative agent, either with a VEGF-targeted therapy or an mTOR inhibitor.[14 and 15] Combination therapy and the development of novel agents may also allow us to overcome resistance.

Adjusting dose

A key consideration following progression is to assess if the optimal dose of therapy has been given to the patient. The importance of dose has been shown in a pharmacokinetic/pharmacodynamic meta-analysis of patients with advanced solid tumours receiving sunitinib.[39] This analysis showed that patients who received higher exposure to sunitinib had longer time to progression and OS. Additionally, increased exposure to sunitinib was associated with an increased likelihood of achieving a complete or partial response in patients with mRCC. Higher exposure to sunitinib was also associated with greater decreases in tumour size.[39] However, it should be noted that this was a retrospective meta-analysis of good quality prospective trials, and included patients with different tumour types which may have affected these results.

The effect of dose escalation with sorafenib in patients with mRCC has been assessed in two phase II studies.[40 and 41] Patients who had previously received a maximum of one prior therapy were enroled to receive 400 mg twice-daily (BID) days 1–28, 600 mg BID days 29–56 and 800 mg BID days 57 throughout.[40] These studies suggested that dose escalation was feasible and resulted in improved median PFS and response rates compared with the standard dose (response rates: 33–55%; median PFS or time to progression: 7.7–8.4 months). As a comparison, the phase III TARGET trial, sorafenib 400 mg BID (standard dose) was associated with PFS of 5.5 months in patients who had received prior therapy.[42] Furthermore, treatment was generally well tolerated with the majority of adverse events (AEs) grade 1/2 in severity.[41] A further multicentre, phase II study assessed this dose-escalation regimen as first-line treatment.[43] Only 21.7% of

patients could tolerate dose escalation per protocol; however, they received dose escalations and reductions as could be tolerated during the study.[43] For patients whose sorafenib dose could be escalated above 400 mg BID, improved clinical benefit was observed (median PFS of 8.5 and 7.4 months in the 600 mg BID and 800 mg BID groups, respectively, versus 3.7 months in the 400 mg BID group).[43] In a further phase II, open-label study comparing sorafenib with IFN-α in patients with advanced RCC, sorafenib dose escalation following disease progression resulted in clinical benefit.[13] Patients with advanced RCC were randomised to receive sorafenib 400 mg BID or IFN-α 9 million U three times weekly. Following progression, patients receiving sorafenib 400 mg BID were dose-escalated to 600 mg BID, while patients receiving IFN-α were switched to sorafenib 400 mg BID.[13] A total of 41.9% of patients who were dose-escalated to sorafenib 600 mg BID showed a reduction in tumour size; however, there were no objective responses. Median PFS was 3.6 months in those escalated to sorafenib 600 mg BID.[13] Overall, although the results of these trials suggest that dose-escalated sorafenib results in improved efficacy, the majority of patients do not appear to be able to tolerate this dose.[43] As such, dose-escalation of sorafenib does not appear to be a viable option for most patients.

Another option regarding dose adjustment is the potential to use serum levels to guide whether the dose should be modified. It has been suggested that this may be useful for agents, such as imatinib.[44] Phase I data with sunitinib suggested that dosing did not need to be adapted based on body surface area.[45] However, based on the data by Houk et al., it may be useful to adapt the dosage of sunitinib in clinical practice based on pharmacokinetic data, while also paying attention to side effects. The only available data on individualising dose and schedule have been published in abstract form and suggest that this strategy is feasible and may allow improvements in tolerability and efficacy.[46] Nevertheless, full publication and confirmation of these results is required. Furthermore, an ongoing study is assessing the feasibility of using individual pharmacokinetics to guide sunitinib dosing in patients with advanced solid tumours (NCT01286896).[27]

Combination therapy

Co-administration of targeted agents can be performed utilising a vertical combination to increase the level of inhibition of a similar pathway or a horizontal combination of drugs acting on different major pathways involved in renal cell tumour growth.

Starting with combination therapy

A recent trial showed that the combination of bevacizumab and everolimus was active and well tolerated as first- and second-line treatment of mRCC.[47] Median PFS was 9.1 months in treatment-naïve patients and 7.1 months in those who had received previous therapy.[47]

However, initial studies have suggested problems with increased toxicity. A phase I study of sunitinib in combination with bevacizumab showed that combination therapy was poorly tolerated at full doses.[48] An additional phase I study evaluating sunitinib in combination with temsirolimus showed that the combination was associated with dose-limiting toxicity (grade 3 rash and grade 3 cellulitis) and the trial was terminated after 3 patients were enroled in cycle 1, cohort 1.[49] Recent data from the randomised phase II TORAVA study showed that the combination of temsirolimus and bevacizumab was associated with high rates of toxicity, including grade 3/4 fatigue, proteinuria and hypertension. Furthermore, the combination of temsirolimus and bevacizumab did not improve efficacy versus sunitinib or bevacizumab plus IFN-α.[50]

Several randomised phase II and phase III trials evaluating different combination therapies have completed accrual, such as the INTORACT trial, evaluating temsirolimus in combination with bevacizumab versus bevacizumab plus IFN-α, and the BeST trial, which is assessing the combination of bevacizumab with either sorafenib or temsirolimus, and the combination of temsirolimus and sorafenib.[27] Pending results of these trials, the current consensus is that sequencing single agents, rather than combination therapy, is preferred in mRCC.

Additionally, it is important to note that this area of research may evolve with the development of novel agents. A recently presented phase I study suggests that the combination of a more selective tyrosine kinase inhibitor (tivozanib) with an mTOR inhibitor (temsirolimus) could be tolerated with full doses of each agent.[51] Agents such as tivozanib and axitinib, are more selective for VEGFR-1, 2 and 3, and do not inhibit as broad a range of tyrosine kinase inhibitors compared with sunitinib and sorafenib. As such, tivozanib and axitinib should cause fewer off-target, non-VEGF related adverse events.[52]

Combination therapy upon progression

The addition of another drug upon progression may also overcome resistance. A small case series showed that the combination of bevacizumab with sunitinib was active in patients who had progressed on sunitinib monotherapy.[53] It should be noted that it is not clear if the clinical benefit was due to the combination or if the same benefit would have been achieved with bevacizumab alone. Nevertheless, as stated by Medioni et al., there is a scientific rationale for adding bevacizumab to sunitinib, as inhibition of VEGFR with sunitinib has been shown to result in the upregulation of plasma VEGF levels. As such, addition of bevacizumab would inhibit the excess plasma VEGF.[53] It is important to note that most combination therapies should not be used outside clinical trials; however, in these circumstances, the ability of a patient to tolerate sunitinib may allow the addition of bevacizumab. We believe that the addition of another therapy upon progression may be most suitable for patients who have initially benefited from VEGF-targeted therapy and have aggressive tumours, in which any interruption or cessation of antiangiogenic inhibition may induce a rapid progression or rebound. The addition of another agent may allow the level of inhibition to be increased.

Switch to another targeted therapy

Different tyrosine kinase inhibitors have different target profiles and different potencies (Fig. 2).[54, 55, 56, 57, 58, 59, 60, and 61] As such, cross-resistance between agents is not inevitable. Indeed, initial studies assessing second-line therapy have shown that patients can gain further clinical benefit by switching to an alternative agent.[14 and 15] Furthermore, sequential therapy should enable the full doses of targeted agents to be administered, without additional toxicity.
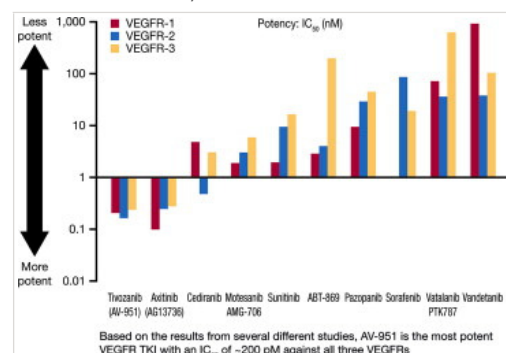

Fig. 2

Relative potencies of VEGFR tyrosine kinase inhibitors.[54, 55, 56, 57, 58, 59, 60, and 61]

Phase III evidence for the use of the sequence of the tyrosine kinase inhibitors, sunitinib and sorafenib, followed by the mTOR inhibitor, everolimus, has been shown in the RECORD-1 trial.[14] Everolimus was shown to significantly improve PFS compared with placebo in patients whose disease had progressed on or within 6 months of stopping sunitinib or sorafenib, or both.[14] Median PFS was 4.9 months in the everolimus group compared with 1.9 months in the placebo group ($p < 0.001$; Fig. 3). OS was similar in both treatment groups (14.8 months with everolimus and 14.4 months with placebo; $p = 0.162$). However, patients who experienced disease progression on placebo were able to cross over and receive everolimus, which may have confounded the OS results.[14] When results were analysed according to prior VEGFR-tyrosine kinase inhibitor, median PFS with everolimus and placebo was 3.9 and 1.8 months, respectively, for patients who had received prior sunitinib. With longer follow-up, the median PFS following first-line sunitinib reached 4.6 months.[62] Median PFS for patients who had received prior sorafenib was 5.9 months with everolimus versus 2.8 months with placebo. Finally, in patients who had received both sorafenib and sunitinib, median PFS was 4.0 months with everolimus versus 1.8 months with placebo (Table 2).[14] We feel that two major points should be noted with regards to these results; firstly, the magnitude of the gain reported by the HR is similar for each drug compared with when patients had previously received both drugs, which supports the fact that everolimus acts in a new way irrespective of the previous treatment with VEGFR TKI. However, there is a difference in PFS with everolimus, dependent on prior sunitinib or sorafenib, which is also the case for the placebo arm. We believe that this highlights that sunitinib is more active than sorafenib in the previous line of therapy. Therefore, when everolimus is administered after use of an agent which had higher levels of inhibition (sunitinib), the overall effect of everolimus on PFS is more limited. As such, we think that everolimus has similar effects in patients who have been treated with either sunitinib or sorafenib and the difference in PFS is related to the difference in activity between sunitinib and sorafenib in the previous line of therapy.
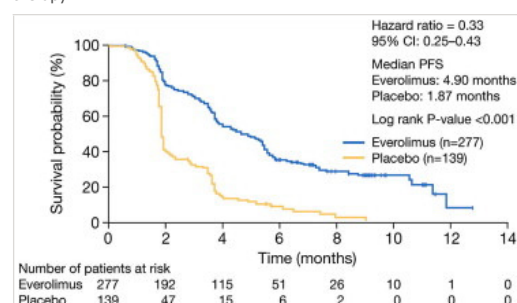

Fig. 3

Median progression-free survival for patients receiving everolimus versus placebo following VEGFR-tyrosine kinase inhibitor treatment in the phase III trial.[14]

Table 2

Median PFS, according to prior treatment, in patients randomised to receive everolimus or placebo.[14]

	Prior sunitinib ($n = 184$)		Prior sorafenib ($n = 124$)		Prior sunitinib and sorafenib ($n = 108$)	
	Everolimus	Placebo	Everolimus	Placebo	Everolimus	Placebo
Median PFS (months)	3.9	1.8	5.9	2.8	4.0	1.8

Hazard ratio (95% CI)	0.34 (0.23–0.51)	0.28 (0.16–0.42)	0.32 (0.19–0.54)

The sequence of giving a tyrosine kinase inhibitor followed by a different tyrosine kinase inhibitor has also demonstrated activity in patients with advanced RCC.[63] In a phase II trial, axitinib, a selective inhibitor of VEGFRs 1, 2 and 3, demonstrated antitumour activity in patients with mRCC after failure of sorafenib and, often, additional therapies.[15] A total of 62 patients were included in the study; of these, all patients had previously received sorafenib and 74.2% of patients had received two or more prior systemic treatments.[15] An objective response rate of 22.6% was observed, with 14 patients achieving a partial response. In the total study population, median PFS was 7.4 months and median OS was 13.6 months (Fig. 4).[15] An exploratory subgroup analysis showed that responses to axitinib were observed in patients with >1 prior antiangiogenic therapies. Of 14 patients who had received both sunitinib and sorafenib, 1 patient had a partial response.[15] Results from the phase III AXIS trial, which compared axitinib and sorafenib in 723 patients who had experienced failure on a first-line RCC treatment, including sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokines, have recently been presented.[64] Axitinib significantly prolonged median PFS versus sorafenib (6.7 versus 4.7 months, respectively; $p < 0.0001$).[64] Median PFS was significantly longer with axitinib versus sorafenib in patients who had received prior cytokines (12.1 versus 6.5 months, respectively; $p < 0.0001$,) and those who received prior sunitinib (4.8 versus 3.4 months, respectively; $p = 0.0107$).[64] We believe that the AXIS trial validates the use of a tyrosine kinase inhibitor followed by another tyrosine kinase inhibitor, and demonstrates that axitinib is an effective option for the second-line treatment of mRCC. The PFS achieved with axitinib, post-sunitinib, is similar to that achieved with everolimus in the RECORD-1 trial; however, it is not possible to draw any firm conclusions from a cross-trial comparison as these trials enroled different patient populations. As such, we can only conclude that both of these drugs may be standard options in the future for second-line treatment. However, additional information is needed to enable us to optimally select which agent to use.
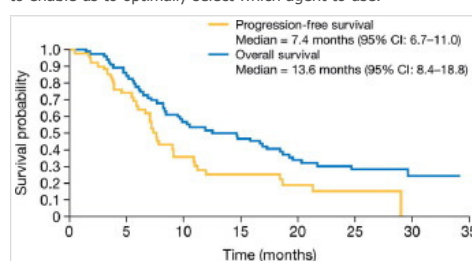

Fig. 4

Median progression-free survival and overall survival in patients receiving second-line axitinib treatment.[15]

A retrospective analysis has also assessed sequential treatment with sunitinib and sorafenib.[65] This analysis suggested that there was a lack of cross-resistance between these two tyrosine kinase inhibitors. Several other studies have also shown that the sequence of sunitinib and sorafenib and vice versa is associated with clinical benefit.[66 and 67] However, switching from sunitinib to sorafenib was associated with limited efficacy.[65, 66, and 67] It should be noted that these were retrospective studies, and as such, caution should be applied when interpreting these results.

A recent retrospective review of 23 patients with mRCC has shown that re-challenging with an agent that patients had previously progressed on can also achieve clinical benefit.[68] Patients were re-challenged with sunitinib after disease progression during sunitinib and one or more further antitumour therapies. Median duration of treatment for sunitinib re-challenge was 6.7 months.[68] Five patients (22%) achieved partial response and 17 patients (74%) had stable disease. Initial treatment with sunitinib was associated with a median PFS of 13.7 months compared with 7.2 months for re-challenge ($p = 0.04$). In six patients, PFS was longer with re-challenge than with initial treatment.[68] Patients who had more than 6 months between sunitinib treatments had significantly longer PFS (median 16.5 months) than those who were re-challenged within 6 months (median 6.0 months).[68] A clinical case of a 60-year-old patient with mRCC who had progressed on sunitinib and everolimus and subsequently received sunitinib (50 mg/day) supports these findings.[69] Re-challenge with sunitinib resulted in a partial response for 12 months. Furthermore, a retrospective analysis assessing patients who had progressed on everolimus and a tyrosine kinase inhibitor, showed that re-challenge with another anti-angiogenic agent was feasible.[70] Of 39 patients who had received at least one prior tyrosine kinase inhibitor followed by everolimus, 15 patients received additional therapy with sunitinib, sorafenib, both tyrosine kinase inhibitors sequentially, bevacizumab plus IFN-α or an investigational agent, after progression. Of 14 evaluable patients, the majority achieved disease control (86%) and median PFS was 5.1 months.[70] Based on the available data and our clinical experience, we believe that re-challenge is an effective strategy for some patients with mRCC. In some patients, it appears that the tumour continues to rely on VEGF throughout the disease course. In particular, we think that re-challenge can be an important option for those patients who have had a prolonged stable disease or objective response with a VEGFR-TKI, have received several lines of standard or investigational treatments and for whom there is no option of a clinical trial. Additionally, they should have a Karnofsky performance status ⩾70%. Sensitivity of tumours to previously effective targeted therapy has also been reported for mTOR inhibitors[71] reinforcing this practical therapeutic notion that a previously effective agent may be an option for therapeutic management when no clinical trial is available.

It has also been proposed that drug 'holidays' may help prevent resistance. The biological effect provided by changing pathway inhibition could also be achieved by giving the patient a drug 'holiday' and maintaining

sensitivity to targeted agents. For example, in the case of a complete response, it has been hypothesised that stopping therapy may allow any residual cancer cells to remain sensitive to VEGF and PDGF-targeted therapy. It has been suggested that continuation of therapy may lead to the development of cells that are resistant to VEGF and PDGF-targeted therapy (Fig. 5).[38] The contrary view is that if therapy is stopped in patients who achieve a complete response, any residual cancer cells will be able to replicate and the tumours may grow again.
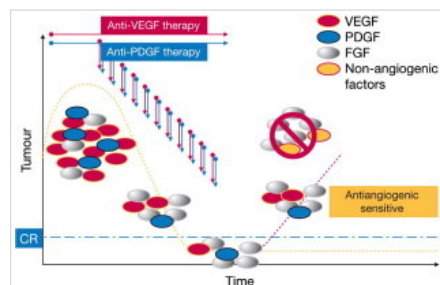

Fig. 5

Proposed mechanism of tumour evolution following stopping therapy after a complete response.[38] Following complete response, there are often residual cancer cells. By stopping anti-VEGF and anti-PDGF therapy, it is hypothesised that the tumour cells may remain sensitive to angiogenic therapy.

The optimal sequence of targeted therapy remains to be determined. Several trials currently ongoing may provide us with further information. In addition to the recently completed, phase III AXIS trial,[27] the INTORSECT study, is evaluating temsirolimus versus sorafenib as second-line treatment in patients with mRCC refractory to sunitinib.[27] A further trial, RECORD-3 is evaluating the sequence of everolimus and sunitinib. Patients are randomised to receive either sunitinib or everolimus first-line until progression, and then receive the other agent as second-line treatment.[27]

Other studies are evaluating cycles of treatment with two agents, using a rotational plan, without waiting for disease progression. For example, in the phase II EVERSUN trial, patients with mRCC will receive two cycles of sunitinib (Schedule 4/2) followed by everolimus for five weeks, with one week rest.[27] Cycles will continue consecutively until disease progression or toxicity.

Currently, in clinical practice, there are no predictive data to help guide second-line treatment choice. Indeed recent evidence suggests that response to first-line VEGF-targeted treatment is not associated with response to second-line VEGF-targeted therapy.[72] We believe that either a second-line tyrosine kinase inhibitor or an mTOR inhibitor are suitable second-line treatment options. Following progression on second-line tyrosine kinase inhibitor, data suggest an mTOR inhibitor can be used.[14] Alternatively, following progression on a second-line mTOR inhibitor, an alternative tyrosine kinase inhibitor may be effective.

Treating early progression following tyrosine kinase inhibitor therapy

Retrospective analyses suggest that the subset of patients who experience an early progression during VEGFR-tyrosine kinase inhibitor treatment (at the first evaluation, around 2–3 months after commencing treatment) may be considered to have an intrinsic resistance to this therapy and thus none of the available agents will be effective.[73 and 74] In these circumstances it is urgently necessary to consider these patients for inclusion in trials that are exploring alternative pathways of inhibition.

Development of novel agents targeting other pro-angiogenic pathways

Further understanding of the mechanisms of resistance associated with tyrosine kinase inhibitors may allow the rational development of agents which target resistance pathways. As described above, Ang2 has been implicated in the development of resistance, generating interest in inhibition of this pathway. AMG 386 is a recombinant peptide-Fc fusion protein, which contains a peptide sequence that binds to Ang1 and Ang2.[75] AMG 386 in combination with sorafenib demonstrated tumour activity in patients with mRCC, including some patients with resistance to VEGFR-targeted therapy.[76] A phase II trial is evaluating the efficacy and safety of sorafenib in combination with AMG 386 or placebo as first-line treatment of patients with mRCC.[27] Recently presented results from this trial suggested that the combination of sorafenib and AMG 386 was tolerable; however, there was no improvement in PFS compared with sorafenib plus placebo.[77] A further phase II trial is assessing AMG 386 in combination with sunitinib as first- or second-line treatment.[27]

As discussed, it has also been suggested that FGF may be an escape mechanism to VEGFR-targeted therapy. TKI258, an inhibitor of VEGFR-1, -2 and -3 and FGFR-1, -2 and -3, is undergoing a phase I/II study in patients with advanced or metastatic RCC.[27] Preliminary results showed that TKI258 at 500 mg/day was well tolerated in heavily pre-treated patients with advanced RCC.[78] Interestingly, patients who had previously received anti-VEGF therapy had high baseline levels of FGF, suggesting activation of this pathway.[78]

Identification of treatment resistance

In addition to the development of treatment strategies to overcome resistance, another important consideration is the clinical definition of resistance and identifying when treatment benefit has ceased, so that subsequent therapy can be initiated. Currently, resistance to therapy is defined by disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which are based on tumour size measurements.[79] However, targeted agents often cause changes to the tumour structure, resulting in reduced tumour vascularity or density, and tumour necrosis, and may not result in changes in tumour

volume.[80] As a result, it may be necessary to use clinical assessment, in addition to information from the scan to determine if treatment should be switched. Other methods of assessing treatment response have been evaluated, including PET and CT imaging,[81] and dynamic contrast-enhanced ultrasonography.[82] These methods may allow earlier and more accurate assessment of response to therapy; however, further validation of these techniques is required.

It is also important to note that in clinical practice, there may be some cases where apparent disease progression should not result in the discontinuation of treatment. For example, when the majority of lesions are under control with current treatment, but one lesion is progressing, it may be preferable to continue targeted therapy and treat the progressing lesion by other means, for example, with surgery, radiotherapy or radiofrequency. Secondly, it is important to note that some metastatic sites may only appear on the CT scan of dense organs (liver, bone) at the first evaluation following treatment. This does not necessarily mean that these are new metastatic sites; however, they may not have been apparent on the baseline scan.

Finally, in some patients, treatment discontinuation may occur due to adverse events rather than disease progression. It is important to note that prompt and proactive therapy management can enable the impact of adverse events to be reduced, allowing patients to remain on-treatment for longer. Several articles have reviewed these therapy management strategies in detail.[83, 84, and 85]

Conclusions

Resistance to targeted therapy is complex and the underlying mechanisms have not yet been fully elucidated. Currently, the majority of patients with RCC who experience disease progression during first-line treatment will receive a second-line treatment. However, the optimal sequence remains to be determined and whether it is necessary to change to an agent with a different mode of action is a matter of debate. Ongoing trials assessing second-line treatment in patients with targeted therapy-refractory mRCC may provide further information.

In conclusion, improved understanding of the mechanisms of resistance associated with targeted therapy may allow us to develop rational long-term treatment approaches, and will allow us to further improve patient outcomes in mRCC.

Conflict of interest

Acknowledgements

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