

TARGETED THERAPIES IN RENAL CELL CARCINOMA

David Pook and Ian D Davis

Ludwig Institute for Cancer Research, Austin Health, Heidelberg, Victoria.

Email: ian.davis@ludwig.edu.au

Abstract

The landscape of treatment for renal cell carcinoma has changed radically over the last few years. Previously, the most effective treatments were too toxic, too expensive or too ineffective. Careful biological studies have uncovered pathways relevant to the survival, growth and spread of renal cell carcinoma and other cancers, and have highlighted rational targets for therapy. New agents aimed at these targets have been shown to be highly effective, but have brought with them a new range of toxicities and other complexities in the management of our patients. This review describes three drugs recently approved in Australia for use in advanced renal cell carcinoma and other agents of clinical and research interest.

Renal cell carcinoma

Renal cell carcinoma is diagnosed in over 2000 Australians every year and about 800 die of the disease annually. It makes up 2% of cancer deaths and affects males more than females.¹ Three quarters of renal cell carcinomas are of so-called conventional clear cell histology, 15% are papillary and the remainder are predominantly made up of chromophobe, oncocytoma and collecting duct tumours.² Most new cases are found incidentally and outcomes are good if the cancer is resectable. However, until recently few treatment options were available for advanced or metastatic disease and the median survival of metastatic renal cell carcinoma was of the order of one year.³

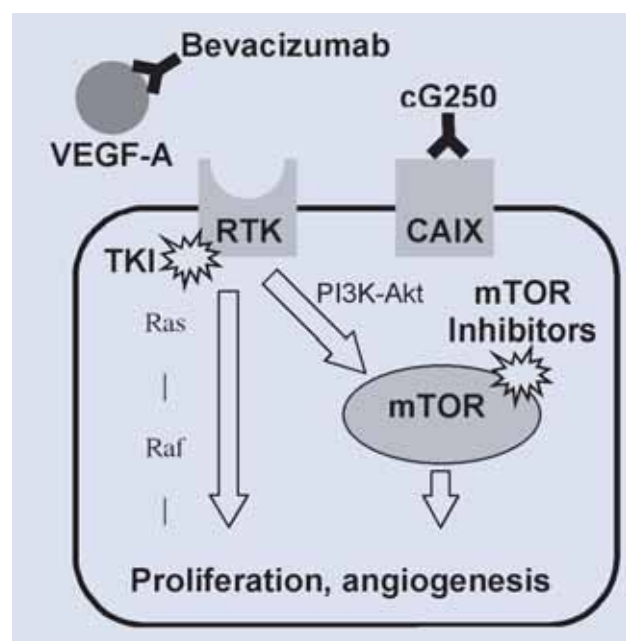
Six prognostic factors that independently predict survival have been derived from studies of patients treated with interferon and have been used in predictive nomograms. These factors are: a Karnofsky Performance Status of less than 80%; an interval from diagnosis to treatment less than one year; anaemia; hypercalcaemia; lactate dehydrogenase elevated to greater than 1.5 the upper limit of normal; and more than two sites of metastatic disease.^{4,5}

Many of the pathways driving the growth of renal cell carcinomas are now much better understood and have provided a rational basis for the development of new therapies. The von Hippel-Lindau protein (VHL) degrades hypoxia-inducible factors in renal cells when oxygen levels are adequate, but allows these factors to accumulate and move to the nucleus to promote expression of factors involved in angiogenesis, glucose transport, pH regulation and the prevention of apoptosis.⁶ In 80% of renal cell carcinomas this pathway is exploited by inactivation of the VHL protein, allowing HIF accumulation despite normal oxygen tension.⁷ This results in expression of growth factors that promote tumour growth and result in many of the characteristics of renal cell carcinoma. These factors include: vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which stimulate angiogenesis

resulting in characteristic vascular tumours; transforming growth factor- α , which can stimulate tumour growth through activation of the epidermal growth factor receptor (EGFR); adipose differentiation related peptide, that results in lipid accumulation and characteristic clear cells; and interleukin-6, which results in fevers common in patients with the disease.⁸

Until recently, the most effective systemic treatments for advanced disease were the cytokines interleukin-2 and interferon- α , however both were limited by potentially severe toxicities. Three agents (sunitinib, sorafenib and temsirolimus) that target the various pathways involved in the growth and spread of renal cell

Figure 1: Sites of action of targeted agents in renal cell carcinoma cells. The tyrosine kinase inhibitors also act on endothelial cells to reduce proliferation. RTK denotes receptor tyrosine kinase; CAIX denotes carbonic anhydrase IX.



carcinoma, have been approved in Australia since late 2006 and even more are in development.

Approved agents

Many of the growth factors involved in the growth of renal cell carcinoma act by binding to receptor tyrosine kinases that mediate signals by phosphorylation of tyrosines on proteins downstream of the receptor. Tyrosine kinase inhibitors (TKIs) are small molecules that prevent signal transduction, usually by interfering with binding of ATP (see figure 1). They vary in their affinity for various receptors and consequently have differing spectra of activity and side-effects.

Sunitinib (Sutent®) is an orally bioavailable TKI with activity against a large number of receptors including VEGF receptor-2 and PDGF receptor β , FLT3, C-KIT, RET and CSF-1.⁹ When compared with interferon-alpha in previously untreated patients with metastatic clear cell renal cell carcinoma and favourable prognostic features, treatment with sunitinib resulted in a 31% response rate and 11 month progression free survival, compared with 6% and five months with interferon.¹⁰ The main side-effects of treatment were diarrhoea, fatigue, nausea, stomatitis, vomiting, hypertension and hand-foot syndrome, but these were rarely severe. Neutropenia was shown to occur in a small proportion of patients. Hypothyroidism is reported in approximately one third of patients and is similar in pattern to thyroiditis, as half of these patients experience a transient fall in thyroid stimulating hormone (biochemical hyperthyroidism) before becoming hypothyroid.¹¹ More recently, cardiomyopathy has been reported in patients treated with sunitinib with an incidence estimated to be from 2.7 to 15.5%.¹²⁻¹⁴ There appear to be two patterns of cardiotoxicity. The first is a rapid onset of congestive cardiac failure, which has been reported to occur after as few as four days of treatment, with sunitinib and often results in death within months.¹³ The second is a gradual decrease in ejection fraction, which occurs over several cycles in about 20% of patients.¹² Regression analysis indicates significant associations with hypertension and coronary artery disease.

Sorafenib (Nexavar®) is an orally bioavailable TKI with affinity for VEGF receptors, PDGF receptors, C-KIT, FLT-3 and RET receptors.¹⁵ It was compared with placebo in a large randomised and double blinded study of patients with clear-cell renal cell carcinoma, who had progressed after one course of systemic therapy, usually cytokines.¹⁶ Patients had a good performance status and did not have poor prognosis of disease. Median progression free survival was 5.5 months compared with 2.8 months on placebo, despite a response rate of only 10%. This observation highlights the fact that conventional response criteria may be less relevant in assessment of clinically meaningful outcomes when this class of agents is being tested. The median overall survival for sorafenib was 19.3 months, but was difficult to compare with placebo as patients were allowed to cross over to sorafenib mid-way through the study. Side-effects included diarrhoea, rash, fatigue, hand-foot

syndrome, alopecia and hypertension. Cardiovascular events were six times more common and bleeding events were twice as common in the sorafenib group.

Temsirolimus (Torisel®) is an intravenously administered inhibitor of the mammalian target of rapamycin (mTOR). mTOR forms a multi-protein complex involved in the control of cell proliferation and angiogenesis and which acts downstream of the receptor tyrosine kinases. Temsirolimus was compared with interferon, and with a combination of the two drugs in previously untreated patients with renal cell carcinoma and at least three poor prognostic factors.¹⁷ Notably, in this trial, 20% of patients had non clear-cell histology and 82% had a Karnofsky performance status of $\leq 70\%$. Temsirolimus improved overall survival from 7.3 to 10.9 months compared with interferon alone. A survival benefit was not observed in the combination arm, possibly because the doses of both drugs were suboptimal due to the toxicity of the combination. The temsirolimus arms had improved progression free survival of between 1.8 and 2.4 months. Side-effects of treatment with temsirolimus were rash, peripheral oedema, mouth ulcers, hyperglycemia and lipid abnormalities. Despite being less toxic than interferon, two-thirds of patients had to delay temsirolimus treatment as a result of toxicity.

Now that several approved agents are available for use in the clinic, the challenge remains as to when and in which order they should be used. As with all decisions on when to treat, possible side-effects of treatment need to be weighed against the probable benefit to the patient. In patients with good prognosis and slowly progressive disease, we will often delay treatment until the patient develops symptoms related to their disease. Symptomatic patients with good prognostic features will generally be treated with sunitinib or sorafenib, unless they have contra-indications such as cardiac failure, for which we screen prior to treatment. As the agents differ in their specificity for receptor tyrosine kinases, we usually use a second TKI on failure of first line therapy if the patient is well enough. At present, temsirolimus is used as second or third line therapy, or as first line therapy in patients with poor prognosis disease, non-clear-cell histology or contra-indications to TKI therapy.

Agents under investigation

Everolimus is an orally bioavailable mTOR inhibitor that has shown activity in early clinical studies.¹⁸ A recent double-blind placebo control trial in patients who had progressed on or within six months of sunitinib and/or sorafenib demonstrated an improved progression free survival of 4.6 months on everolimus compared with 1.9 months with placebo.¹⁹ Side-effects of treatment were similar to temsirolimus, but also included asthenia, pneumonitis, hypophosphataemia, thrombocytopenia, anaemia and hepatotoxicity.

Pazopanib is an oral TKI with activity against VEGF receptor, PDGF receptor and C-KIT. In patients previously treated with cytokines or bevacizumab, treatment with pazopanib resulted in a 35% response

rate and a 12 month progression free survival.²⁰ Side-effects included diarrhoea, hypertension, hair colour changes, fatigue and hepatotoxicity. Similarly, cediranib and axitinib, both VEGF receptor targeted TKIs, induced responses in 38% and 20% of patients and progression free survival of 8.7 and 7.7 months respectively, with side-effects including hypertension, fatigue and dyspnoea.^{21,22}

Erlotinib is a TKI that targets EGFR and is registered for treatment of lung cancer. A small study showed a long progression free survival of 27 months in untreated papillary renal cell carcinoma despite a response rate of only 11%.²³

Bevacizumab is a humanised monoclonal antibody against the ligand VEGF-A rather than the VEGF receptor. It has activity in various cancers when combined with chemotherapy and modest activity against renal cell carcinoma as a single agent.²⁴ When compared with interferon in previously untreated patients, a combination of interferon and bevacizumab improved progression free survival from 5.4 to 10.2 months.²⁵ Toxicities such as fatigue and weakness were mainly related to interferon, however treatment with bevacizumab resulted in proteinuria, hypertension, bleeding and a small incidence of gastrointestinal perforation and arterial and venous thrombotic events.

G250 or carbonic anhydrase IX is a membrane protein found on 85% of renal cell carcinoma, but in normal tissues is only found on gastric epithelium, biliary ducts and some pancreatic acini.²⁶ A chimeric monoclonal antibody to this protein (cG250) is able to target radioisotopes to renal cell carcinoma effectively in order to deliver radiotherapy to the site of the tumour.²⁷ Studies of cG250, bound to different radioisotopes and in combination with chemotherapy or cytokines, are ongoing to determine whether its efficacy can be improved.^{28,29}

Conclusions

Options for treatment of advanced renal cell carcinoma have increased rapidly over the last few years, with agents targeting different aspects of the pathways involved in cancer growth, as well as targeting the cancer cells themselves. Substantial improvements in cancer outcomes such as progression free survival and overall survival have been seen, although these do not always correlate with radiological response rates. However, despite significant activity, none of these agents have been shown to cure renal cell carcinoma, complete remissions are uncommon and each causes side-effects that must be weighed against benefit. More work needs to be done to characterise the optimal sequence and combinations of the various drugs now available and to determine whether there may be benefit of their use in the adjuvant setting. Nevertheless, it is now possible to say that renal cell carcinoma is a highly treatable cancer.

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