Drug treatment of renal cancer

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Summary

Renal cell cancer is best diagnosed early and treated by complete surgical excision. There is currently no standard effective drug therapy for advanced or metastatic renal cell cancer. Chemotherapy is ineffective, and immunotherapy has only modest activity and an uncertain effect on survival. Advances in the understanding of the biology of renal cell cancer have identified tumour angiogenesis as a target for drug therapy. New therapies have therefore emerged aimed at vascular endothelial growth factor and other growth factors mediating angiogenesis. These include bevacizumab, an antibody against vascular endothelial growth factor, and the oral drugs sunitinib and sorafenib.

Key words: angiogenesis inhibitors, bevacizumab, sorafenib, sunitinib.

(Aust Prescr 2006;29:151–3)

Introduction

In Australia, renal cell cancer is the eighth most common cancer in males and the ninth in females. In 2001 there were 2458 new cases (2.8% of all new cancers). The peak incidence occurs between 50 and 70 years. Renal cell cancers arising from the kidney epithelium account for 90–95% of all primary renal cell cancers and clear cell is the most common histology (75%).[1]

While patients may classically present with local symptoms and signs (flank pain, haematuria, abdominal mass), renal cell cancer is increasingly being diagnosed by the coincidental finding of a renal mass on imaging performed for other reasons. Despite this fortuitous presentation, 25–30% of patients will have advanced or metastatic disease.[1] Common metastatic sites include lung, soft tissue, bone, liver and central nervous system. Manifestations of advanced disease include fatigue (often with anaemia), fever, weight loss and hypercalcaemia.

Renal cell cancer is generally a very vascular tumour which is insensitive to chemotherapy and only modestly sensitive to immunotherapy. The best outcome for patients is with complete excision of localised disease. Some patients with limited metastatic disease may also benefit from surgical removal of metastases. About one in three patients will relapse following curative nephrectomy[1], hence the need for an effective systemic therapy remains.

Diagnosis and staging

The standard minimum evaluation of patients with a suspected renal cell tumour is a CT scan of abdomen and pelvis, a chest X-ray and urine analysis. A CT scan of the chest is more sensitive for small metastases.

The tumour stage is the most important prognostic factor. Patients with renal vein or vena cava involvement are still curable by complete resection. Hilar lymph node involvement is a worse prognostic sign. Patients with stage IV disease may have more distant local node involvement or distant metastases. Their five-year survival is less than 10%, but the prognosis can be somewhat variable. It is occasionally long and rarely (less than 1%) associated with spontaneous remission. Survival is dependent on histological grade, histological type, performance status, age, number and location of metastatic sites, time to appearance of metastases, and prior nephrectomy.

Treatment overview

Nephrectomy is the mainstay of treatment for patients with disease confined to the kidney, including those with involvement of local veins. Limited resection (partial nephrectomy) may be used in patients with small tumours (less than 4 cm), solitary kidneys or with tumours in both kidneys. Nephrectomy in patients with metastatic disease may be needed to alleviate haemorrhage or pain from the primary tumour.

Adjuvant therapy

The use of adjuvant systemic therapy following radical curative nephrectomy does not improve survival.[1] In selected patients with metastatic disease and good performance status at diagnosis, radical nephrectomy followed by interferon alfa may improve survival when compared with interferon alfa alone.[2]

Systemic therapy of advanced or metastatic disease

Until recently there was little evidence to support the routine use of systemic treatment. Chemotherapy has response rates (defined as a reduction of more than 50% in tumour size) of under 8% and is therefore of little value. This is because of the multidrug resistance protein found in proximal tubule cells, from which clear cell and papillary renal cell carcinoma are thought to originate.

A systematic review of immunotherapy has revealed little proven impact on the survival of patients with advanced renal cell cancer.[3] Interferon alfa alone is associated with only a modest tumour response rate (in approximately 15% of patients) and a median duration of response of approximately six months. High doses of interleukin-2 are associated with higher response rates (21%) and longer durations of response (up to 130 weeks) than lower doses, but with greater toxicity (nausea, vomiting, malaise and hypotension).[2] In view of these modest results, immunotherapy is not funded by the Pharmaceutical Benefits Scheme nor is it routinely used across Australia.

Combination immunotherapy and immunochemotherapy have been associated with greater tumour regression but at the cost of greater toxicity and without proven impact on survival. Other areas under study include tumour vaccines.

Biologic advances in renal cancer and angiogenesis

The greatest recent developments in renal cell cancer have involved improved understanding of its molecular pathogenesis, particularly the von Hippel-Lindau (VHL) tumour suppressor gene and its relationship to the angiogenesis mediated by vascular endothelial growth factor (VEGF).[1,4] VHL syndrome is an autosomal dominant disorder (germline mutation in one VHL gene allele) with inherited susceptibility to vascular tumours including clear cell renal cell cancer. Inactivation of the gene leads to overexpression of VEGF, which stimulates the angiogenesis that enables tumour growth. The lifetime risk of renal cell cancer in patients with the syndrome approaches 50%. Recently, the genetics underlying sporadic (non-hereditary) renal cell cancer have been shown to be similar with deletion of the VHL gene allele being found in 84–98% of patients with sporadic renal tumours.[1,4]

New treatments are focusing on gene products in the angiogenesis pathway. These include VEGF, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and transforming growth factor alpha (TGF-α).[1,3,4] VEGF exerts its biologic effect through interaction with transmembrane tyrosine kinase receptors found on the cell surface (VEGFR-1 to -4, with VEGFR-2 being most important for angiogenesis).[5] These angiogenic proteins are the targets of several drugs.

Bevacizumab

This humanised VEGF neutralising monoclonal antibody was the first of the anti-angiogenic drugs to show efficacy in renal cell cancer.[4,6] In a randomised, double-blind, phase II study in 116 patients with metastatic clear cell renal cell cancer, the time to progression of disease was significantly prolonged with high-dose bevacizumab (10 mg/kg intravenously fortnightly) compared with placebo (4.8 vs 2.5 months, $p < 0.001$). The trial was stopped after the interim analysis. Adverse drug reactions included reversible hypertension (8% needed treatment) and asymptomatic proteinuria (25% of patients).

Bevacizumab is approved in Australia for treatment of advanced colorectal cancer. The results of an international phase III trial of first-line interferon alfa with either bevacizumab or placebo in patients with metastatic renal cell cancer are awaited.

Tyrosine kinase inhibitors

In almost all cancers, overexpression of the epidermal growth factor receptor (EGFR) has been shown to correlate with a poorer prognosis and a more malignant phenotype. Erlotinib is a small molecule which inhibits the tyrosine kinase associated with EGFR. As 80–90% of patients with renal cell cancer have EGFR overexpression, trials of erlotinib with bevacizumab are in progress. Erlotinib's main adverse reactions are an acneiform skin rash and diarrhoea.

Sunitinib

Sunitinib is an oral tyrosine kinase inhibitor acting on, at least, PDGF and VEGFR-2. The activity of sunitinib (50 mg/day for 4–6 weeks) was recently reported in 63 patients with metastatic renal cell cancer who had previously been treated with either interferon alfa or interleukin-2.[6] There was a partial response in 25 patients and 17 had stable disease for three months or more. Median time to progression in the 63 patients was 8.7 months. Treatment was generally tolerated but was associated with fatigue, diarrhoea, stomatitis and leucopenias. A randomised trial comparing first-line interferon alfa and sunitinib has just been completed.[7] In this trial of 750 patients the response rate was significantly greater with sunitinib (24.8% vs 4.9%, $p < 0.001$), as was progression-free survival (47.3 weeks vs 24 weeks, $p < 0.001$).

Sorafenib

Sorafenib inhibits a variety of receptor kinase molecules that are involved in tumour growth and angiogenesis. Oral sorafenib has been evaluated in patients with advanced renal cell cancer who have previously received one systemic therapy, usually interleukin-2. A prospective randomised multicentre trial compared sorafenib (400 mg twice daily) to placebo in 769 patients.[6] Progression-free survival was doubled with sorafenib (24 compared to 12 weeks for placebo, $p < 0.000001$). The effect of sorafenib was seen across different risk groups and was unaffected by the prior therapy being interleukin-2 or interferon alfa. Sorafenib's effect on progression-free survival was mainly due to disease stabilisation as the tumour response rate was only 2%. Its effect on survival awaits further follow-up. The most common adverse effects were a hand-foot reaction (40%), rash and hypertension (requiring treatment in 17%).

Future directions

The plethora of new drugs in renal cell cancer has raised hope for patients. As the data from clinical trials are published, a number of options may emerge for treating patients to prolong disease-free and/or overall survival, with relatively mild toxicity. Sorafenib and sunitinib have just completed randomised

phase III trials in Australia. Ongoing research into molecular profiling and biomarkers may assist in identifying which patients will get the greatest benefit from these new treatments.

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[R] randomised controlled trial

Dr Pavlakis has served on advisory boards for Roche (bevacizumab in colon cancer and non-small cell lung cancer) and Pfizer (sunitinib for non-small cell lung cancer).

Self-test questions

The following statements are either true or false (answers on page 171)

1. Only 2–3% of patients with asymptomatic renal cell cancer have metastatic disease.
2. Adjuvant chemotherapy of renal cell cancer improves the survival of patients after radical curative nephrectomy.

Medicinal mishap

Brand confusion with digoxin

Prepared by John Balassa, General practitioner, Marrickville, New South Wales

Case

A 74-year-old retired man attended our surgery with a five-day history of upset stomach, nausea, an aversion to food, but no diarrhoea. He blamed some takeaway chicken for his problem.

His past history included valvular heart disease (mitral and aortic), myocardial infarction, chronic atrial fibrillation and partial thyroidectomy. The patient's usual medications were:

- Lanoxin PG (digoxin 62.5 microgram) three times a day
- Coumadin (warfarin)
- Lasix (frusemide)
- Neo-Mercazole (carbimazole).

On examination the physical findings were non-specific. The patient was given a proton pump inhibitor.

The patient returned 12 days later as he was still unwell. His pulse rate was 38 and irregular. He was having visual problems and he described blurred vision with honey coloured 'lakes' in his visual field, surrounded by yellow beads and dragonfly wing coloured areas.

Xanthopsia can be a sign of digoxin toxicity so his serum digoxin was checked. It was 6.2 nanomol/L which is a toxic concentration (therapeutic range 0.6–2.6 nanomol/L).

The patient's medications were reviewed and I found that a different brand of digoxin from his Lanoxin PG had been recommended. The box had a label of Sigmaxin PG, but it contained digoxin 250 microgram tablets. The patient had therefore been taking four times his usual dose. The digoxin was stopped and the concentration returned to normal. His pulse rate increased to 48 and gradually his xanthopsia disappeared. He developed marked oedema while off digoxin.

Comment

Any person with stomach upsets needs to have their medications checked. Loss of appetite is an early sign of digoxin toxicity. It may also cause nausea, vomiting, diarrhoea and abdominal pain. Xanthopsia (yellow vision) is a rare symptom.

The proliferation of new brands for old drugs can cause confusion. The patient took the new tablets but probably would have realised that he had not received his usual 'little blue' tablets. It is therefore important to explain to patients when there is going to be a change in their brand of medication. They need to understand why the substitution is being made and that they are not being given an additional medicine.

The different brands of digoxin are marketed by different companies, however these companies seem to belong to the same corporation. The need for different brands therefore appears to be unnecessary.