NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Bevacizumab, sorafenib and sunitinib for renal cell carcinoma

Draft scope

Remit/Appraisal objective

To appraise the clinical and cost-effectiveness of bevacizumab, sorafenib and sunitinib for renal cell carcinoma.

Background

Renal cell carcinoma (RCC), also called renal adenocarcinoma or hypernephroma, is a cancer usually originating in the lining of the tubules of the kidney. RCC accounts for 90% kidney cancers and approximately 3% of all adult cancers.

Early, small RCC tumours are usually asymptomatic; the diagnosis of early RCC is usually incidental after abdominal scans for other indications. The most common presenting symptoms of advanced RCC are blood in the urine (haematuria), a palpable mass in the flank or abdomen and abdominal pain. Others non-specific symptoms include fever, night sweats, malaise and weight loss.

In 2002, 5,872 new kidney cancers were diagnosed in England and Wales, of which an estimated 90% were RCC. RCC is nearly twice as common in men, than in women, and most commonly affects adults aged 50-80 years old. Approximately 3,000 people died of kidney cancer in 2004 in England and Wales (a mortality rate of 6.2 per 100,000 population). In 2000-2001 five year survival for all kidney cancer was approximately 50% for men and women.

The stage of RCC is usually reported using the tumour, node and metastasis (TMN) classification. This is based on the extent of the primary tumour (T), whether lymph nodes are affected (N) and whether metastases are present (M). Advanced and metastatic RCC fall within stages III and IV, stage III denotes disease that is locally advanced and/or has spread to regional lymph nodes and stage IV denotes that distant metastasis has occurred.

Approximately 25% of patients present with advanced or metastatic disease (stage III or stage IV). An estimated 50% of patients who have curative resection for earlier stages will develop recurrent and/or metastatic disease. Without treatment, these patients have a median survival rate of only 6-12 months and a two-year survival rate of 10-20%.

Surgical resection to remove the entire kidney (radical nephrectomy) or part of the kidney (partial nephrectomy) is the only accepted curative treatment for patients with non metastatic RCC (TNM stage I –III), and the success of surgery depends on the stage of disease. Standard treatment of metastatic RCC (stage IV) is immunotherapy with interleukin-2 (IL-2) (sometimes called

aldesleukin) or interferon alpha (IFN-alpha) which may lead to tumour shrinkage. Palliative surgery, arterial embolisation or radiotherapy may also be considered in these patients.

The technologies

Bevacizumab (Avastin; Roche Pharmaceuticals) binds to vascular endothelial growth factor (VEGF) and thereby inhibits the binding of VEGF to its receptors. This reduces the vascularisation of tumours, thereby inhibiting tumour growth. Bevacizumab has no marketing authorisation for the use in RCC in the UK. In clinical trials bevacizumab is being used in combination with INF-alpha.

Sorafenib (Nexavar; Bayer/Onyx) is an orally administered multikinase inihibitor. It has a dual action that inhibits the raf cascade, and the VEGF/platelet-derived growth factor (PDGFR) receptors on cancer cells, vascular endothelial cells and pericytes therefore inhibiting proliferation of tumour cells and development of tumour vasculature. Sorafenib has EU orphan drug designation for RCC and has received its marketing authorisation for use in patients with advanced renal cell carcinoma (RCC) who have either failed prior therapy with IFN-alpha or IL-2 or are unsuitable for such therapy.

Sunitinib (Sutent; Pfizer) is an orally administered multi-targeted tyrosine kinase inihibitor. Sunitinib inhibits the VEGF/PDGFR, two receptors on cancer cells, vascular endothelial cells and pericytes therefore inhibiting proliferation of tumour cells and development of tumour vasculature. Sunitinib has a marketing authorisation in the UK for the treatment of advanced and/or metastatic renal cell carcinoma.

Intervention(s)	First-line therapy: • Bevacizumab (in combination with INF-alpha) • Sunitinib • Sorafenib tosylate (in patients who are unsuitable for IFN-alpha or IL-2 therapy) • *[Temsirolimus[1]]* Second-line therapy: • Sorafenib tosylate • Sunitinib
Population(s)	Patients with advanced and/or metastatic renal cell carcinoma

[1] Subject to consultation and Ministerial referral. See question for consultation below.

Standard comparators	First-line therapy: • best supportive care • immunotherapy (IFN-alpha or IL-2) without the addition of bevacizumab • appropriate interventions will be compared to each other Second-line therapy: • best supportive care • appropriate interventions will be compared to each other
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • tumour response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation should be sufficiently long so as to incorporate all the important costs and benefits. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Where evidence permits, the appraisal should identify patient subgroups (e.g. resected versus unresected primary tumour and clear cell versus non clear cell carcinoma [histological type]) for whom the technology is particularly appropriate. Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Interventional Procedures: NICE Interventional Procedure Guidance No.91 – Percutaneous radiofrequency ablation of renal cancer (September 2004) Related Cancer Service Guidance: NICE Cancer service guidelines CSG - Improving outcomes in urological cancer (September 2002)

Question for consultation

The Institute would welcome Consultees' and Commentators' views on whether temsirolimus should be considered as an intervention in this appraisal. The inclusion of temsirolimus is subject to Ministerial referral.

- Temsirolimus (Torisel, CCI-779; Wyeth) administered by intravenous infusion, blocks the function of the mammalian target of rapamycin (mTOR), a key protein within cells that regulates cell proliferation, growth and survival. Temsirolimus has no marketing authorisation for the use in RCC in the UK. In clinical trials temsirolimus has been used as a first-line therapy for advanced renal cell carcinoma in patients who have 3 or more of 6 poor prognostic factors.