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Title **Bevacizumab, Sorafenib Tosylate and Sunitinib for Renal Cell Carcinoma: A Systematic Review and Economic Evaluation**

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Aim

To assess the clinical effectiveness and cost-effectiveness of bevacizumab, combined with interferon (IFN), sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic renal cell carcinoma (RCC).

Conclusions and results

Treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC. In people with three of six risk factors for poor prognosis, temsirolimus had clinically relevant advantages over treatment with IFN, and sorafenib tosylate was superior to best supportive care as second-line therapy. The frequency of adverse events associated with bevacizumab plus IFN, sunitinib and temsirolimus was comparable with that seen with IFN, although the adverse event profile is different. Treatment with sorafenib was associated with a significantly increased frequency of hypertension and hand–foot syndrome. Estimates from the PenTAG model suggested that none of the interventions would be considered cost-effective at a willingness-to-pay threshold of 30 000 pounds sterling (GBP) per QALY. A total of 888 titles and abstracts were retrieved in the clinical effectiveness review, including reports of eight clinical trials. Treatment with bevacizumab plus IFN or sunitinib had clinically relevant and statistically significant advantages over treatment with IFN alone, in terms of progression-free survival and tumor response, doubling median progression-free survival from approximately 5 months to 10 months. Temsirolimus had similar advantages over treatment with IFN in terms of progression-free and overall survival, increasing median overall survival from 7.3 to 10.9 months [hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.58 to 0.92)], as did sorafenib in comparison with best supportive care in terms of overall survival, progression-free survival and tumor response, with a doubling of progression-free survival (HR 0.51; 95% CI 0.43 to 0.60). However, the last was associated with an increased frequency of hypertension and hand–foot skin reaction compared with placebo. No fully published economic evaluations of any of the interventions could be located. However, estimates from the PenTAG model suggested that none of the interventions would be considered cost-effective at a willingness-to-pay threshold of 30 000 GBP per quality-adjusted life-year (QALY). Estimates of cost per QALY ranged from 71 462 GBP for sunitinib to 171 301 GBP for bevacizumab plus IFN. Although there are many similarities in the methodology and structural assumptions employed by PenTAG and the manufacturers of the interventions, in all cases the cost-effectiveness estimates from the PenTAG model were higher than those presented in the manufacturers' submissions. Cost-effectiveness estimates were particularly sensitive to variations in the estimates of treatment effectiveness, drug pricing (including dose intensity data), and health-state utility input parameters.

Recommendations

For further details see Executive Summary link at www.hta.ac.uk/project/1711.asp.

Methods

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Further research/reviews required

There are clear gaps in the evidence base needed to fully appraise the clinical effectiveness and cost-effectiveness of these four interventions in accordance with their marketing authorizations: More randomized clinical trials in the following areas would be useful: in patients unsuitable for treatment with IFN because of contraindications or who have been defined as having intermediate and poor prognosis and therefore unlikely to benefit from IFN; studies of sorafenib tosylate, sunitinib, bevacizumab plus IFN and best supportive care; and comparative trials of sunitinib and sorafenib as second-line therapy. For further details see Executive Summary link at www.hta.ac.uk/project/1711.asp.

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