Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation

CRD summary
This review concluded that bevacizumab plus interferon and sunitinib had clear advantages over interferon alone for patients with metastatic renal cell carcinoma. Temsirolimus had clinically relevant advantages over interferon for patients with poor prognosis. Sorafenib tosylate was more effective than best standard care as second-line therapy. The conclusions of this well-conducted review are likely to be reliable.

Authors' objectives
To evaluate the effectiveness and cost-effectiveness of bevacizumab combined with interferon (interferon), sorafenib tosylate, sunitinib and temsirolimus in the treatment of advanced and/or metastatic renal cell carcinoma.

Searching
The Cochrane Library, MEDLINE, EMBASE, Science Citation Index, ISI Proceedings and BIOSIS were searched up to September/October 2007. Bibliographies of included studies and relevant conference proceedings (2006 and 2007) were searched. All searches were rerun in February 2008. Conference abstracts that provided sufficient detail to assess quality or reporting updated results of included trials were included. Search terms were reported. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of patients with advanced and/or metastatic renal cell carcinoma that assessed bevacizumab plus interferon-alpha, temsirolimus (as first-line therapies), sunitinib or sorafenib tosylate (first- or second-line treatments) were eligible for inclusion. Eligible comparators were immunotherapy (interferon-alpha) alone for suitable patients and those with three or more of six poor prognostic factors) or best standard care for those not suitable for treatment with immunotherapy (as first-line therapies) or best standard care (as second-line therapy).

Primary outcomes were overall survival and progression-free survival. Secondary outcomes were tumour response rate, adverse events/toxicity and health-related quality of life. Trials were eligible if they reported at least one of the primary outcomes. In case of insufficient evidence from good quality RCTs, data from phase II trials and non-randomised studies were considered.

Details of interventions assessed in the included studies were presented.

Most patients in the included trials had a diagnosis of metastatic clear cell renal cell carcinoma and had undergone previous nephrectomy. No details of age or sex were reported.

Studies were selected independently by two reviewers. Discrepancies were resolved by discussion.

Assessment of study quality
Study quality was assessed using an extensive list of 25 criteria for participant recruitment, assignment to treatment groups, blinding, drop-out and analyses.

One reviewer performed the quality assessment. Judgments were checked by a second reviewer and disagreements were resolved by discussion, with the help of a third reviewer as necessary.

Data extraction
For survival outcomes, median survival in months with 95% confidence intervals (CI) was extracted to enable calculation of hazard ratios and 95% CIs. Authors of primary studies were contacted for more information where required. In studies where patients were allowed to move from comparator to active treatment after demonstration of efficacy in interim analyses, only data collected before crossover were extracted.
Data extraction was performed by one reviewer and checked by a second. Disagreements were resolved by discussion, with the help of a third reviewer where needed.

**Methods of synthesis**
Where head-to-head comparisons between interventions were not possible, the feasibility of undertaking indirect comparisons was assessed (test for internal validity and similarity of trials) and performed when deemed appropriate, adjusting for prognostic factors using the methods of Bucher et al.

**Results of the review**
Eight clinical trials (five RCTs, one randomised discontinuation study and two single arm trials) with a total of 4,031 patients were included in the review. Seven trials were identified as large good-quality multicentre trials.

**Bevacizumab plus interferon and sunitinib compared with interferon as first-line therapy:**

Two RCTs compared bevacizumab plus interferon with interferon plus placebo or interferon alone and one RCT compared sunitinib with interferon. Both treatments were statistically significantly more effective than interferon alone and increased progression-free survival from about five months to between 8.5 and 11 months. Both treatments showed some improvement in overall survival, although data were limited due to early crossover of control patients following interim analyses.

An indirect comparison of both treatments suggested that sunitinib may be more effective than bevacizumab plus interferon in terms of progression-free survival (HR 0.67, 95% CI 0.50 to 0.89; two RCTs) and overall survival (HR 0.82, 95% CI 0.53 to 1.28; two RCTs) although results for overall survival did not reach statistical significance.

**Bevacizumab plus interferon, sorafenib, sunitinib, temsirolimus and best supportive care compared with interferon as first-line therapy in people with poor prognosis:**

One RCT showed that temsirolimus was statistically significantly more effective than interferon for patients with poor prognosis and increased median overall survival from 7.3 to 10.9 months (HR 0.73, 95% CI 0.58 to 0.92). Patients on temsirolimus had median progression-free survival of 5.6 months compared to 3.2 months for the interferon group (HR 0.74, 95% CI 0.60 to 0.91).

The difference in progression-free survival between bevacizumab plus interferon and interferon alone was minimal and may not be statistically significant. No evidence was found for sorafenib and sunitinib as first-line therapy in this population.

**Sorafenib tosylate and sunitinib compared with best supportive care as second-line therapy:**

Sorafenib was statistically significantly more effective than best supportive care in terms of progression-free survival (median 5.5 months versus 2.8 months; HR 0.51, 95% CI 0.43 to 0.60) and in overall survival (HR 0.72, 95% CI 0.54 to 0.94) according to one large RCT.

Two single-arm phase II trials suggested that sunitinib may be efficacious for patients as second-line therapy. Results were reported for secondary outcomes tumour response, adverse events and health-related quality of life.

**Cost information**
An economic evaluation suggested that none of the interventions were cost-effective at a willingness-to-pay threshold of £30,000 per quality-adjusted life-year (QALY). Costs per QALY were estimated at £171,301 for bevacizumab plus interferon and £71,462 for sunitinib compared with interferon alone as first-line therapy. For people with poor prognosis, temsirolimus had a cost per QALY of £81,687. Sorafenib second-line therapy compared with best supportive care had a cost per QALY of £102,498.

**Authors’ conclusions**
Bevacizumab plus interferon and sunitinib had clinically relevant and statistically significant advantages compared to interferon alone for patients with metastatic renal cell carcinoma. Evidence suggested that temsirolimus has clinically relevant advantages over interferon for patients with poor prognosis. Sorafenib tosylate was more effective than best
standard care as second-line therapy. Adverse events were equally frequent with bevacizumab plus interferon, sunitinib and temsirolimus. Sorafenib was associated with significantly higher rates of hypertension and hand-foot syndrome.

**CRD commentary**

The review addressed well-defined questions and had clear inclusion criteria. The search for studies was thorough. Validity of included studies was assessed with appropriate criteria and the results were used in the synthesis. Measures were taken to minimise errors and bias in study selection, data extraction and validity assessment. Full details of the included studies were available in the report.

Indirect comparisons were tested and used when deemed appropriate. Results from such comparisons should be interpreted with greater caution than head-to-head comparisons (as acknowledged by the review authors) so the results of the indirect comparison between sunitinib and bevacizumab plus interferon should be interpreted with caution.

Although few studies were included, the quality of the evidence was generally good and the conclusions of this well-conducted review are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further randomised clinical trials of sorafenib, sunitinib, bevacizumab plus interferon and best standard care were needed. These should focus on patients unsuitable for interferon treatment either due to contraindications or because they have an intermediate or poor prognosis. Comparative trials of sunitinib and sorafenib as second-line therapy were needed. Further research on the impact of the interventions on health-related quality of life during progression-free survival and progressed disease would help inform treatment decisions made by clinicians and patients. More research on the combination and order of treatments to provide maximum benefit in each patient population was needed.

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Record Status
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