Multikinase inhibitors in metastatic renal cell carcinoma: indirect comparison meta-analysis

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CRD summary
The review concluded that some multikinase inhibitors show favourable progression free survival for patients with metastatic renal cell carcinoma compared with placebo or interferon-α and that sunitinib might offer some clinical benefit over sorafenib. Based on the small number of trials, poor reporting and reliance on indirect comparisons, the reliability of the authors' conclusion is uncertain.

Authors' objectives
To determine the clinical effectiveness of multikinase inhibitors in the treatment of metastatic renal cell carcinoma, as well as the optimal treatment among these agents.

Searching
MEDLINE, EMBASE, CANCERLIT and The Cochrane Library were searched for articles published in English from January 2008 to March 2010. Key search terms were reported. Conference abstracts from the American Society of Clinical Oncology and the Genitourinary Cancers Symposium (2007 and 2009) were also searched. Reference lists of included trials were manually checked for additional trials. Abstracts were included if there was sufficient data to assess outcomes and trial quality.

Study selection
Eligible randomised controlled trials (RCTs) of patients with metastatic renal cell carcinoma evaluated the efficacy of multikinase inhibitors sunitinib, sorafenib or pazopanib compared with a control intervention. Primary outcome was progression-free survival; other outcomes of interest included overall survival.

Comparisons included sorafenib versus placebo or interferon-α, sunitinib versus interferon-α and pazopanib versus placebo. All trials included patients with a diagnosis of metastatic clear-cell renal cell carcinoma and a life expectancy greater than or equal to 12 weeks. Where reported, most participants had undergone a nephrectomy or had received a cytokine-based treatment. Most participants were classed as intermediate or low risk based on the Memorial Sloan-Kettering Cancer Center prognostic score. The median age ranged from 58 to 62 years, with the proportion of male participants ranging from 57% to 75%.

Two reviewers independently selected trials for inclusion in the review and any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed the quality of the included trials using the Jadad scale. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted hazard ratios (HRs) and 95% confidence intervals (CIs) for survival data. Any disagreements were resolved by consensus.

Methods of synthesis
Trials were pooled where more than one trial assessed the agent of interest. Trials were pooled using a random-effects model. Heterogeneity was assessed using $X^2$ and $I^2$. Lack of head-to-head comparisons between multikinase inhibitors meant that adjusted indirect comparison method (Bucher et al.) was used to determine the optimal treatment among agents.

Results of the review
Four RCTs (reported in six publications) were included in the review (2,277 patients, range 189 to 903); three phase III trials and one phase II trial. Two trials scored a 5 and two trials scored a 3 on the Jadad scale. All trials were conducted...
A significant effect on progression-free survival was found in favour of sorafenib or sunitinib when compared with interferon-α (HR 0.47, 95% CI 0.32 to 0.71; p<0.001; two RCTs) and sorafenib or pazopanib when compared with placebo or interferon-α (HR 0.45, 95% CI 0.04 to 0.86; $I^2=0\%$, three RCTs). No between group differences were found for sorafenib and sunitinib compared with interferon-α or placebo (three RCTs), or sorafenib and pazopanib compared with placebo (two RCTs). Trials were not pooled for overall survival as completed data were not available in all trials.

The results of the indirect comparison (with interferon-α as the comparator) found a significant effect on progression-free survival in favour of sunitinib versus sorafenib (HR 0.47, 95% CI 0.32 to 0.71; p<0.001). No significant difference was found between sorafenib versus pazopanib with placebo as the comparator.

**Authors' conclusions**

Some multikinase inhibitors have shown favourable progression-free survival for patients with metastatic renal cell carcinoma compared with interferon-α or placebo, and sunitinib might offer some clinical benefit over sorafenib but these conclusions were based on two indirect comparisons of single RCTs.

**CRD commentary**

The review question was supported by clearly defined inclusion and exclusion criteria. Several electronic databases were searched and some attempt was made to identify grey literature. The search was restricted to English language studies so the possibility of language bias cannot be ruled out. Appropriate steps were taken to minimise the likelihood of reviewer error or bias in the selection of trials, data extraction and assessment of trial quality. The quality of the trials was assessed with a standardised tool which included some relevant criteria; only a summary score was reported. The trials were pooled with appropriate techniques but poor reporting meant that the possibility that some patients were included in the analysis twice could not be ruled out. Such double-counting would cast doubt on the reliability of the synthesis.

Based on the small number of trials, poor reporting and reliance on indirect comparisons the reliability of the authors' conclusions was uncertain.

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

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

**Research:** The authors stated that more trials were required to confirm these findings and investigate the clinical effectiveness of multikinase inhibitors for metastatic renal cell carcinoma.

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