Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis
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CRD summary
The authors concluded that cancer patients treated with sorafenib had a significantly greater risk of developing hypertension. Analyses based on small amounts of data, statistical variation, and a lack of reported detail mean that the authors' conclusion may not be reliable.

Authors' objectives
To determine the risk of hypertension in patients with cancer who receive sorafenib.

Searching
MEDLINE was searched from inception to July 200. Web of Science citation database and abstracts presented at the American Society of Clinical Oncology (2004-2007) were also searched to identify any additional relevant studies. Search terms were reported. The search was restricted to English language papers.

Study selection
Prospective clinical trials that assessed sorafenib as a single drug (starting dose of 400mg twice daily) in patients with cancer that reported events or incidences of hypertension were eligible for inclusion in the review. Randomised phase II and III trials, single arm phase II trials and an expanded access programmes were included in the review. All the included participants had renal-cell carcinoma or other solid tumours. The underlying malignancies reported were renal cell carcinoma, melanoma, non-small-cell lung cancer, prostate cancer, non-gastrointestinal stromal tumour and neuroendocrine tumours. The median age of participants ranged from 53 to 64 years.

One reviewer selected studies for inclusion in the review.

Assessment of study quality
The authors did not state that validity was assessed.

Data extraction
For each trial, the proportion of patients with hypertension was calculated, with 95% confidence intervals (CIs). For studies with a control group, the relative risk (RR) of hypertension was also calculated. Hypertension was recorded according to versions 2 or 3 of the Common Terminology Criteria for Adverse Events (CTCAE) and assigned a grade from 1 (asymptomatic, transient - under 24 hours increase in blood pressure by more than 20mmHg diastolic or to more than 150/100mmHg if previously within normal limit) to 4 (life threatening consequences, such as hypertensive crisis). Incidence of hypertension, grade 1 or above, was included in the analysis.

The authors did not state how data were extracted for the review or how many reviewers performed the data extraction.

Methods of synthesis
Studies were combined in a meta-analysis using both fixed-effect and random-effects models. Summary estimates were reported as incidence (percentage) with 95% confidence intervals for all-grade and high-grade (grades 3 and 4) hypertension and relative risks with 95% confidence intervals for the risk of sorafenib associated hypertension versus control in the two RCTs of patients with renal-cell carcinoma. Where significant statistical heterogeneity was found, a random-effects model was reported. Statistical heterogeneity was assessed using the Cochran's Q statistic (significant level p<0.1) and I².

Results of the review
Nine studies were included in the review (4,599 patients).
The overall incidence of all-grade hypertension in patients treated with sorafenib was 23.4% (95% CI 16.0 to 32.9) and high-grade (CTCAE grade 3 and 4) hypertension was 5.7% (95% CI 2.5 to 12.6).

When only patients with renal cell carcinoma treated with sorafenib were considered (four studies; 3,252 patients), the overall incidence of all-grade hypertension was 23.6% (95% CI 14.3 to 36.5; number of events=587; I²=96.4%) and high-grade hypertension was 6.5% (95% CI 1.8 to 2.11; number of events=205; I²=98.1%). Evidence of significant heterogeneity was found in both analyses.

When only patients with non-renal cell carcinoma (non-renal cell carcinoma) treated with sorafenib were analysed, the overall incidence of all-grade hypertension was 23.0% (95% CI 16.0 to 31.9; three studies; number of events 25; 111 patients) and high-grade hypertension was 5.3% (95% CI 2.7 to 10.0; five studies; number of events 15; 315 patients).

No statistically significant difference was found between patients with renal cell carcinoma or a non-renal cell carcinoma malignancy on incidence of all-grade hypertension (RR 1.03, 95% CI 0.73 to 1.45) and high grade hypertension (RR 1.23, 95% CI 0.76 to 1.99) who were treated with sorafenib.

Sorafenib was associated with an increased risk of all-grade hypertension in patients with renal cell carcinoma (RR 6.11, 95% CI 2.44 to 15.32; two RCTs; 1,089 patients) compared with control groups. Evidence of moderate heterogeneity was found (I²=63.7%).

**Authors' conclusions**

Patients with cancer treated with sorafenib had a significantly greater risk of developing hypertension.

**CRD commentary**

The review question was supported by clear inclusion criteria. Several sources were used to locate relevant papers. The literature search was restricted by language, so some relevant papers may have been missed. Whilst publication bias was not assessed, the authors made some attempt to locate unpublished papers. Methods used to select studies for inclusion in the review were not likely to have minimised the possibility of reviewer error and bias. The authors did not report the methods used to extract data, so the likelihood of reviewer error and bias being introduced at this stage could not be assessed.

The quality of the included studies was not assessed, which limited interpretation of the results. Standard meta-analytic methods were used. However, significant heterogeneity suggested that pooling of studies may not have been appropriate. Insufficient study details were reported.

The authors conclusion about 'increased risk' appears to be based on data from two studies (most of the included studies only gave incidence rather than comparative data). This might mean that the authors' conclusion is not reliable.

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

Practice: The authors stated that early detection and effective management of hypertension might allow for safer use of this drug, and that the hypertensive and cardiovascular side-effects of sorafenib needed thorough post-marketing surveillance and reporting.

Research: The authors stated that future studies were needed to identify the mechanism and appropriate treatment of sorafenib induced hypertension.

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