Sorafenib in treatment of patients with advanced hepatocellular carcinoma: a systematic review

CRD summary
The authors concluded that sorafenib-based therapy benefited patients with advanced hepatocellular carcinoma but was less effective for patients with extrahepatic spread, normal alpha-fetoprotein level and elevated level of bilirubin. The authors’ conclusion reflects the evidence presented but for single-arm trials this conclusion is uncertain. Caution is warranted due to the limitations in the review process and analyses.

Authors’ objectives
To assess the efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma.

Searching
PubMed, EMBASE and Web of Knowledge (SCI –Expanded) were searched from January 2005 to June 2011. Limited search terms were reported. Conference proceedings of Web of Knowledge (CPCI-S) and 2010 American Society of Clinical Oncology meeting were also searched for additional information.

Study selection
Eligible studies were comparisons of sorafenib or sorafenib-based (sorafenib combined with other agent) therapy with placebo or placebo-based (placebo with the same agent that combined with sorafenib), in patients with advanced hepatocellular carcinoma who received no systemic treatment. Eligible study designs were randomised controlled trials (RCTs) or single-arm trials with available data or retrospective studies.

Three out of six studies were randomised controlled trials (two compared 400mg sorafenib with placebo and one compared doxorubicin 60mg/m2 plus 400mg sorafenib with doxorubicin 60mg/m2 plus placebo); and the remaining three studies were single arm trials, where dosage of 400mg or 800mg sorafenib were used. Median age of the patients ranged from 51 to 69 years. The Child-Pugh score (assessed severity of liver cirrhosis) was graded A in 72 to 100% of the patients. Where reported, the percentage of patients with macroscopic vascular invasion ranged from 26 to 57% and patients with extrahepatic spread ranged from 32 to 79.6%. Between 83.7 to 100% of patients were in Eastern Cooperative Oncology Group (ECOG) performance status (assessed disease progression) grade 0 to 1.

Four reviewers were involved in the study selection.

Assessment of study quality
Study quality of the randomised controlled trials was assessed by the Cochrane Risk of Bias tool, which covered random sequence generation, allocation concealment, blinding, addressing incomplete outcome data, selective reporting and other sources of bias.

The authors did not state how many reviewers were involved in the quality assessment.

Data extraction
Data were extracted to calculated hazard ratios, odds ratios, relative risks with their 95% confidence interval. The primary outcomes of interest were overall survival and time to progression. For single-arm trials, the placebo or placebo-containing group from well matched RCTs was introduced as the control arm. Study authors were contacted for additional information.

The authors did not state how many reviewers extracted the study data.

Methods of synthesis
Pooled hazard ratios using a generic inverse variance method, and odds ratios and relative risks using the Mantel-Haenszel test, with their 95% confidence interval were calculated. Statistical heterogeneity was assessed with $X^2$ and $I^2$. 
A fixed-effect model was used in all analyses unless there was heterogeneity (P<0.1 or I² greater than 50%). Publication bias was assessed using Begg's rank correlation method.

**Results of the review**

Six trials (three RCTs and three single-armed trials) were included in the review (1,164 patients). All RCTs were considered good quality. The Begg's test showed no publication bias.

The meta-analysis showed that, compared to placebo, sorafenib increased overall survival (HR 0.66, 95% CI 0.56 to 0.78; I²=0%; three RCTs) as did sorafenib-based therapy (HR 0.69, 95% CI 0.56 to 0.84; I²=38%; three single-arm trials). Both reduced time to progression: sorafenib (HR 0.57, 95% CI 0.47 to 0.68; I²=0%; three RCTs) and sorafenib-based therapy (HR 0.64, 95% CI 0.52 to 0.78; I²=0%; three single-arm trials). There was no heterogeneity in any of the above analyses.

Sorafenib or sorafenib-based therapy was associated with significant increase in partial response rate for the three single-arm trials (OR 3.56, 95% CI 1.22 to 10.39; I²=0%) but not for the three randomised controlled trials. No heterogeneity was observed for this outcome.

Subgroup analysis indicated that sorafenib was less effective in patients with extrahepatic spread, with normal alpha-fetoprotein level (AFP) and with elevated level of serum bilirubin. Regarding adverse events, sorafenib significantly increased the risk of grades 3 and 4 hand-foot skin reaction, diarrhoea, fatigue and rash/desquamation (four trials).

**Authors’ conclusions**

Sorafenib-based therapy benefited patients with advanced hepatocellular carcinoma. Sorafenib was less effective for patients with extrahepatic spread, with normal alpha-fetoprotein level and with elevated level of bilirubin.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. Relevant data sources were searched but it was unclear whether language restrictions were applied and unpublished studies were sought; hence language and publication bias could not be ruled out. Following formal assessment there was no evidence of publication bias, but the assessments were not reliable for fewer than 10 studies.

Attempts were made to reduce the risk of potential errors and bias in study selection, but it was unclear whether similar methods were used for data extraction and quality assessment. The quality of randomised controlled trials was assessed using an appropriate tool and the results showed good quality. However the quality of the single arm studies was uncertain. Appropriate methods were used to pool data for RCTs and assess heterogeneity but it may not have been appropriate to use the control group from randomised controlled trials to compare with single-arm trials and may introduce potential confounding factors. Also there was inconsistency in the reporting of the adverse events. In the text and tables the authors reported adverse events as Grade 3 and 4 which usually indicates severe or life threatening events. However, in the discussion the authors reported the adverse events as being mild to moderate. All RCTs were supported by Bayer Healthcare Pharmaceuticals.

The authors' conclusion reflects the evidence presented for RCTs but for the single-arm trials the conclusion of these results is uncertain. Concerns about the appropriateness of some meta-analyses and limitations in the review process, and the small number of included studies means that the authors’ conclusions should be interpreted with caution.

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

**Practice:** The authors stated that more reasonable administration of sorafenib be adopted during clinical practice based on these results to tailor a more-cost effective sorafenib therapeutic strategy. Also clinicians should pay more attention to sorefenib-based treatment related adverse reactions such as hand-foot skin reaction, diarrhoea, fatigue, and rash/desquamation.

**Research:** The authors stated that further studies were needed. The authors stated that further investigation of sorafenib being less effective in patients with extrahepatic spread, with a normal AFP level and an elevated level of serum bilirubin was required.

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