Sorafenib improves the survival of patients with advanced hepatocellular carcinoma: a meta-analysis of randomized trials


CRD summary

This review concluded that sorafenib was superior to placebo-based chemotherapy for the treatment of advanced hepatocellular carcinoma in terms of time to progression and overall survival, without an increase in severe toxic effects. The authors’ conclusions appeared to reflect the evidence, but the paucity of available trials and risk of missing data should be considered when interpreting these conclusions.

Authors' objectives

To assess the effectiveness of sorafenib for the treatment of patients with advanced hepatocellular carcinoma.

Searching

PubMed was searched from January 2000 to December 2008; search terms were reported. In addition, abstracts from the past ten conferences of the American Society of Clinical Oncology and the European Society for Medical Oncology were searched for further studies. Reference lists of retrieved studies and the Physician Data Query Registry of clinical trials were also checked. Both unpublished and published trials were eligible for inclusion. No language restrictions were applied.

Study selection

Randomised controlled trials (RCTs) that compared sorafenib monotherapy or sorafenib-based combination chemotherapy regimens versus alternative placebo or combination therapy regimens, in patients with advanced hepatocellular carcinoma, were eligible for inclusion in the review. Trials where the intervention was confounded by other agents or interventions were excluded.

Primary outcomes were overall survival and time to progression. Secondary outcomes were objective response rate and toxic events.

Included trials were published in 2008 and 2009; two compared 400mg sorafenib with placebo and one compared doxorubicin 60mg/m² plus 400mg sorafenib with doxorubicin 60mg/m² plus placebo. Most of the included patients were male (range 66 to 87%); their age ranged from 51 to 66 years. The performance status ranged from 0 to 1 in 84 to 95% of patients; the Child-Pugh status was graded as ‘A’ in 95 to 100%. Macroscopic vascular invasion was present in 28 to 41% of patients, with disease classified as extra-hepatic in 50 to 69%.

The authors did not state how papers were selected for the review.

Assessment of study quality

The authors did not state how the validity assessment was performed.

Data extraction

Two reviewers independently extracted the data and trial authors were contacted for further published and unpublished data. Intention-to-treat data for overall survival and time to progression were extracted. Hazard ratios (HRs) with 96% confidence (CIs), where reported, were extracted. Odds ratios (ORs), with 95% confidence intervals, were calculated for objective response rate and the rate of adverse events.

Methods of synthesis

Odds ratios and hazard ratios were pooled, with 95% confidence intervals, using the fixed-effect model (the authors reported that similar results were found for random-effects analyses, but these were not reported in the paper). Heterogeneity was assessed using standard methods including the I² statistic and Q statistic. Publication bias was assessed using funnel plots and the Egger test.
Results of the review
Three RCTs were included in the review (n=924 patients); sample sizes ranged from 96 to 602 patients. The authors did not report any information about the individual quality of the trials, but stated that there were no significant differences between the three trials; all were double-blind and reported Intention-to-treat data.

Sorafenib-based therapy was significantly better than control therapies for time to progression (HR 0.58, 95% CI 0.49 to 0.69; three RCTs) and overall survival (HR 0.66, 95% CI 0.55 to 0.78; three RCTs) patients with advanced hepatocellular carcinoma. There were no significant differences between the three trials for response rate. No significant heterogeneity was detected.

Sorafenib-based therapy was associated with significant increases in hand-foot syndrome (OR 13.43, 95% CI 3.53 to 71.47; three RCTs) and diarrhoea (OR 2.41, 95% CI 0.99 to 5.86; three RCTs) in comparison with control therapies. There were no significant differences in the other reported adverse events.

There was no evidence of significant publication bias.

Authors’ conclusions
Sorafenib was superior to placebo-based chemotherapy in patients with advanced hepatocellular carcinoma in terms of time to progression and overall survival, without an increase in severe toxic effects.

CRD commentary
This review assessed a well-defined review question and searched a number of relevant sources. Both published and unpublished data were sought. Although this suggested that the risk of publication bias would be low, the authors acknowledged there may be some risk of bias and that their tests for publication bias were unlikely to be reliable given the small number of included trials. The authors made some attempt to reduce the risk of reviewer error and bias when extracting the study data, but it was unclear whether similar precautions were taken when selecting the studies for inclusion in the review. Also, the authors did not report how many reviewers assessed the quality of the trials.

Although appropriate criteria appear to have been used for quality assessment, the findings were not reported. Therefore, the reliability of the data was unclear. However, the methods used to synthesis the data, including the time to event data such as survival, appeared to be appropriate.

Overall, the authors’ conclusions appeared to reflect the evidence available, but the paucity of trials and the risk of missing data should be considered when interpreting the review conclusions.

Implications of the review for practice and research
Practice: The authors stated that in sorafenib may be a new effective therapy for the treatment of advanced hepatocellular carcinoma.

Research: The authors did not state any implications for research.

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