Adjuvant therapy options following curative treatment of hepatocellular carcinoma: a systematic review of randomized trials
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CRD summary
This review found that adjuvant interferon was definitely associated with increased overall survival after curative treatment of hepatocellular carcinoma, and that acyclic retinoid, intra-artery iodine-131-labelled lipiodol and autologous tumour vaccination may also improve overall survival. Due to poor trial quality, questionable methods used for quality grading and differences between included trials, the authors' conclusions require cautious interpretation.

Authors' objectives
To assess the efficacy and safety of adjuvant therapies after curative treatment of hepatocellular carcinoma.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched with no language restrictions up to July 2011. Search terms were reported. Reference lists of relevant articles were checked.

Study selection
Eligible studies were randomised controlled trials (RCTs) of adjuvant or chemo-preventative therapy for hepatocellular carcinoma after curative treatment (by resection or local ablation) versus curative treatment alone. Participants were required to have clear histological margins or no residual tumour on computed tomography (CT) one month after treatment. Review outcomes were overall survival, disease-free survival, recurrence (primary outcomes) and adverse events attributable to the intervention (secondary outcome). Trials of metastatic disease were excluded.

Most of the included trials were set in Japan or China. Child-Pugh classification varied widely, where reported. The proportion of participants with cirrhosis of the liver ranged from 48% to 100%; participants who were hepatitis B surface antigen-positive, anti-hepatitis C virus-positive or had vascular invasion varied across trials (from 0 to 100%, where reported). The interventions assessed were interferon, vitamin K2, acyclic retinoid, transarterial chemoembolisation, transarterial and systemic chemotherapy (separately or combined), intra-artery iodine-131-labelled lipiodol, adoptive immunotherapy, autologous tumour vaccination, and heparanase inhibitor PI-88.

Two reviewers independently selected the studies, with discrepancies arbitrated by a third.

Assessment of study quality
Trial quality was assessed for sequence generation, allocation concealment, blinding and use of intention-to-treat analysis. Trials were ranked as high quality if they reported sequence generation in detail and used allocation concealment or performed intention-to-treat analysis. Trial were ranked as moderate quality if they fulfilled the first or second of these criteria. Low quality trials did not fulfil the first and second criteria.

Two reviewers independently assessed study quality, with discrepancies resolved by consensus.

Data extraction
Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated. Due to variability across the trials in reported follow-up times, a single time-point for reporting was selected by the reviewers for some comparisons.

Two reviewers independently extracted the data, with discrepancies resolved by consensus.

Methods of synthesis
For some comparisons, trials were statistically combined to calculate pooled risk ratios and 95% confidence intervals. Heterogeneity was assessed using $X^2$ and $I^2$. Where there was heterogeneity or sample size was limited, data were combined in a narrative synthesis.

Publication bias was assessed by means of a funnel plot.
**Results of the review**

Twenty-eight RCTs were included in the review (2,989 patients, range 20 to 548). Twenty trials were ranked as high quality, four as moderate quality and four as low quality; 22 trials were rated as acceptable for sequence generation, 14 for allocation concealment, five for blinding of participants, five for blinding of outcome assessment and 16 for conducting intention-to-treat analysis. Duration of follow-up ranged from 48 weeks to 150 months (where stated).

At two years, interferon significantly reduced the risk of recurrence (RR 0.84, 95% CI 0.73 to 0.97; eight RCTs; $I^2=9\%$) and improved overall survival (RR 1.15, 95% CI 1.07 to 1.22; seven RCTs; $I^2=46\%$). There was significant heterogeneity for the analysis of overall survival. No evidence of publication bias was detected.

At one year, vitamin K2 did not significantly reduce the risk of recurrence (RR 0.60, 95% CI 0.28 to 1.27; five RCTs; $I^2=74\%$), but it significantly improved overall survival (RR 1.03, 95% CI 1.00 to 1.05; five RCTs; $I^2=0\%$). There was significant heterogeneity for the analysis of recurrence. No evidence of publication bias was detected.

For other comparisons, data were not pooled. Both disease-free and overall survival were significantly higher ($p<0.05$) in the intervention group in studies of acyclic retinoid, intra-artery iodine-131-labelled lipiodol and autologous tumour vaccination (one RCT each; 39 to 89 patients). Tumour recurrence was significantly reduced in the intervention group in trials of transarterial chemotherapy with or without embolisation ($p<0.05$; four RCTs) and adoptive immunotherapy ($p<0.05$; three RCTs). Tumour recurrence was non-significantly reduced with heparanase inhibitor PI-88 ($p<0.07$; one RCT). Findings for systemic chemotherapy were inconsistent.

Interferon was associated with a range of adverse events, which required discontinuation of therapy in 11% of patients; the dose had to be reduced in most of those who received continuous interferon. Other commonly-reported adverse events included nausea, neuropathy and liver dysfunction associated with chemotherapy, and fever associated with immunotherapy. Other adverse events were described in the review.

**Authors’ conclusions**

Adjuvant interferon was definitely associated with increased overall survival after curative treatment of hepatocellular carcinoma. Acyclic retinoid, intra-artery iodine-131-labelled lipiodol and autologous tumour vaccination may also improve overall survival.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies with no limitation by language. It was unclear whether specific efforts were made to retrieve unpublished studies; if not, the review may be subject to publication bias, although there was no evidence of such bias on formal testing. The processes of study selection, quality assessment and data extraction were undertaken in duplicate to minimise error and bias.

The grading system used for quality assessment was of questionable value, as trial quality was rated as high even in the large number of trials without evidence of adequate randomisation and/or allocation concealment. As the authors noted, drop-outs exceeded 15% in some trials, adherence to protocol was very low, and only half the trials used intention-to-treat analysis. In view of these factors, along with the low sample size of most of the trials, overall trial quality appeared poor. The authors used either fixed-effect or random-effects models in their analyses, without a rationale of when and why a particular model was used. There was marked methodological and clinical heterogeneity between the trials, and a potential for selection bias in the choice by reviewers of specific time-points for assessing survival rates. When statistically significant heterogeneity was detected, the possible explanations were not explored.

In light of the questionable methods used for quality grading of and differences between the included trials, the authors’ conclusions require cautious interpretation.

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

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

**Research**: The authors stated that more research was needed on the effectiveness of combinations of treatments given after curative treatment of hepatocellular carcinoma.

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