Octreotide therapy for hepatocellular carcinoma: a systematic review of the evidence from randomized controlled trials
Jia WD, Zhang CH, Xu GL, Ge YS, Wang W

CRD summary
The evidence did not demonstrate a clear benefit for treatment of advanced hepatocellular carcinoma with octreotide. Further well-conducted research is needed. Given the limited evidence available, the authors' recommendation to interpret the findings with caution should be borne in mind, and their recommendation for further research seems appropriate.

Authors' objectives
To assess the effectiveness of octreotide therapy in the treatment of patients with advanced hepatocellular carcinoma.

Searching
PubMed was searched up to January 2009. Search terms were reported. Reference lists were manually searched.

Study selection
Randomised controlled trials (RCTs) that compared the effects of short-acting or long-acting octreotide monotherapy versus placebo or no treatment in patients with primary hepatocellular carcinoma at any stage of the disease were eligible for inclusion. Trials of patients who had previously received anti-tumour treatment for hepatocellular carcinoma, trial that used octreotide therapy for other reasons, and trials that compared octreotide therapy with some other form of systemic therapy were excluded.

The primary outcome of interest was mortality. Secondary outcomes included tumour response, quality of life and adverse events.

Included trials were conducted in Greece, Hong Kong, Germany and Switzerland. The mean age of participants ranged from 54.8 to 69.5 years; most were male. Octreotide regimens varied across the trials. One three-armed trial included somatostatin receptor-negative patients. Patient characteristics varied, with hepatocellular carcinoma reported to be hepatitis C virus related, hepatitis B virus related, or attributed to alcohol. Tumour size ranged between 7.4 and 8.0cm (where reported). Small proportions of patients reported distant of lung metastasis, and from 44 to 60% of patients reported portal vein thrombosis (where reported).

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Two reviewers independently assessed trial quality using the Jadad scale, including criteria on randomisation, blinding, withdrawals and drop-outs. Trials received a score between zero and 5 points, with trials scoring 3 or more considered high quality. Disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the number of patients surviving and number of tumour responses. Data were entered into a 2x2 contingency table. Where the percentages of survival events were not reported, they were estimated from survival curves. Data on mean and overall survival time (minutes) were also extracted. Primary authors were contacted for further information, where necessary. Disagreements were resolved through discussion and consensus.

Methods of synthesis
Meta-analysis was intended, but given the significant clinical heterogeneity among trials, this was not appropriate and data were presented as a narrative synthesis.

Results of the review
Four RCTs (n=373 patients, range 58 to 126) were included in the review. Quality scores ranged from 2 to 5; three RCTs were high quality and one was low quality. Mean follow-up ranged from 1.93 to 32.5 months (where reported). However, survival was only assessed up to 12 months.

Findings were mixed for survival; two RCTs reported improved survival in hepatocellular carcinoma patients with octreotide treatment; two RCTs reported no beneficial effect. Only one of four RCTs reported beneficial effects on tumour size in patients treated with octreotide. Findings were also mixed for quality of life; two RCTs reported improvements; two RCTs reported no difference compared with placebo. Of the three high quality trials, only one reported a beneficial effect on survival and quality of life.

Few serious adverse effects were reported; most patients tolerated octreotide therapy.

**Authors' conclusions**
The evidence did not demonstrate a clear benefit with octreotide therapy for the treatment of advanced hepatocellular carcinoma. Further well-conducted research is needed.

**CRD commentary**
The review question and supporting inclusion criteria were clearly stated. The literature search was limited; the authors acknowledged the potential for publication bias. The authors conducted data extraction and quality assessment in duplicate, but it was unclear whether this was true for study selection, so reviewer error and bias could not be ruled out.

Trial quality was assessed using appropriate criteria. The authors acknowledged the heterogeneity among trials, so a narrative synthesis was appropriate. However, the data on survival was somewhat limited and hazard ratios would have been more informative, although this may have been a limitation of the included trials. The authors also acknowledged the small evidence base and suggested that the findings should be interpreted with caution. Follow-up duration for survival was short-term.

Given the limited evidence available, the authors' recommendation to interpret the findings with caution should be borne in mind, and their recommendation for further research seems appropriate.

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

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

**Research:** The authors stated that larger well-designed multicentre randomised clinical trials, with clearly defined study population characteristics, are needed to evaluate the effectiveness of octreotide in the treatment of hepatocellular carcinoma. Further research is also needed to investigate the mechanisms of sensitivity and resistance to octreotide.

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