Octreotide for advanced hepatocellular carcinoma:
a meta-analysis of randomized controlled trials

Tian-Kang Guo · Xiang-Yong Hao · Bin Ma · Ke-Hu Yang · Yi-Ping Li · Hong-Ling Li · Yuan-Hui Gu · Hui Cai · Ya-Li Liu · Yuan Li · Wei-Peng Zhan

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Abstract

Purpose To evaluate the effectiveness of octreotide in advanced hepatocellular carcinoma participants on the basis of randomized controlled trials.

Methods We searched the Cochrane Center Register of Controlled Trials in The Cochrane Library, PubMed, EMBASE, Chinese Biomedical Literature Database, China Journal Full-text Database, Chinese Scientific Journals Database up to June 2008 in any language. Randomized controlled trials of octreotide for advanced hepatocellular carcinoma were selected and evaluated by two investigators. Any disagreement was solved by discussion. Analyses were performed using Review Manager 4.2.

Results Six randomized controlled trials totaling 352 participants were included. The median survival time was reported in four randomized controlled trials. The results between the octreotide group and the control group (the placebo or best supportive care group) were as follows: 13.0 versus 4.0 months, 1.93 versus 1.97 months, 4.7 versus 5.3 months, and 7.0 versus 2.5 months. Three randomized controlled trials reported 6-month survival rates and 12-month survival rates and meta-analysis results in these two outcomes [(RR 1.35, 95% CI 0.92–1.97); (RR 1.35, 95% CI 0.66–11.16) respectively] were not found to be statistically significant by random-effects model. When we analyzed 6-month survival rates by fixed-effect model (RR 1.30, 95% CI 1.02–1.66), meta-analysis result reached statistical significance.

Conclusions As for the limitations of the included trials, the result may not demonstrate a significant superiority of octreotide administration in participants with advanced hepatocellular carcinoma from the available evidence.

Keywords Hepatocellular carcinoma · Octreotide · Liver disease · Meta-analysis

Introduction

Hepatocellular carcinoma (HCC) ranks eighth in frequency among malignancies worldwide, representing the third largest cause of cancer-related death, with an estimated mortality rate of almost 600,000 deaths annually (Parkin et al. 2005; Aguayo and Patt 2001). High incidence areas include Eastern Asia, Central Africa, and some countries of Western Africa (Bosch et al. 1999). Most cases are associated with cirrhosis, predominantly due to chronic infections with hepatitis B and hepatitis C viruses, alcohol, aflatoxin or hemochromatosis. Although a screening program increases the chance of receiving more curative treatment (Yuen et al. 2000; McMahon et al. 2000), many participants still present at a relatively late stage with advanced disease.

Liver transplantation and resection are the only potentially curative therapies. Due to advanced or decompensated cirrhosis, comorbidity, and multicentricity of the HCC, lesions in 70–80% of participants are inoperable at the time of diagnosis (Bismuth et al. 1993). A variety of
treatment protocols are used for the treatment of non-resectable HCC, including transcatheter arterial chemoembolization (TACE) (Llovet et al. 2002), percutaneous ethanol injection (PEI) (Livraghi et al. 1992), radiofrequency ablation (RFA) (Livraghi et al. 1999) and chemotherapy (Leung and Johnson 2001; Urabe et al. 1998). Despite the extensive efforts in exploring the treatment of HCC, the prognosis remains dismal. TACE has shown to improve survival only in well-selected HCC patients. From all HCC patients only 10–15% of them can be considered as candidates for this treatment modality (Bruix et al. 2004). Percutaneous ethanol injection is only applicable for tumors less than 3 cm (Yamamoto et al. 2001). The local ablative therapy is not suitable for participants with large HCC or advanced HCC with portal vein thrombosis with or without distant metastasis. Sorafenib is an oral multikinase inhibitor that targets two classes of kinases, which are known to be involved in both tumor proliferation and angiogenesis. These kinases include Raf kinases and the vascular endothelial growth factor (VEGF) receptor. Very recently, sorafenib was approved for advanced hepatocellular cancers due to its overall survival improvement (Zhu 2008).

On the other hand, cirrhosis with portal hypertension predisposes to therapy-related leukopenia and thrombocytopenia. Therefore, the ideal anti-cancer drug for advanced HCC would not require hepatic metabolism, and with minimal or no bone marrow suppression. A potential agent fulfilling this goal is octreotide.

The somatostatin analog octreotide has been demonstrated to be efficacious in the treatment of neuroendocrine tumors, principally by reducing symptomatic hormonal secretion, but also by a direct antineoplastic effect (Lamberts et al. 1996; Shojamanesh et al. 2002). These results lead to a wider application of octreotide in the treatment of other solid malignancies including advanced HCC (Scarpignato and Pelosini 2001; Hejna et al. 2002). The molecular mechanisms involved in the antineoplastic activity of somatostatin relate to direct and indirect growth inhibitory effects mediated by specific somatostatin receptors expressed on target tissues (Lamberts et al. 1996; Froidevaux and Eberle 2002). Verhoef et al. (2008) have recently reported a detection rate of 67% for the somatostatin receptor subtype 2 (SST 2) in human HCC tissues. Ligation of somatostatin receptors may directly inhibit entry into the cell cycle reducing cell proliferation or induce cell death by apoptosis (Froidevaux and Eberle 2002). Indirect antineoplastic effects include reduced or inhibited secretion of growth promoting hormones and growth factors, or the inhibition of angiogenesis (Froidevaux and Eberle 2002; Lamberts et al. 2002). Approximately 40% of advanced HCC express somatostatin receptors (Reubi et al. 1999), and in vitro data suggest a direct antitumor effect of octreotide in advanced HCC (Papalampros et al. 2002). Taken together with the superior safety profile of octreotide and its favorable results in reducing portal hypertension (Burroughs and Panagou 1995), there exists a good rationale for the evaluation of octreotide in advanced HCC therapy. Indeed, there are now numerous reports exploring octreotide or somatostatin analogs for therapy in cases of advanced HCC.

Nonetheless, this therapy remains controversial (Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Yuen et al. 2002; Dimitroulopoulos et al. 2007; Becker et al. 2007; Ou et al. 2007) and data from the clinical setting of octreotide for advanced hepatocellular carcinoma have been scanty to date. It is therefore necessary to carry out a meta-analysis to evaluate the effectiveness of octreotide in advanced hepatocellular carcinoma participants on the basis of randomized controlled trials in order to provide a more comprehensive understanding of the available data rather than just considering randomized trials.

Methods

Study selection

We identified randomized controlled trials comparing the octreotide group with the control group (the placebo or best supportive care group) for participants with advanced hepatocellular carcinoma from the Cochrane Center Register of Controlled Trials in The Cochrane Library (2008 issue 2), PubMed (1966 to June 2008), EMBASE (1974 to June 2008), Chinese biomedicine literature database (1978 to June 2008), China Journal Full-text Database (1994 to June 2008), and Chinese Scientific Journals Database (1989 to June 2008). The following medical subject headings and/or key words and/or text words were used: “octreotide,” “sandostatin,” “hepatocellular carcinoma,” “hepatocarcinoma,” “hepatoma,” “HCC,” “hepatic tumor,” “liver tumor,” “hepatic cancer,” “liver cancer,” and the results were then combined with the Cochrane highly sensitive search strategies for identifying randomized trials. Trials were included regardless of blinding, publication status (full publication or abstract), and language. If there was any doubt whether the trials share the same participants, completely or partially (by identifying common authors and centers), the authors of the trials were contacted to clarify whether the trial has been duplicated. We resolved any differences in opinion through discussion.

Data extraction

Two investigators independently performed the search, reviewed and extracted the following data from each study.
according to pre-specified protocol: first author, year of publication, inclusion and exclusion criteria, study population characteristics, study design, the number of participants lost to follow-up, the data of the primary outcomes and the secondary outcomes. Then these two investigators evaluated study quality, followed the instructions given in the Cochrane Handbook for Systematic Reviews of Intervention. Any unclear or missing information was sought by contacting the authors of the individual trials. Disagreement was solved by discussion.

Inclusion criteria

1. The inclusion criteria for this analysis were randomized controlled trials that compared the octreotide group to the control group (the placebo or best supportive care group) for participants with advanced hepatocellular carcinoma.

2. The preoperative diagnosis of untreated and inoperable HCC participants was based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver (Bruix et al. 2001). HCC was diagnosed by at least two radiologic images showing characteristic features of HCC, or one radiologic image showing characteristic features of HCC associated with AFP >400, or histologically proven HCC.

Types of intervention

Octreotide at any dose and for any duration used alone versus placebo or best supportive care.

Types of outcome measures

a) The primary outcomes include: (1) The median survival time, (2) 6-month survival rates, and (3) 12-month survival rates.

b) The secondary outcomes include: (1) Alpha fetoprotein levels, (2) Quality of life, and (3) side effects.

Statistical analysis

The meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines (Moher et al. 2000). For dichotomous variables, we calculated the risk ratio (RR) with 95% confidence interval. For continuous variables, we calculated the weighted mean difference (WMD) with 95% confidence interval. We used the random-effects model and the fixed-effect model. In case of discrepancy between the two models (e.g., one giving a significant intervention effect, the other no significant intervention effect) we reported both results, otherwise we reported only the results from the fixed-effect model. We used the $\chi^2$ statistic to assess heterogeneity between trials and the $I^2$ statistic to assess the extent of inconsistency. If substantial heterogeneity was found in the included studies, the result was reported from the random-effects model. A $P$ value of 0.05 was used as the cut-off value to determine statistical significance. The meta-analyses were carried out by using Review Manager 4.2 provided by The Cochrane Collaboration. If the data were not available for meta-analysis or if meta-analysis was considered inappropriate in the included studies, some outcomes were presented in a descriptive way.

Results

Using the predefined search strategy, the electronic searches yielded 253 records from PubMed, 172 records from EMBASE, 40 records from the Cochrane Central Register of Controlled Trials, 8 records from Chinese Biomedicine Literature Database, 38 records from China Journal Full-text Database, 16 records from Chinese Scientific Journals Database. In the end, six randomized controlled trials [one study (Farooqi and Farooqi 2000) of them was an abstract] totaling 352 participants were identified and constituted the basis for this analysis (Fig. 1). The characteristics and quality of included studies are respectively shown in Tables 1 and 2. The two groups were comparable.

Of the 352 participants enrolled, 177 were allocated to the octreotide group, and 175 were allocated to the control group (the placebo or best supportive care group). The results between two groups are as follows:

The median survival time was reported in four randomized controlled trials (Kouroumalis et al. 1998; Yuen et al. 2002; Becker et al. 2007; Ou et al. 2007). The results between the octreotide group and the control group (the placebo or best supportive care group) were as follows: 13.0 versus 4.0 months, 1.93 versus 1.97 months, 4.7 versus 5.3 months, and 7.0 versus 2.5 months. The two studies, namely, (Yuen et al. 2002; Becker et al. 2007) (1.93 vs. 1.97 months and 4.7 vs. 5.3 months) reported that the difference between these two groups was not found to be statistically significant. One study (Ou et al. 2007) (7.0 vs. 2.5 months) reported that the result reached statistical significance ($P < 0.05$). Another study (Kouroumalis et al. 1998) (13.0 vs. 4.0 months) also reported that the result reached statistical significance ($P = 0.002$).

Six-month survival rates were based on three studies (Kouroumalis et al. 1998; Dimitroulopoulos et al. 2007; Becker et al. 2007). The test for homogeneity showed that the results were consistent across trials ($P = 0.09, I^2 = 58.8\%$). When we incorporated the data into a fixed-effect model and
compared with the control group (the placebo or best supportive care group), octreotide group is associated with longer survival rates. The pooled RR was 1.30 with a 95% confidence interval of 1.02–1.66. This result reached statistical significance \( P = 0.03 \) (Fig. 2). When we incorporated the data into a random-effects model and compared with the control group (the placebo or best supportive care group), octreotide group is associated with similar survival rates. The pooled RR was 1.35 with a 95% confidence interval of 0.92–1.97. The difference between these two groups was not found to be statistically significant \( P = 0.12 \) (Fig. 3).

Twelve-month survival rates were based on three studies (Kouroumalis et al. 1998; Dimitroulopoulos et al. 2007; Becker et al. 2007). The test for homogeneity showed that results were inconsistent across trials \( (P = 0.005, I^2 = 80.9\%) \). As the significant heterogeneity in the included studies, we incorporated the data into a random-
effects model and the pooled RR was 2.72 with a 95% confidence interval of 0.66 to 11.16. The difference between these two groups was not found to be statistically significant ($P = 0.16$) (Fig. 4).

Alpha fetoprotein level was reported in four studies (Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Yuen et al. 2002; Ou et al. 2007) and because of the different report method in the included studies, the data were not available for meta-analysis and we carried out a descriptive analysis. The result showed that three studies (Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Ou et al. 2007) reported a reduction in AFP concentrations after octreotide treatment, and one study (Yuen et al. 2002) showed that there was no significant difference in the reduction of AFP concentrations between the octreotide-treated group and the control group (the placebo or best supportive care group). The quality of life was reported in five studies (Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Dimitroulopoulos et al. 2007; Becker et al. 2007; Ou et al. 2007) but not quantitatively compared. Four studies

<table>
<thead>
<tr>
<th>Study</th>
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<th>Blinding</th>
<th>Median follow-up months octreotide/control group</th>
<th>Follow-up months (range) octreotide/control group</th>
<th>Loss of follow-up</th>
<th>Number of dropout octreotide/control group</th>
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<tr>
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<td>Not described</td>
<td>Not used</td>
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<td>No</td>
<td>Not described</td>
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<tr>
<td>Yuen et al.</td>
<td>Adequate</td>
<td>Unclear</td>
<td>Not used</td>
<td>1.93/1.97</td>
<td>0.53–15.6/0.37–10.6</td>
<td>No</td>
<td>0/0</td>
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<tr>
<td>Dimitroulopoulos et al.</td>
<td>Adequate</td>
<td>Unclear</td>
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<td>No</td>
<td>7/0</td>
</tr>
<tr>
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<td>No</td>
<td>1 in octreotide group</td>
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<tr>
<td>OU et al.</td>
<td>Adequate</td>
<td>Unclear</td>
<td>Not specified</td>
<td>Not specified</td>
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Fig. 2 Meta-analysis of included studies analyzing 6-month survival rates of the octreotide group versus the control group (the placebo or best supportive care group) for participants with advanced hepatocellular carcinoma (fixed-effect model)

Fig. 3 Meta-analysis of included studies analyzing 6-month survival rates of the octreotide group versus the control group (the placebo or best supportive care group) for participants with advanced hepatocellular carcinoma (random-effects model)
(Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Dimitroulopoulos et al. 2007; Ou et al. 2007) reported remarkable improvement in it, and one study (Becker et al. 2007) showed that there was no significant difference between the two groups. Side effects were reported in five studies (Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Yuen et al. 2002; Becker et al. 2007; Ou et al. 2007) but not quantitatively compared. However, these studies showed that octreotide was well tolerated by most participants.

**Discussion**

The objective of our meta-analysis was to assess the effectiveness of octreotide in advanced hepatocellular carcinoma participants on the basis of randomized controlled trials. Meta-analysis results in 6-month survival rates and 12-month survival rates between the octreotide group and the control group (the placebo or best supportive care group) were not found to be statistically significant by random-effects model. When we analyzed 6-month survival rates by fixed-effect model, meta-analysis result reached statistical significance and compared with the control group (the placebo or best supportive care group); the RR of 1.30 denotes that octreotide for advanced hepatocellular carcinoma increased 6-month survival rates by 30%.

Of these included randomized controlled trials (Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Yuen et al. 2002; Dimitroulopoulos et al. 2007; Becker et al. 2007; Ou et al. 2007), only the Becker et al., study (Becker et al. 2007) investigated the efficacy of octreotide in a placebo-controlled double-blind design. In the other included studies (Kouroumalis et al. 1998; Farooqi and Farooqi 2000; Yuen et al. 2002; Dimitroulopoulos et al. 2007; Ou et al. 2007), the control group did not receive a placebo, and there was no blinding of participants or care providers. In addition, none of the included studies mentioned allocated concealment, as well as the small number of participants in the included studies. Therefore, as the limitations of the included trials, the evidence was insufficient to afford us a reliable conclusion. Although 6-month survival rates in meta-analysis result reached statistical significance by fixed-effect model and there was a reduction in AFP concentrations after octreotide treatment, and octreotide was tolerated by most participants in the included studies, the result may not demonstrate the significant superiority of octreotide administration in participants with advanced hepatocellular carcinoma from the available evidence. Our results are supported by previous reports (Yuen et al. 2002; Becker et al. 2007; Jenkins et al. 2001; Slijkhuis et al. 2005).

On the other hand, there were some important differences between the included studies and they may explain the obvious inconsistency of the results. Compared with the other included studies, the study by Becker et al. (2007) had a lower proportion of HCC participants with advanced tumor stage and the lower proportion of participants with distant metastasis and portal vein infiltration or thrombosis. Also, approximately 90% of participants in Becker et al., study (Becker et al. 2007) had a compensated liver function, which is a strong predictor of survival. Moreover, the difference in the outcome between different studies may be due to the difference in the causative agents for HCC. In the study of Becker et al. (2007), approximately 50% of chronic liver disease was due to alcohol; in the study of Kouroumalis et al. (1998), 50% of participants had chronic HCV infection; in the study of (Dimitroulopoulos et al. 2007), about 60% of participants had chronic HCV infection, and in the study of Yuen et al. (2002), more than 80% of participants had chronic HBV infection. In addition, the study by Becker et al. (2007) showed no objective tumor regression on ultrasonographic examination or serum alpha-fetoprotein reduction in participants treated with octreotide.

The study by Yuen et al. (2002) is characterized by a high proportion of participants with advanced HCC (CLIP score >4.54% in the octreotide group and 66% in the control group). In any case, such participants are moribund and no treatment may be effective. This is exemplified by the fact that 21 out of 35 treated participants in the study of Yuen et al. (2002) received either none or only one injection of long-acting octreotide. Therefore, participants
with such a short expected survival like those reported by Yuen et al. (2002) should not be suitable for the detection of any benefit by octreotide treatment. Besides, the poor survival of 1.9 months in their participants was probably related to the fact that 48–60% and 14–20% of their participants had portal vein thrombosis and distant metastases, respectively. These two parameters are not included for grading in the Okuda staging system. Therefore, their participants had advanced stage of hepatocellular carcinoma (HCC) despite the fact that nearly 80% of their participants were in Okuda stage I or II.

A major drawback of the studies of Kouroumalis, Ou, and Dimitroulopoulos et al., is that they did not address important characteristics of participants including Cancer of the Liver Italian Program (CLIP) score, portal vein thrombosis, or presence or absence of extrahepatic disease. Therefore, an imbalance between the treatment arms cannot be excluded. In the study by Kouroumalis et al. (1998), a survival benefit from octreotide treatment could be demonstrated only after at least 6 months of treatment. The participants in the study of Ou et al. (2007) were all in Okuda stage III and there were no distant metastases.

All meta-analysis are subject to potential bias because of systematic and random errors. The conclusion from this meta-analysis of randomized controlled trials may have several limitations as follows: not all the relevant studies were identified from computerized searching and communication with the authors of clinical trials was unsuccessful. The number of the included studies and participants was relatively small and the methodological quality of the included studies was moderate. Moreover, because of the differences in the study population regarding etiology, liver function, and tumor stage, it is difficult to compare the different studies with respect to survival.

Therefore, in future research, more adequate randomization should be carried out such as stratified randomization that could ensure balance between intervention groups. Blinding is really important for assessment of subjective outcomes, such as quality of life and side effects. Effective blinding can also ensure that the compared groups receive a similar amount of attention, ancillary treatment and diagnostic investigations. In addition, not only the participants and investigators but also the outcome assessors and data analysts (e.g. statisticians) should be strictly blind. Future research should also clearly spell out how to implement allocation concealment and it might prevent selective bias in the trials.

Besides, the selection of participants in any study of HCC treatment is critical. It was suggested that participants of Barcelona Clinic Liver Cancer (BCLC) stage D should be excluded. In addition, whether there are any added beneficial effects by combining somatostatin analogs with other established cytotoxic agents or local therapies (e.g., radiofrequency thermal ablation or percutaneous ethanol injection) in participants with early stages of HCC would require further investigation. In addition, it will be interesting to explore in the future, whether short-acting octreotide has any pharmacological advantages over long-acting octreotide in treating HCC and determine whether a relationship exists between the presence of somatostatin receptors and clinical outcomes in future research. The question of cost assessment and a sample size calculation for participants should be taken into account in future research. Uniform diagnosis of all relevant outcome measures should be carried out, and all the outcomes should be reported in line with the Consolidated Standards of Reporting Trials statement.

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Conflict of interest statement The authors declare that they have no competing interests.

References


