Peri-operative use of sorafenib in liver transplantation: A time-to-event meta-analysis

Hao-Long Qi, Bing-Jie Zhuang, Chang-Sheng Li, Quan-Yan Liu

Hao-Long Qi, Bing-Jie Zhuang, Chang-Sheng Li, Quan-Yan Liu, Department of General Surgery, Research Center of Digestive Diseases, Zhongnan Hospital, Wuhan University, Wuhan 430071, Hubei Province, China

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Correspondence to: Quan-Yan Liu, Professor, Department of General Surgery, Research Center of Digestive Diseases, Zhongnan Hospital, Wuhan University, No. 299 Ba Yi Road, Wuhan 430071, Hubei Province, China. 1459195529@qq.com

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Abstract

AIM: To evaluate whether the application of sorafenib during the peri-operative period of liver transplantation improves prognosis in liver cancer patients.

METHODS: We searched PubMed, EMBASE and MEDLINE for eligible articles. A total of 4 studies were found that fulfilled the previously agreed-upon standards. We then performed a systematic review and meta-analysis on the enrolled trials that met the inclusion criteria.

RESULTS: Out of the 104 studies identified in the database, 82 were not clinical experiments, and 18 did not fit the inclusion standards. Among the remaining 4 articles, only 1 was related to the preoperative use of sorafenib, whereas the other 3 were related to its postoperative use. As the heterogeneity among the 4 studies was high, with an $I^2$ of 86%, a randomized effect model was applied to pool the data. The application of sorafenib before liver transplantation had a hazard ratio (HR) of 3.29 with a 95% confidence interval (CI) of 0.33-32.56. The use of sorafenib after liver transplantation had an HR of 1.44 (95%CI: 0.27-7.71). The overall pooled HR was 1.68 (95%CI: 0.41-6.91).

CONCLUSION: The results showed that the use of sorafenib during the peri-operative period of liver transplantation did not improve patient survival significantly. In fact, sorafenib could even lead to a worse prognosis, as its use may increase the hazard of poor survival.

Key words: Liver transplantation; Sorafenib; Peri-operative period; Kaplan-Meier curve; Hazard ratio

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Core tip: The data were extracted from the Kaplan-Meier curves of every study identified and then input into a hazard ratio calculation spreadsheet. The HRs generated from the sheet were combined with RevMan5.0. To the best of our knowledge, this is the first meta-analysis assessing the use of sorafenib in the peri-operative period of liver transplantation.
INTRODUCTION

Liver cancer is the sixth most common cancer in the world and represents the third most common cause of cancer-related death\[^1\]. Surgical resection and liver transplantation have been considered the most potentially curative treatments up to now. For patients with a solitary lesion < 5 cm or three nodules < 3 cm that are not suitable for resection [III, A], liver transplantation is the ultimate best choice. However, sufficient improvements in 5-year disease-free and overall survival rates for patients receiving transplantations have not been obtained, as the post-transplantation recurrence rate of carcinoma is as high as 66.7\%\[^2\]. As a result, there is an urgent need for an effective method to decrease the post-transplantation recurrence rate.

Sorafenib is a multi-kinase inhibitor that is able to block the Raf/mitogen-activated protein kinase extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway\[^3\]. Due to the involvement of this pathway in tumorigenesis, including liver carcinogenesis, sorafenib could be used to restrain the proliferation and survival of tumor cells. Consequently, sorafenib has been introduced for the treatment of liver cancer.

Up to now, there have been several clinical experiments focusing on the peri-operative utility of sorafenib in liver transplantation, rating its validity as an adjuvant therapy for cancer patients. However, sufficiently large multi-center studies to provide an overall evaluation of sorafenib in the peri-operative period of liver transplantation are still lacking. The present meta-analysis was intended to combine all of the relevant studies to assess the curative effect of sorafenib as an adjuvant therapy.

MATERIALS AND METHODS

Literature search

Articles were identified by an electronic search of PubMed, EMBASE, and MEDLINE using the keywords “liver transplantation” and “sorafenib”, and the personal bibliographies of two of the authors were also included. The bibliographies reported in any of the studies identified were used for further trial identification.

The articles are limited to published trials with at least an abstract given in English. No contact was made with the authors to obtain unpublished data.

Selection of trials

A total of 104 articles was obtained, spanning No-
did not directly provide the HRs and corresponding 95%CIs, although the survival curves were available. Using widely proven, accepted scientific methods[8,9], the data were extracted from the survival curves with Engauge 4.0. Then, the data were input into the HR calculation spreadsheet, which was created by Tierney et al.[10]. Using the methodology stated above, the HRs, standard errors (SEs) and their corresponding 95%CIs were estimated from the curves. The detailed process is shown in Figures 2 and 3.

**Statistical analysis**

HRs and their SEs were analyzed as a whole using Review Manager 5.0, and statistical heterogeneity was defined as \(P < 0.10\) or \(I^2 > 50\%\). As the potential heterogeneity was determined using the standard above, a randomized effect model was used to measure the outcomes.

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**Figure 3** An example depicting the process by which the data extracted from the K-M curves are input into the HR calculation spreadsheet, step by step[10]. Data input screens (A, B and D), generated curves (C and E) and output screen (F) from the calculations spreadsheet.
analysis to examine the use of sorafenib in the peri-operative period of liver transplantation. As a targeted drug, sorafenib was first used to treat renal cell carcinoma. Then, it only took a few years before sorafenib was first applied as a novel adjuvant treatment for hepatocellular carcinoma, especially for patients requiring liver transplantation [11].

Although sorafenib has anti-tumor potentiality in theory, the outcomes of multi-center cohort or case-control trials indicate that sorafenib does not have any apparent effect in improving overall survival. Moreover, sorafenib therapy may lead to a poor prognosis, as it can increase the hazard of poor survival. Considerable side effects have been observed among patients receiving sorafenib [12]. Based on the published literature [13], high grade toxicities were reported in 25%-30% (Yoon et al, 4/13 patients; Pfiffer et al, 2/8 patients) of patients under sorafenib/calcineurin inhibitor (CNI) combination therapy and in 55% (Kim et al, 5/9 patients) in another series using sorafenib in combination with mTORi. From the authors’ perspective, the following reasons may account for the present discouraging conclusion. Sorafenib, as a newly developed targeted drug, has been used for too short a time for true analysis, and its popularization and application have been constricted due to its costs, which are too high for patients. Furthermore, liver transplantation, as the final treatment for liver cancer, is not available for all cancer patients. As a result, the number of participants that could have been included in the experiments is small, and we here may have underestimated the potential of sorafenib.

In conclusion, sorafenib should not be recommended for patients suffering from liver cancer or those waiting for or having received liver transplantation. Unfortunately, only 4 eligible articles were included in the present study; sorafenib has not yet been applied in liver transplantation for a very long period.

### RESULTS

As shown in the forest figure, the HRs, as extracted from the Kaplan-Meier curves using the formula recommended by Parmar, Tierney et al [9,10], were transformed to In[HR] to make the data fulfill a normal distribution (Figure 4).

Among the four studies identified, one was related to sorafenib use before liver transplantation, whereas the other three investigated the use of sorafenib after liver transplantation.

The present meta-analysis showed that the use of sorafenib during liver transplantation did not significantly improve the overall survival. The use of sorafenib before liver transplantation had an HR of 3.29 (95%CI: 0.33-32.56), and the therapy used after liver transplantation had an HR of 1.44 (95%CI: 0.27-7.71). The overall HR was 1.68 (95%CI: 0.41-6.91). Based on the funnel plot, publication bias might have been detected (Figure 5).

### DISCUSSION

To the best of our knowledge, this is the first meta-analysis to examine the use of sorafenib in the peri-operative period of liver transplantation. As a targeted drug, sorafenib was first used to treat renal cell carcinoma. Then, it only took a few years before sorafenib was first applied as a novel adjuvant treatment for hepatocellular carcinoma, especially for patients requiring liver transplantation [11].

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Sorafenib use in liver transplantation

Because of the limited data, we could consider only the overall survival rates and the estimated HRs in our analysis, making the results of this study not very persuasive. However, the present study represents the first effort in this new area, and our work could provide some suggestive evidence.

More cohort trials and, optimally, RCTs are needed to verify our conclusion. Research on sorafenib and any other targeted drugs should be encouraged, as such drugs may have as-yet-underestimated anti-tumor abilities.

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