World Journal of Hepatology

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DOI: 10.4254/wjh.v8.i23.957

World J Hepatol 2016 August 18; 8(23): 957-960
ISSN 1948-5182 (online)

EDITORIAL

Adjuvant sorafenib in hepatocellular carcinoma: A cautionary comment of STORM trial

Jian-Hong Zhong, Xue-Ke Du, Bang-De Xiang, Le-Qun Li

Jian-Hong Zhong, Bang-De Xiang, Le-Qun Li, Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Xue-Ke Du, Department of Anesthesia, Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Author contributions: Zhong JH, Du XK and Xiang BD contributed equally to this work; Zhong JH and Du XK designed the study and wrote the manuscript; Zhong JH, Xiang BD and Li LQ analyzed the data from the included studies; all authors reviewed the manuscript and approved publication.

Supported by Guangxi Science and Technology Development Projects, No. 14124003-4; Guangxi University of Science and Technology Research Projects, No. KY2015LX056; the Self-Raised Scientific Research Fund of the Ministry of Health of Guangxi Province, Nos. Z2015621, Z2015601, GZZC15-34 and Z2014241; and the Innovation Project of Guangxi Graduate Education, No. YCBZ2015030.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Manuscript source: Unsolicited manuscript

Correspondence to: Le-Qun Li, MD, Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, He Di Rd #71, Nanning 530021, Guangxi Zhuang Autonomous Region, China. xitongpingjia@163.com
Telephone: +86-771-5330855
Fax: +86-771-5312000

Received: April 29, 2016
Peer-review started: May 4, 2016
First decision: July 4, 2016
Revised: July 6, 2016
Accepted: July 29, 2016
Article in press: August 1, 2016
Published online: August 18, 2016

Abstract

Recurrence rate of hepatocellular carcinoma (HCC) is very high even after curative surgery, and no postoperative therapies have been definitively shown to prevent HCC recurrence. Sorafenib is proved to be effective for advanced HCC by two large randomized controlled trials in 2008 and 2009. Therefore it stands to reason to expect that adjuvant sorafenib may improve post-surgery outcomes of patients with HCC. However, many questions still exist about the value of sorafenib for patients with HCC after surgery or transarterial chemoembolization. In this editorial, we complehensively reviewed the safety and efficacy of adjuvant sorafenib for patients with hepatocellar carcinoma after surgery or transarterial chemoembolization. We emphasized the positive and negative role of sorafenib.

Key words: Adjuvant; Hepatocellular carcinoma; Tumor recurrence; Sorafenib

Core tip: Sorafenib is effective for advanced hepatocellular carcinoma (HCC). However, its positive role as adjuvant therapy for HCC after surgery or transarterial chemoembolization is controversy.

Zhong JH, Du XK, Xiang BD, Li LQ. Adjuvant sorafenib in hepatocellular carcinoma: A cautionary comment of STORM trial. *World J Hepatol* 2016; 8(23): 957-960 Available from:

URL: http://www.wjgnet.com/1948-5182/full/v8/i23/957.htm
DOI: http://dx.doi.org/10.4254/wjh.v8.i23.957

INTRODUCTION

Large randomized controlled trials have shown transarterial chemoembolization (TACE)[1,2] and sorafenib[3,4] monotherapy to extend median overall survival by approximately 3 mo over best supportive care in patients with hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer (BCLC) stage B or C. Though hepatic resection is the mainstay treatment for HCC, tumor recurrence is very high after surgery[5]. Therefore it stands to reason to expect that sorafenib may improve post-resection outcomes of patients with multinodular HCC or patients at high risk of HCC recurrence.

STUDY ANALYSIS

In the recent issue of the *World J Gastroenterol*, Li *et al*[6] reported a small retrospective study which enrolled 36 male patients with BCLC stage C HCC after hepatic resection. Twelve patients received resection plus sorafenib while other 24 patients received resection alone. The authors found patients in the resection plus sorafenib group had a significantly longer time-to-tumor progression (TTP) and median overall survival compared to patients in the resection alone group.

However, the phase Ⅲ placebo-controlled study STORM trial[7], which included 1602 patients from 28 countries with early-stage HCC following surgical resection or local ablation, found that adjuvant sorafenib did not significantly affect recurrence-free survival, time to recurrence or overall survival. The authors concluded that no evidence of clinical benefit exists for adjuvant sorafenib therapy in such patients.

Also, the phase Ⅱ SPACE trial comparing the efficacy and safety of TACE with or without sorafenib failed to meet its endpoint of prolonging TTP[8]. This raises important questions about the use of adjuvant sorafenib in the clinic.

The SPACE trial[8], which involved 307 Asian and non-Asian patients with multinodular HCC in BCLC stage B, showed that the combination of TACE and sorafenib did not significantly increase TTP or overall survival over TACE alone. This negative result adds to another previous study calling into question the clinical benefits of adjuvant sorafenib. A phase Ⅲ trial involving 458 Asian patients with HCC in stage B or C found that sorafenib did not significantly prolong TTP or overall survival in patients who responded to TACE[9]. In addition to non-efficacy, sorafenib add the incidence of adverse events or may worsen outcomes in certain patients[3,7,10].

REASONS OF NEGATIVE RESULTS

These negative results (Table 1) call for caution in the adjuvant use of sorafenib. Why the results would be negative when our therapeutic aim shifts from control of established tumor cells to the eradication of occult micrometastases? One reason for caution lies in the mechanism of sorafenib, which inhibits tumor angiogenesis. Preclinical studies suggest that anti-angiogenic therapy can, in principle, increase the likelihood of tumor invasion and spread[11], and that tumor angiogenesis can rapidly recover when anti-angiogenic therapy is halted[12]. Another reason for caution is that sorafenib may not be effective against recurrent or metastatic tumors, even if it is effective against primary tumors. The two types of tumors behave differently, and it is possible that recurrent or metastatic tumors are more malignant because they were not eliminated by initial therapy (TACE, resection, ablation). In fact, studies suggest that sorafenib has poor efficacy against intrahepatic metastases (derived from the primary tumor) as well as multicentric tumors arising spontaneously in the residual liver[7].

While previous works strengthens the arguments for re-assessing adjuvant use of sorafenib, some of their results should be interpreted with caution. For example, the findings of Li *et al*[6] were based on a very small retrospective study; Lencioni *et al*[8] reported that the combination of TACE and sorafenib showed greater benefit in Asian patients than in non-Asian ones, yet median TTP was nearly the same (24 mo) in Asian and non-Asian subgroups as well as the total study population[8]. This TTP is substantially longer than the 5.4 mo reported in another phase Ⅲ trial involving only Asian patients[9].

Lack of efficacy with sorafenib has been attributed to insufficient duration of therapy[8], such as because of delays in starting sorafenib after TACE, as well as to insufficient daily sorafenib doses[9]. These explanations seem less likely given that all published phase Ⅱ or Ⅲ multicenter randomized controlled trials concur that adjuvant anti-angiogenic agents, including sorafenib, are associated with negative TTP, overall survival, or recurrence-free survival for solid cancers[7-9,13]. In fact, a large dosing study involving 1943 patients with non-metastatic renal-cell carcinoma supports the notion that disease-free survival does not depend on treatment duration[13].

PERSPECTIVE

The growing evidence for lack of adjuvant sorafenib efficacy against HCC[7-9], and substantial evidence against adjuvant anti-angiogenic therapy against solid cancers in general[13-16], should lead clinicians to re-assess their treatment approaches. In this sense, some ongoing trials of adjuvant anti-angiogenic agents for solid cancers (*e.g.*, NCT00908752, NCT01009801) are already terminated.

Nowadays, more and more trials revealed the definite efficacy of postoperative antiviral treatment with nucleot(s)ide analogs for hepatitis B virus-related HCC[17-19]. Adjuvant adoptive immunotherapy may also improve recurrence-free and overall survival[20]. But more rando-

Table 1 Adjuvant sorafenib for hepatocellular carcinoma

Ref.	Recruited period	Sample size (T/C)	HCC characteristics	First therapy	Adjuvant therapy	Outcomes
Li *et al*[6], 2016	2009-2013	12/24	With portal vein thrombus	Hepatic resection	Sorafenib (200-800 mg/d)	TTP, $P = 0.041$ OS, $P = 0.01$
Bruix *et al*[7], 2015	2008-2010	556/558	Early stage HCC	Hepatic resection or ablation	Sorafenib (400 mg) twice a day	RFS, $P = 0.26$ OS, $P = 0.48$
Lencioni *et al*[8], 2016	-	154/153	Intermediate stage multinodular HCC	TACE with doxorubicin-eluting beads	Sorafenib (400 mg) twice a day	TTP, $P = 0.07$ OS, $P = 0.29$
Kudo *et al*[9], 2011	2006-2009	229/227	Unresectable HCC who responded to TACE	Conventional TACE	Sorafenib (400 mg) twice a day	TTP, $P = 0.25$ OS, $P = 0.79$

C: Control group; HCC: Hepatocellular carcinoma; OS: Overall survival; RFS: Recurrence-free survival; T: Adjuvant treated group; TACE: Transarterial chemoembolization; TTP: Time-to-tumor progression.

mized trials are warranted because of inconsistent findings from new randomized trials[21,22]. For HCC patients with high risk of recurrence, adjuvant TACE has positive effect in terms of improving overall survival[23]. However, each postoperative or adjuvant therapy has its own indication, revealing that not all patients with HCC after surgery should receive specific postoperative or adjuvant therapy. New drugs may help further define therapeutic directions for the future.

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P- Reviewer: Hernanda PY, Takeda H, Tarazov PG
S- Editor: Gong ZM **L- Editor**: A **E- Editor**: Li D

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