**Name of Journal: *World Journal of Hepatology***

**ESPS Manuscript NO: 26921**

**Manuscript Type: Minireviews**

**Adjuvant sorafenib in hepatocellular carcinoma: a cautionary comment of STORM trial**

Zhong JH *et al*. Adjuvant sorafenib in HCC

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

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

**Xue-Ke Du,** Anesthesia Department, 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** the Innovation Project of Guangxi Graduate Education, No. YCBZ2015030.

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

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Le-Qun Li,** **MD,** Hepatobiliary Surgery Department, 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:**

**Published online:**

**Abstract**

Recurrence rate of hepatocellular carcinoma is very high even after curative surgery, and no postoperative therapies have been definitively shown to prevent hepatocellular carcinoma recurrence. Sorafenib is proved to be effective for advanced hepatocellular carcinoma 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 hepatocellular carcinoma. However, many questions still exist about the value of sorafenib for patients with hepatocellular carcinoma 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; Sorafenib; Tumor recurrence

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Sorafenib is effective for advanced hepatocellular carcinoma. However, its positive role as adjuvant therapy for hepatocellular carcinoma 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; In press

**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 months 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 months 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 randomized 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.

**References**

1 **Llovet JM**, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J; [Barcelona Liver Cancer Group](http://www.ncbi.nlm.nih.gov/pubmed/?term=Barcelona%20Liver%20Cancer%20Group%5BCorporate%20Author%5D). Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734-1739 [PMID: 12049862 DOI: 10.1016/S0140-6736(02)08649-X]

2 **Lo CM**, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164-1171 [PMID: 11981766 DOI: 10.1053/jhep.2002.33156]

3 **Bruix J**, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; **57**: 821-829 [PMID: 22727733 DOI: 10.1016/j.jhep.2012.06.014]

4 **Cheng AL**, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, Yang TS, Tak WY, Pan H, Yu S, Xu J, Fang F, Zou J, Lentini G, Voliotis D, Kang YK. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer* 2012; **48**: 1452-1465 [PMID: 22240282 DOI: 10.1016/j.ejca.2011.12.006]

5 **Zhong JH**, Ma L, Li LQ. Postoperative therapy options for hepatocellular carcinoma. *Scand J Gastroenterol* 2014; **49**: 649-661 [PMID: 24716523 DOI: 10.3109/00365521.2014.905626]

6 **Li J**, Hou Y, Cai XB, Liu B. Sorafenib after resection improves the outcome of BCLC stage C hepatocellular carcinoma. *World J Gastroenterol* 2016; **22**: 4034-4040 [PMID: 27099447 DOI: 10.3748/wjg.v22.i15.4034]

7 **Bruix J**, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Bolondi L, Lee KS, Makuuchi M, Souza F, Berre MA, Meinhardt G, Llovet JM; [STORM investigators](http://www.ncbi.nlm.nih.gov/pubmed/?term=STORM%20investigators%5BCorporate%20Author%5D). Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015; **16**: 1344-1354 [PMID: 26361969 DOI: 10.1016/S1470-2045(15)00198-9]

8 **Lencioni R**, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, Paik SW, Reig M, Kim do Y, Chau GY, Luca A, Del Arbol LR, Leberre MA, Niu W, Nicholson K, Meinhardt G, Bruix J. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol* 2016; **64**: 1090-1098 [PMID: 26809111 DOI: 10.1016/j.jhep.2016.01.012]

9 **Kudo M**, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh DJ, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; **47**: 2117-2127 [PMID: 21664811 DOI: 10.1016/j.ejca.2011.05.007]

10 **Zhong JH**. The STORM trial and beyond: narrowing the horizon of adjuvant sorafenib for postoperative hepatocellular carcinoma. *Tumour Biol* 2015; **36**: 8271-8272 [PMID: 26499777 DOI: 10.1007/s13277-015-4279-0]

11 **Pàez-Ribes M**, Allen E, Hudock J, Takeda T, Okuyama H, Viñals F, Inoue M, Bergers G, Hanahan D, Casanovas O. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell* 2009; **15**: 220-231 [PMID: 19249680 DOI: 10.1016/j.ccr.2009.01.027]

12 **Mancuso MR**, Davis R, Norberg SM, O'Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hu-Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. *J Clin Invest* 2006; **116**: 2610-2621 [PMID: 17016557 DOI: 10.1172/JCI24612]

13 **Haas NB**, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, Jewett M, Dutcher JP, Atkins MB, Pins M, Wilding G, Cella D, Wagner L, Matin S, Kuzel TM, Sexton WJ, Wong YN, Choueiri TK, Pili R, Puzanov I, Kohli M, Stadler W, Carducci M, Coomes R, DiPaola RS. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet* 2016; **387**: 2008-2016 [PMID: 26969090 DOI: 10.1016/S0140-6736(16)00559-6]

14 **Kudo M**, Han G, Finn RS, Poon RT, Blanc JF, Yan L, Yang J, Lu L, Tak WY, Yu X, Lee JH, Lin SM, Wu C, Tanwandee T, Shao G, Walters IB, Dela Cruz C, Poulart V, Wang JH. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. *Hepatology* 2014; **60**: 1697-1707 [PMID: 24996197 DOI: 10.1002/hep.27290]

15 **Cameron D**, Brown J, Dent R, Jackisch C, Mackey J, Pivot X, Steger GG, Suter TM, Toi M, Parmar M, Laeufle R, Im YH, Romieu G, Harvey V, Lipatov O, Pienkowski T, Cottu P, Chan A, Im SA, Hall PS, Bubuteishvili-Pacaud L, Henschel V, Deurloo RJ, Pallaud C, Bell R. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. *Lancet Oncol* 2013; **14**: 933-942 [PMID: 23932548 DOI: 10.1016/S1470-2045(13)70335-8]

16 **de Gramont A**, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, Cunningham D, Cartwright TH, Hecht JR, Rivera F, Im SA, Bodoky G, Salazar R, Maindrault-Goebel F, Shacham-Shmueli E, Bajetta E, Makrutzki M, Shang A, André T, Hoff PM. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol* 2012; **13**: 1225-1233 [PMID: 23168362 DOI: 10.1016/S1470-2045(12)70509-0]

17 **Zhong JH**, Ma L, Li LQ. Postoperative Antiviral Therapy With Nucleos(t)ide Analogs in Patients With Hepatitis B Virus-related Hepatocellular Carcinoma. *Ann Surg* 2015; Epub ahead of print [PMID: 25822679 DOI: 10.1097/SLA.0000000000001224]

18 **Huang G**, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F, Zhou WP, Wu MC. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. *Ann Surg* 2015; **261**: 56-66 [PMID: 25072444 DOI: 10.1097/SLA.0000000000000858]

19 **Yin J**, Li N, Han Y, Xue J, Deng Y, Shi J, Guo W, Zhang H, Wang H, Cheng S, Cao G. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. *J Clin Oncol* 2013; **31**: 3647-3655 [PMID: 24002499 DOI: 10.1200/JCO.2012.48.5896]

20 **Zhong JH**, Ma L, Wu LC, Zhao W, Yuan WP, Wu FX, Zhang ZM, Huang S, You XM, Li LQ. Adoptive immunotherapy for postoperative hepatocellular carcinoma: a systematic review. *Int J Clin Pract* 2012; **66**: 21-27 [PMID: 22171902 DOI: 10.1111/j.1742-1241.2011.02814.x]

21 **Xu L**, Wang J, Kim Y, Shuang ZY, Zhang YJ, Lao XM, Li YQ, Chen MS, Pawlik TM, Xia JC, Li SP, Lau WY. A randomized controlled trial on patients with or without adjuvant autologous cytokine-induced killer cells after curative resection for hepatocellular carcinoma. *Oncoimmunology* 2016; **5**: e1083671 [PMID: 27141337 DOI: 10.1080/2162402X.2015.1083671]

22 **Lee JH**, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW, Yoon JH. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. *Gastroenterology* 2015; **148**: 1383-91.e6 [PMID: 25747273 DOI: 10.1053/j.gastro.2015.02.055]

23 **Zhong JH**, Li LQ. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: A meta-analysis. *Hepatol Res* 2010; **40**: 943-953 [PMID: 20887328 DOI: 10.1111/j.1872-034X.2010.00710.x]

**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.