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

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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 comprehensively reviewed the safety and efficacy of adjuvant sorafenib for patients with hepatocellular carcinoma after surgery or transarterial chemoembolization. We emphasized the positive and negative role of sorafenib.

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

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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.

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INTRODUCTION
Large randomized controlled trials have shown transarterial chemoembolization (TACE)\(^{1,2}\) and sorafenib\(^{3,4}\) 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\(^{10}\).

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\(^{13}\).

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\(^{8}\). 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\(^{10-13}\), 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 adjuvant treatment with nucleo(s)ide analogs for hepatitis B virus-related HCC\(^{14-19}\). Adjuvant adoptive immunotherapy may also improve recurrence-free and overall survival\(^{20}\). But more rando-
mized trials are warranted because of inconsistent findings from new randomized trials\cite{21,22}. For HCC patients with high risk of recurrence, adjuvant TACE has positive effect in terms of improving overall survival\cite{33}. 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, Montanà X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Brúix J. Barcelona Liver Cancer Group. 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, Fan ST, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Yamaguchi I, Ohyama K, Teinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. J Cancer 2011; 47: 2117–2127 [PMID: 21664811 DOI: 10.1016/j.jca.2011.05.007]

3. Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, Tori H, Kumada H, Hayashi N, S salesman O, Tsambouchi H, Huh DJ, Furuse J, Oosaka T, Tanaka K, Matsu S, Wada M, Yamaguchi I, Ohyama K, Teinhardt 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.jca.2011.05.007]

4. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Real MI, Montanà X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Brúix J. Barcelona Liver Cancer Group. 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]

5. Brúix J, Raoul JL, Sherman M, Mazzaferrero V, Bolondi L, Craxi A, Galle P, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Guandalini S, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovic M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of phase III trial. J Hepatol 2012; 57: 821–829 [PMID: 22772733 DOI: 10.1016/j.jhep.2012.06.014]

6. 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: randomized controlled trial. Lancet Oncol 2015; 16: 1344–1354 [PMID: 26361969 DOI: 10.1016/S1470-2045(15)00196-9]

7. 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 L, Lebere 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]

8. Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, Tori H, Kumada H, Hayashi N, S salesman O, Tsambouchi H, Huh DJ, Furuse J, Oosaka T, Tanaka K, Matsu S, Wada M, Yamaguchi I, Ohyama K, Teinhardt 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.jca.2011.05.007]

9. Haas NB, Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

10. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

11. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

12. Haas NB, Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

13. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

14. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

15. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

16. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]

17. Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hsu­Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. Cancer Cell 2009; 15: 220–231 [PMID: 19240680 DOI: 10.1016/j.cccr.2009.01.027]
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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, Dong 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 chemomobilization 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]
