Feasibility of combining adjuvant transarterial chemoembolization with nucleos(t)ide analog therapy for patients with HBV-associated hepatocellular carcinoma after hepatectomy (Review)

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Abstract. Hepatocellular carcinoma (HCC) is the third leading cause of cancer-associated mortalities, and its prevalence is expected to increase in future decades. Hepatitis B virus (HBV) infection is the leading cause of HCC. Although hepatectomy is the preferred curative treatment for HCC, tumor recurrence is common, which is the most frequent cause of mortality in patients with HCC. HCC recurrence may originate from the primary tumor or be associated with remnant liver tissue, and include high viral load and hepatic inflammatory activity. Adjuvant transarterial chemoembolization and postoperative nucleos(t)ide analogs therapy are the two corresponding therapies. Following systematic searching of the PubMed database, the indications for adjuvant transarterial chemoembolization and nucleos(t)ide analog therapies for HBV-related HCC after hepatectomy were acquired. Additionally, the feasibility of combining these two therapies were also reviewed.

Contents

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1. Introduction

Hepatocellular carcinoma (HCC), the third leading cause of cancer-associated mortality worldwide, is characterized by poor prognosis and low long-term overall survival (1). Hepatitis B virus (HBV) infection is a well-documented risk factor for hepatocarcinogenesis, and ~90% of patients with HCC in China have chronic HBV infection and concomitant reduced liver function (2,3). Therefore, the prognosis of patients with HBV-associated HCC depends on both tumor status and HBV activity.

Hepatectomy remains the standard curative treatment for HCC, however, postoperative tumor recurrence is notbaly high, with 5 year rates as high as 74% for patients with disease in the intermediate or advanced stages (2). Disease-free survival is similarly low, with 5 year rates of 26% for patients with large/multinodular HCC and 18% for those with macrovascular invasion (3). Tumor recurrence is the most frequent cause of mortality in patients with HCC. Therefore, identifying postoperative therapies that reduce the risk of tumor recurrence is essential.

2. Risk factors of HCC recurrence

HCC recurrence can be classified as early, occurring <2 years after surgery, and late, occurring >2 years after surgery. Early recurrence is predominantly due to intrahepatic metastasis arising from the primary tumor, while late recurrence results primarily from *de novo* (multicentric) metastasis. Risk factors of early recurrence are associated with the HCC itself and include tumor size and number, tumor differentiation, vascular invasion, tumor capsule and resection margin (4,5). By contrast, risk factors of late recurrence are associated with remnant liver tissue and include high viral load and hepatic inflammatory activity (4,5).

These different recurrence mechanisms mean that clinicians must carefully consider each patient's risk factor profile following hepatectomy in order to design a treatment strategy that targets both types of recurrence. Although official HCC treatment guidelines do not definitively recommend adjuvant

or antiviral therapies for patients with HBV-associated HCC following hepatectomy (6,7), increasing evidence supports their clinical use (8-10).

3. Indications for adjuvant transarterial chemoembolization

The goal of adjuvant transarterial chemoembolization (TACE) is to destroy small intrahepatic metastases that may not have been detected during surgery, as well as to eliminate tumor cells that may have been released during surgical manipulation of the liver (11). Adjuvant TACE appears to benefit only patients with HCC at high risk of early recurrence, including patients with multiple nodules, large tumors, vascular invasion, poor tumor differentiation, incomplete or absent tumor capsule, or a resection margin <1 cm. The idea that only high-risk patients benefit from adjuvant TACE is supported by retrospective studies (12,13) and a meta-analysis based on randomized studies (14). This meta-analysis, which included six randomized trials involving 659 patients with HCC at a high risk of recurrence, revealed that adjuvant TACE decreased 1- and 3 year mortality, however, not 5 year mortality rates (14). One retrospective study (15) involving 1,924 patients with HCC following curative hepatectomy found that adjuvant TACE improved overall survival in patients with tumors >5 cm, who also had other risk factors, including 2-3 nodules or microvascular invasion. However, adjuvant TACE actually reduced the overall survival of patients with a single tumor <5 cm without microvascular invasion. This lack of clinical benefit was confirmed in a more recent retrospective study (16) involving 229 patients with HCC lacking factors associated with elevated risk of recurrence or reduced overall survival. Adjuvant TACE did not improve the overall survival or reduce recurrence.

4. Indications for nucleos(t)ide analog (NA) therapy after hepatectomy

Postoperative antiviral therapy with NAs is another therapy commonly used following hepatectomy in patients with HBV-associated HCC (17,18). The goal of postoperative antiviral therapy in HBV-associated HCC is to reduce the viral load of HBV, protect liver function, decrease tumor recurrence, increase overall survival and improve quality of life. The only two randomized trials (19,20) that we identified in literature searches, as well as large cohort studies (18,19,21) examining NA therapy, found that it significantly reduced late HCC recurrence and improved long-term overall survival in patients with HBV-associated HCC following curative hepatectomy. However, the therapy fails to provide obvious clinical benefits for reducing early tumor recurrence or improving short-term overall survival (18-21). This may reflect the fact that the majority of patients in these trials (19,20) were in the early stages of HCC. A longer follow-up of these patients suggested certain clinical benefit. The available evidence, therefore, suggests that postoperative NA therapy affects primarily late recurrence, and it does so by controlling hepatitis activity and reducing chronic inflammation in the remnant liver.

Since numerous patients in advanced stages of HCC exhibit high rates of early recurrence and low long-term overall survival, postoperative NA therapy is likely to be more effective in patients with early-stage HCC following curative

Table I. Previous studies evaluating postoperative antiviral therapy and survival, stratified by tumor stage.

Author	Sample size (T/C)	Liver function (T), A/B	Drug used	Disease-free survival		Overall survival		(Refs.)
				Early stage HCC	Late stage HCC	Early stage HCC	Late stage HCC	
Chan *et al*, 2011	42/94	42/0	Lamivudine (100 mg/d) or entecavir (0.5 mg/d)	P=0.04[a] or 0.04[b]	P=0.84[c] or 0.58[d]	P=0.02[a] or 0.004[b]	P=0.10[c] or 0.97[d]	(22)
Ke *et al*, 2013	141/337	141/0	Lamivudine (100 mg/d)	-	-	BCLC A/B stage: P=0.035	BCLC C stage: P=0.775	(23)
Zhang *et al*, 2014	40/47	33/6	Entecavir (0.5 mg/d)	Tumor size ≤3: P=0.006	Tumor size >3: P=0.209	Tumor size ≤3: P=0.184	Tumor size >3: P=0.246	(24)

[a]American joint committee on cancer stage I and II. [b]Patients without major vascular invasion. [c]American joint committee on cancer stage III. [d]Patients with major vascular invasion. BCLC, barcelona clinical liver cancer; C, control group; T, antiviral group. A/B, no. of patients with Child-Pugh A versus Child-Pugh B liver function.

hepatectomy. Indeed, this indication is supported by subgroup analyses in retrospective studies (22-24), which showed that postoperative NA therapy can significantly improve disease-free and overall survival in patients in relatively early stages of HCC. However, no significant clinical benefit was observed for those in relatively late stages of HCC (Table I).

5. Feasibility of adjuvant TACE combined with NA therapy

These considerations highlight the fact that the indications for adjuvant TACE differ from those for postoperative NA therapy in certain respects. This is important to take into consideration when treating patients with HBV-associated HCC following hepatectomy, particularly since the two therapies are the ones most frequently administered to such patients in HBV-endemic areas (25,26). This raises the question of whether the two therapies can be combined for an improved prognosis. Systematic searches of PubMed, EMBASE, the Cochrane Library revealed two small retrospective studies (27,28) investigating the efficacy of adjuvant TACE combined with antiviral therapy for HBV-associated HCC following hepatectomy. The first retrospective study (27) involved 60 patients, of whom 41 received both therapies and 19 received only TACE. The two groups exhibited similar 1, 2 and 3 year recurrence rates. The other study (28) included 176 patients with Child-Pugh A liver function, of whom 58 received combination therapy and 118 received TACE alone. The two groups exhibited similar disease-free survival (P=0.322), however, the combination group revealed a marginally improved overall survival (P=0.048). However, when analyses were performed with 51 pairs of propensity score-matched patients, the combination group exhibited significantly higher overall survival (P=0.033) and marginally higher disease-free survival (P=0.048). The authors concluded that the combination of adjuvant TACE and NA therapy may prevent HCC recurrence and improve the overall survival following curative hepatectomy (28).

The optimal indications for combined adjuvant TACE and NA therapy remain to be elucidated (29). The two retrospective studies (27,28) mentioned above included patients with advanced-stage HCC, and no subgroup analyses based on tumor stage were performed (27,28). Based on the indications for adjuvant TACE or postoperative NA monotherapy on their own, patients who have HBV-associated, relatively early-stage HCC and who are at high risk of recurrence may be the most suitable candidates for the two therapies combined. Adjuvant TACE is not, however, recommended for patients who have early-stage HBV-associated HCC and who lack risk factors of recurrence (15,16). Combination therapy may also be appropriate for patients with HBV-associated HCC in advanced stages. Although postoperative NA therapy in such patients may not significantly prolong their survival (22-24), it can decrease the rate of HBV reactivation and improve liver function (30,31). Two previous studies suggested that the combination of TACE and NA therapy in such patients can lead to significantly higher overall survival compared with TACE alone (32,33).

Physicians and patients must weigh the pros and cons of treatment options, including associated costs, for managing HBV-associated HCC following hepatectomy. Long-term treatment with NAs will be expensive. Additionally, drug resistance and side effects must also be determined. The most extensive evidence must also be taking into consideration, since future studies may change the picture presented here.

6. Future perspective

Several international guidelines already recommend antiviral therapy for patients with chronic HBV, however, no standardized international guidelines exist regarding postoperative antiviral therapy for patients with HBV-associated HCC following hepatectomy at present. In general, the clinical practice of antiviral therapy in HBV-associated HCC is based on the management of chronic hepatitis B. The primary goal of antiviral therapy with NAs is to continuously suppress virus replication in order to prevent progression of fibrosis and cirrhosis, and thereby reduce the incidence of liver failure and HCC recurrence. Postoperative antiviral therapy with NAs not only improves liver function, but also reduces the incidence of HBV reactivation and long-term tumor recurrence. The net result is an increase in long-term overall survival. While it is possible that patients at any stage of HBV-associated HCC can benefit from postoperative NA therapy, the precise indications and contradictions of this treatment, as well as the optimal drugs and doses, remain to be clarified. Future studies must elucidate how postoperative NA therapy prevents tumor recurrence and improves overall survival.

No international guidelines definitively recommend adjuvant TACE for patients with HCC following hepatectomy, however, evidence is mounting to suggest a clinical benefit to patients at high risk of recurrence. The present review concluded that, on the basis of existing evidence, the most suitable candidates for adjuvant TACE combined with antiviral NA therapy are patients who exhibit HBV-associated HCC and are at a high risk of recurrence.

References

1. Bruix J, Gores GJ and Mazzaferro V: Hepatocellular carcinoma: Clinical frontiers and perspectives. Gut 63: 844-855, 2014.
2. Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, Peng T, Xie GS and Li LQ: Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 260: 329-340, 2014.
3. Zhong JH, Rodriguez AC, Ke Y, Wang YY, Wang L and Li LQ: Hepatic resection as a safe and effective treatment for hepatocellular carcinoma involving a single large tumor, multiple tumors, or macrovascular invasion. Medicine (Baltimore) 94: e396, 2015.
4. Sohn W, Paik YH, Kim JM, Kwon CH, Joh JW, Cho JY, Gwak GY, Choi MS, Lee JH, Koh KC, *et al*: HBV DNA and HBsAg levels as risk predictors of early and late recurrence after curative resection of HBV-related hepatocellular carcinoma. Ann Surg Oncol 21: 2429-2435, 2014.
5. Wu JC, Huang YH, Chau GY, Su CW, Lai CR, Lee PC, Huo TI, Sheen IJ, Lee SD and Lui WY: Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. J Hepatol 51: 890-897, 2009.
6. European Association for Study of Liver; European Organisation for and Research and Treatment of Cancer: EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. Eur J Cancer 48: 599-641, 2012.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers version 2, 2015.
8. Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, Gwak GY, Kim KM, Kim YJ, Lee JW and Yoon JH: Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. Gastroenterology 148: 1383-1391, 2015.

9. Zheng Z, Liang W, Wang D, Schroder PM, Ju W, Wu L, Zheng Z, Shang Y, Guo Z and He X: Adjuvant chemotherapy for patients with primary hepatocellular carcinoma: A meta-analysis. Int J Cancer 136: E751-E759, 2015.
10. Zhong JH, Ma L and Li LQ: Postoperative therapy options for hepatocellular carcinoma. Scand J Gastroenterol 49: 649-661, 2014.
11. Cheng AL, Amarapurkar D, Chao Y, Chen PJ, Geschwind JF, Goh KL, Han KH, Kudo M, Lee HC, Lee RC, *et al*: Re-evaluating transarterial chemoembolization for the treatment of hepatocellular carcinoma: Consensus recommendations and review by an international expert panel. Liver Int 34: 174-183, 2014.
12. Ren ZG, Lin ZY, Xia JL, Ye SL, Ma ZC, Ye QH, Qin LX, Wu ZQ, Fan J and Tang ZY: Postoperative adjuvant arterial chemoembolization improves survival of hepatocellular carcinoma patients with risk factors for residual tumor: A retrospective control study. World J Gastroenterol 10: 2791-2794, 2004.
13. Nonami T, Isshiki K, Katoh H, Kishimoto W, Harada A, Nakao A and Takagi H: The potential role of postoperative hepatic artery chemotherapy in patients with high-risk hepatomas. Ann Surg 213: 222-226, 1991.
14. Zhong JH and Li LQ: Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: A meta-analysis. Hepatol Res 40: 943-953, 2010.
15. Chen X, Zhang B, Yin X, Ren Z, Qiu S and Zhou J: Lipiodolized transarterial chemoembolization in hepatocellular carcinoma patients after curative resection. J Cancer Res Clin Oncol 139: 773-781, 2013.
16. Jiang JH, Guo Z, Lu HF, Wang XB, Yang HJ, Yang FQ, Bao SY, Zhong JH, Li LQ, Yang RR and Xiang BD: Adjuvant transarterial chemoembolization after curative resection of hepatocellular carcinoma: Propensity score analysis. World J Gastroenterol 21: 4627-4634, 2015.
17. Zhong JH, Xiang BD and Li LQ: Letter: Pre- and post-operative anti-viral therapy is important for patients with hepatitis B virus-related hepatocellular carcinoma. Aliment Pharmacol Ther 41: 789-790, 2015.
18. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS and Lin JT: Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 308: 1906-1914, 2012.
19. Yin J, Li N, Han Y, Xue J, Deng Y, Shi J, Guo W, Zhang H, Wang H, Cheng S and 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 31: 3647-3655, 2013.
20. Huang G, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F, Zhou WP and Wu MC: Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: A randomized controlled trial. Ann Surg 261: 56-66, 2015.
21. Su CW, Chiou YW, Tsai YH, Teng RD, Chau GY, Lei HJ, Hung HH, Huo TI and Wu JC: The influence of hepatitis B viral load and pre-s deletion mutations on post-operative recurrence of hepatocellular carcinoma and the tertiary preventive effects by anti-viral therapy. PLoS One 8: e66457, 2013.
22. Chan AC, Chok KS, Yuen WK, Chan SC, Poon RT, Lo CM and Fan ST: Impact of antiviral therapy on the survival of patients after major hepatectomy for hepatitis B virus-related hepatocellular carcinoma. Arch Surg 146: 675-681, 2011.
23. Ke Y, Ma L, You XM, Huang SX, Liang YR, Xiang BD, Li LQ and Zhong JH: Antiviral therapy for hepatitis B virus-related hepatocellular carcinoma after radical hepatectomy. Cancer Biol Med 10: 158-164, 2013.
24. Zhang ZY, Zhou ZQ and Zhou GW: Higher efficacy of antiviral therapy after major hepatectomy in patients with hepatitis B virus-related hepatocellular carcinoma of less than 3 cm. Eur J Gastroenterol Hepatol 26: 1116-1124, 2014.
25. Zhong JH, Zhong QL, Li LQ and Li H: Adjuvant and chemopreventive therapies for resectable hepatocellular carcinoma: A literature review. Tumour Biol 35: 9459-9468, 2014.
26. Yu LH, Li N, Shi J, Guo WX, Wu MC and Cheng SQ: Does anti-HBV therapy benefit the prognosis of HBV-related hepatocellular carcinoma following hepatectomy? Ann Surg Oncol 21: 1010-1015, 2014.
27. Yan Q, Ni J, Zhang GL, Yao X, Yuan WB, Zhou L and Zheng SS: Efficacy of postoperative antiviral combined transcatheter arterial chemoembolization therapy in prevention of hepatitis B-related hepatocellular carcinoma recurrence. Chin Med J (Engl) 126: 855-859, 2013.
28. Zhu SL, Zhong JH, Ke Y, Xiao HM, Ma L, Chen J, You XM and Li LQ: Comparative efficacy of postoperative transarterial chemoembolization with or without antiviral therapy for hepatitis B virus-related hepatocellular carcinoma. Tumour Biol 36: 6277-6284, 2015.
29. Ma SL, Lv Y and Jiang JH: Efficacy of combined adjuvant transarterial chemoembolization and antiviral therapy in patients with HBV-related hepatocellular carcinoma after surgery. Tumour Biol 36: 7395-7396, 2015.
30. Zhong JH: Nucleos(t)ide analogue therapy for HBV-related HCC after hepatic resection: Clinical benefits and unanswered questions. Tumour Biol 35: 12779-12784, 2014.
31. Huang G, Lai EC, Lau WY, Zhou WP, Shen F, Pan ZY, Fu SY and Wu MC: Posthepatectomy HBV reactivation in hepatitis B-related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. Ann Surg 257: 490-505, 2013.
32. Xu X, Huang P, Tian H, Chen Y, Ge N, Tang W, Yang B and Xia J: Role of lamivudine with transarterial chemoembolization in the survival of patients with hepatocellular carcinoma. J Gastroenterol Hepatol 29: 1273-1278, 2014.
33. Toyoda H, Kumada T, Tada T, Sone Y and Fujimori M: Transarterial chemoembolization for hepatitis B virus-associated hepatocellular carcinoma: Improved survival after concomitant treatment with nucleoside analogues. J Vasc Interv Radiol 23: 317-322, 2012.