Tumor Biol. (2014) 35:12779–12784
DOI 10.1007/s13277-014-2881-1

EDITORIAL

Nucleos(t)ide analogue therapy for HBV-related HCC after hepatic resection: clinical benefits and unanswered questions

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Received: 5 November 2014 / Accepted: 19 November 2014 / Published online: 28 November 2014

Hepatic resection (HR) and radiofrequency ablation (RFA) remain the most frequent curative therapies for hepatocellular carcinoma (HCC) because of strict indications for liver transplantation and shortages of donated livers. Nevertheless, recurrence occurs in up to 75 % of patients with intermediate or advanced HCC at 5 years after HR [1]; in these patients, 5-year recurrence-free survival (RFS) is lower than 25 %, and tumor recurrence is the main cause of death [2]. Therefore, inhibiting tumor recurrence is a key to improving HCC patients' overall survival (OS).

Hepatitis B virus (HBV) is the most common cause of HCC around the world, which inspired clinicians to treat patients with HBV-related HCC using nucleos(t)ide analogues (NAs) to inhibit HBV replication and therefore reduce risk of HCC incidence. High HBV load and replication are associated with greater risk of HCC incidence [3], and large studies with long follow-up have shown that NA therapy can dramatically reduce HCC incidence and death in patients with liver cirrhosis who are chronically infected with HBV [4, 5]. NA therapy also appears to reduce risk of HCC recurrence after HR [6, 7], suggesting that it may improve OS for patients with HBV-related HCC after curative HR or RFA.

Many retrospective studies have suggested that adjuvant NA therapy does reduce risk of HBV-related HCC recurrence after curative treatments [7–19]. Meta-analysis of these studies have concluded that NA therapy is associated with significantly lower tumor recurrence and liver-related mortality and significantly higher OS in patients with HBV-related HCC than no adjuvant therapy after curative treatments [20, 21]. Unfortunately, the retrospective design of these studies limits the strength of their evidence. The strongest evidence of whether NA therapy offers clinical benefits would come, in principle, from a randomized controlled trial (RCT). However, carrying out an RCT is ethically and logistically difficult because oral NA therapy has already proven effective at preventing disease progression in patients chronically infected with HBV and because such therapy is becoming more affordable and does not cause significant side effects. Therefore, few patients with HBV-related HCC would volunteer for an RCT.

Despite these obstacles, Yin et al. managed to publish in 2013 the first RCT examining the efficacy of adjuvant NA therapy in 180 patients newly diagnosed with HBV-related HCC after curative HR [22]. All patients had serum HBV DNA levels greater than 100 IU/mL. After median follow-up of 39.9 months, per-protocol analysis revealed that patients receiving lamivudine (100 mg/day) showed significantly higher short- and long-term RFS and OS than patients receiving no adjuvant therapy. In 2014, Huang and coworkers [23] performed an RCT examining the efficacy of adjuvant adefovir therapy in 200 patients newly diagnosed with HBV-related HCC after curative HR. In contrast to the earlier RCT, all patients in this study had serum HBV DNA levels greater than 2000 IU/mL. After median follow-up of 60 months, intention-to-treat analysis revealed that patients receiving adefovir (10 mg/day) showed significantly higher RFS and OS than patients receiving no adjuvant. Multivariate analysis showed that adefovir therapy was an independent protective factor of late tumor recurrence, which occurs >2 years after curative treatment and involves de novo tumorigenesis, but not of early HCC recurrence, which occurs <2 years after treatment and involves intrahepatic metastasis.

This evidence base of primarily retrospective studies and two RCTs (Table 1) makes a reasonably strong case that NA therapy offers clinical benefits in patients with HBV-related HCC after curative treatments like HR. However, there are

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Table 1 Characteristics and outcomes of patients with hepatitis B virus-related hepatocellular carcinoma treated by hepatic resection or radiofrequency ablation, followed by adjuvant nucleos(t)ide analogues

Study	No. of patients (T/C)	Mean tumor size (cm) (T/C)	Mean HBV DNA level (log 10 copies/mL)	Mean ALT (U/L)	Initial treatment for HCC (HR/RFA)	NA	Median follow-up (mo)	Overall survival (%)				Recurrence-free survival (%)			
								1 year	3 years	5 years	*P*	1 year	3 years	5 years	*P*
Randomized controlled trials															
Huang et al. 2014 [23]	100/100	4.9/5.1	>3.3	52.6/51.4	200/0	ADV	60	96/94	78/67	63/42	0.001	85/84	50/38	46/27	0.026
Yin et al. 2013 [22]	81/82	≥3 cm: 86.4 %/ 93.9 %	4.9/4.6	47.3/37.5	163/0	LAM	39.9	98/86	88/51	NA	<0.001	81/50	46/20	NA	<0.001
Non-randomized studies															
Chan et al. 2011 [8]	42/94	9.3/9.0[a]	NA	58.0/42.5	136/0	38 LAM+4 ETV	NA	88/77	79/48	71/44	0.005	67/49	51/34	51/34	0.05
Chuma et al. 2009 [9]	20/30	1.7/2.1	6.0/5.9[a]	43.1/37.7	10/10	15 LAM+5 ETV	35.5/49.2	NA	NA	NA	NA	90/86	55/50	45/44	>0.05
Hung et al. 2008 [7]	10/62	NA	NA	NA	72/0	LAM	18.9	NA	NA	NA	NA	90/75	NA	NA	0.03
Ke et al. 2013 [10]	141/141	4.5/5.5[a]	4.9/4.7	39/42	282/0	LAM	24/23	92/90	84/66	79/52	0.009	73/69	55/48	45/43	0.503
Kubo et al. 2007 [11]	14/10	2.4/2.8	6.0/6.0	53/56[a]	24/0	LAM	36.7/7.3	NA	NA	NA	NA	90/55	90/28	78/28	0.009
Kuzuya et al. 2007 [12]	16/33	NA	6.2/4.1[a]	56.6/54.2	31/18	LAM	38.0/32.6[b]	100/87	100/47	NA	0.063	87/87	65/47	NA	0.622
Li et al. 2010 [13]	43/46	7.1/8.5	6.5/7.3	60.8/56.5	79/0	LAM	12/12	42/33	NA	NA	0.009	23/8	NA	NA	0.072
Su et al. 2013 [14]	62/271	2.7/4.2[a]	5.9/5.5[a]	45/42[a]	333/0	40 LAM+19 ETV+3 IFN	45.9	99/84	96/64	89/49	<0.001	90/64	64/44	58/34	<0.001
Urata et al. 2012 [15]	46/13	2.8/3.4	4.7/6.1	46.8/58.0	59/0	22 LAM+24 ETV	36.2	100/85	97/68	90/60	0.002	72/62	57/19	43/19	0.048
Wu et al. 2012 [16]	518/4051	NA	NA	NA	4569/0	159 LAM+292 ETV+36 LDT+31 combined	31.7/26.2[b]	94/91	81/74	73/62	0.002	87/78	66/56	54/47	<0.001
Yan et al. 2013 [17]	35/25	4.7/5.0	>5: 54.3 %/72.0 %	41.5/35.8	60/0	LAM	NA	NA	NA	NA	NA	74/80	11/0	NA	0.283
Yin et al. 2013 [22]	215/402	≥3 cm: 89.3 %/ 92.3 %	4.5/3.8	>42: 48.8 %/ 36.8 %	617/0	LAM	23.8	84/75	60/50	NA	0.04	52/43	38/21	NA	<0.001
Yoshida et al. 2008 [18]	33/71	2.6/2.8	≥3.7: 100 %/63 %	54/36[a]	0/104	LAM	33/47[b]	100/100	80/85	59/70	>0.05	NA	NA	NA	>0.05
Zhang et al. 2014 [19]	17/19	≤3 cm	<4: 0/2; ≥4: 17/17	49/46	36/0	ETV	31	100/100	92/92	NA	0.184	100/100	93/48	NA	0.006
	23/28	>3 cm	<4: 2/7; ≥4: 21/21	58/56	51/0	ETV	31	100/100	43/23	NA	0.246	100/100	25/10	NA	0.209

ADV adefovir, *C* control, *ETV* entecavir, *HR* hepatic resection, *LAM* lamivudine, *LDT* telbivudine, *NA* nucleos(t)ide analogue, *NR* not reported, *RFA* radiofrequency ablation, *T* total

[a] Median values

[b] Mean values

five major questions about NA therapy that have been neglected in the literature and that must be answered to maximize its efficacy in the clinic.

How does NA therapy prevent HCC recurrence and improve OS?

Though one RCT has reported that NAs significantly improve short- and long-term RFS [22], no study has directly established that the analogues exert antitumor effects. It is possible that NAs improve survival primarily by reducing HBV load. Lower HBV load in serum, indicative of reduced viral replication, is associated with lower risk of HCC occurrence in HBV carriers, irrespective of whether they have hepatitis [3, 4, 24]. Meta-analysis of eight studies involving 1610 patients with HCC chronically infected with HBV showed that lower viral load was associated with significantly lower risk of recurrence after HR or RFA [25]. Reducing HBV load improves genetic stability in hepatocytes and facilitates their regeneration following destruction by the virus.

The RCT by Huang et al. [23] reported that NA therapy reduced late HCC recurrence, but not early HCC recurrence. This is consistent with multivariate analysis of 193 patients with HBV-related HCC who underwent HR, in which late recurrence was found to depend on high viral load and hepatic inflammation, whereas early recurrence depended on tumor factors [26].

Since NA therapy can reduce hepatitis activity and reduce chronic inflammation in the remnant liver after HR, it may improve survival by maintaining hepatic functional reserve. Therefore, the available evidence suggests that NA therapy improves OS in patients with HBV-related HCC after HR through two main mechanisms: improving hepatic functional reserve and indirectly preventing late tumor recurrence. However, large, properly controlled studies are needed to test this hypothesis directly.

When is the optimal time to initiate NA therapy, and how long should it last?

Patients with HBV-related HCC suffer from both malignancy and chronic HBV infection, and although HR may treat the malignancy at least in the short term, it may also cause HBV reactivation. This can lead to fulminant hepatitis, liver failure, or even mortality. Post-resection rates of HBV reactivation range from 16 to 28 % in patients not taking antiviral therapy [27–30], while the corresponding numbers are 0 and 2.9 % in patients taking antiviral therapy [27–29]. Huang et al., the team that published one of the two RCTs on NA therapy [23], earlier investigated the risk of HBV reactivation in individuals with low serum levels of HBV DNA (<2000 IU/mL) at the time of HR. [31] HBV reactivation occurred in 19.1 % of patients by 1 year after surgery, and rates of liver failure were significantly higher in these patients than in those who did not suffer reactivation (10.5–11.8 % vs. 2.7–6.4 %) [28, 31], while 3-year RFS and OS were significantly lower [31]. Given the strong potential for HBV reactivation and the fact that persistent HBV replication increases the risk of recurrence [32], we suggest that NA therapy be initiated before HR in patients with HBV-related HCC and detectable serum levels of HBV DNA. This recommendation should be examined directly in properly controlled trials.

Official guidelines for treating patients chronically infected with HBV differ in how long they recommend continuing NA therapy [33–35]. Moreover, it is unclear whether these guidelines are optimal or even appropriate for patients with HBV-related HCC [36]. Since NA therapy cannot completely eradicate HBV and the treatment goal is to reduce HBV replication as much as possible to minimize the risk of reactivation, some investigators have advocated continuing antiviral treatment indefinitely, regardless of whether HBV DNA levels are undetectable or HBeAg seroconversion occurs [37, 38]. Those investigators argue that lifelong antiviral treatment may help prevent hepatitis flare-ups and maximally inhibit hepatocarcinogenesis.

Lack of official consensus on optimal NA therapy duration reflects a lack of studies on this question. In their RCT, Huang et al. [23] continued antiviral treatment unless there was unacceptable toxicity or withdrawal of consent. In contrast, Yin et al. kept the patients in their RCT on NA therapy until HBsAg seroconversion [22]. It is possible that halting NA therapy at HBsAg seroconversion may provide inadequate protection against future HCC recurrence or reactivation. Large, properly controlled trials are needed to examine the optimal duration of adjuvant NA treatment. These trials should take into account the problem of resistance to NAs that sometimes accompanies long-term NA monotherapy (see below).

What are the indications for NA therapy?

Whether NA therapy provides clinical benefit to all patients with HBV-related HCC undergoing HR is unknown. Current guidelines and clinical practices about patient selection for NA therapy revolve around three factors: serum level of HBV DNA, grade of liver function, and tumor stage. The literature provides no answers to the question of whether it is appropriate to administer adjuvant antiviral therapy to patients in whom serum levels of HBV DNA are undetectable or below the internationally recommended thresholds of 2000 IU/mL. Many guidelines recommend such therapy only for patients with chronic HBV infection, evidence of active viral replication (>2000 IU/mL) and elevated levels of alanine

aminotransferase. However, there is no international consensus on this point, in large part reflecting the fact that patients with low preoperative HBV load (<2000 IU/mL) can show HBV reactivation rates as high as 19.1 % after HR. [31] The Chinese Medical Association [39] recommends that patients with HBV-related HCC take NAs as long as they show detectable levels of HBV DNA, regardless of alanine aminotransferase levels.

The question of whether and when to stop NA therapy is made even more complex by the fact that NAs can affect post-HR outcomes related not only to HCC but also to remnant liver function. Cirrhosis in patients chronically infected with HBV strongly predicts HCC occurrence and disease-related mortality [40]. The finding that NAs can reduce hepatitis activity in such patients, coupled with their good tolerability, argues for prescribing analogues to most patients with HBV-related HCC for as long as possible after HR, especially patients with progressive cirrhosis. Controlled trials are needed to address this question.

Since all patients in the two RCTs [22, 23] on NA therapy had Child-Pugh A liver function, and only some patients in the retrospective literature had Child-Pugh B liver function [10, 13], it is unclear whether patients with HBV-related HCC and Child-Pugh B or C liver function should receive adjuvant NA therapy after HR. The available evidence suggests that patients with reduced liver function can still benefit from this treatment. Lamivudine therapy rapidly suppressed HBV DNA load and improved the Child-Pugh score in patients with decompensated cirrhosis chronically infected with HBV [41, 42]. Antiviral therapy improved liver function in patients with HBV-related HCC [28, 43]. Large, controlled studies should examine directly whether NA therapy provides clinical benefits to patients with Child-Pugh B or C liver function.

The observation that NA therapy appears to affect primarily late recurrence, coupled with the high rate of early recurrence and low long-term OS of patients with advanced HCC, suggests that antiviral treatment should be more effective in patients with early-stage HCC. This hypothesis is supported by subgroup analysis of 478 patients with HBV-related HCC who underwent curative HR. [10] Adjuvant NA therapy was associated with significantly higher OS than no adjuvant antiviral therapy in HCC patients in Barcelona Clinical Liver Cancer (BCLC) stage A or B, but not in patients with BCLC stage C disease [10]. Similarly, a retrospective study of 163 patients with HBV-related HCC found that NA therapy was associated with higher OS and RFS than no adjuvant antiviral therapy in patients with stage I or II tumors without major vascular invasion, but not in patients with stage III tumors or tumors of any stage showing major vascular invasion [8]. Finally, another retrospective study of 87 patients with HBV-related HCC after curative HR found that NA therapy led to significantly higher RFS than no adjuvant antiviral therapy in patients with HCC tumors up to 3 cm, but not in patients with tumors larger than 3 cm [19]. Given the relatively small populations in these studies, and their retrospective design, RCTs are needed to explore the efficacy of NA therapy in different HCC stages in the presence of different HCC comorbidities such as vascular invasion and portal hypertension.

Which NA drug(s) should be used?

Five NAs are currently used in the clinic to treat patients chronically infected with HBV: lamivudine, adefovir, telbivudine, entecavir, and tenofovir. While all these drugs are associated with similarly low toxicity, they can differ slightly in clinical efficacy and, most importantly, in how often they lead to resistance in patients on long-term monotherapy. Lamivudine monotherapy led to resistance in 22 % patients in the RCT by Yin et al. [22] and to resistance-associated breakthrough hepatitis in 14 % of patients in a systematic review of four retrospective studies [44]. Adefovir monotherapy led to primary nonresponse in 3 % of patients and resistance in 15 % of patients in the RCT by Huang et al. [23] Telbivudine monotherapy was reported in one prospective study to lead to resistance in 10.8 % of HBeAg-negative patients and 25.1 % in HBeAg-positive ones at 2 years [45]. Entecavir monotherapy for long-term treatment of chronic HBV infection led to resistance in 1.2 % of patients in one prospective study [46]. Alone among the five NAs, tenofovir has been associated with a zero rate of resistance among patients with chronic hepatitis B [47]. Given the drug's antiviral potency and minimal toxicity, it may be the most suitable analogue. In fact, official guidelines [33–35] recommend entecavir and tenofovir as first-line antiviral therapy in patients chronically infected with HBV because of their superior ability to suppress viral replication and because of high genetic barriers to the development of resistance. However, we are unaware of RCTs or even retrospective studies comparing different NAs in parallel in patients with HBV-related HCC. Such studies should also specifically examine the perioperative use of entecavir and tenofovir.

Future studies should address the cost-effectiveness of NA therapy for HCC patients, since the literature has given conflicting results [48] and NA treatment costs remain prohibitive in HBV-endemic areas.

Can multimodal treatment improve on NA therapy?

Some evidence suggests that adjuvant or chemopreventive therapies may be useful supplements to NA therapy to further reduce late recurrence as well as inhibit early recurrence, thereby increasing survival from HCC [49, 50]. These previous studies are retrospective and involve relatively small

patient populations. Large RCTs should compare multimodal treatments with NA therapy alone.

In conclusion, the available evidence strongly suggests that adjuvant NA therapy in patients with HBV-related HCC improves liver function, significantly reduces late recurrence and improves OS following curative treatments such as HR. However, optimal implementation of NA therapy will require answering at least five unresolved questions: how the treatment prevents HCC recurrence and improves OS, when is the optimal time to initiate the treatment and how long it should be continued, for what patients the treatment is suitable, which NAs are the most cost-effective, and whether combining NA therapy with other treatments can further improve patient prognosis.

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