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Long-term clinical benefit of Peg-IFNα and NAs sequential antiviral therapy on HBV related HCC

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Analysis of the value of long-term antiviral therapy using sequential Peg-IFN therapy and nucleos(t)ide analogues (NAs) improves the prognosis of HBV-related HCC. HBV-related HCC patients were classified into sequential therapy with Peg-IFNα-2a and NAs, and NAs therapy alone. All patients were followed up for 5 years. The survival rate, HCC recurrence rate, Child-Pugh score, and side effects of drugs were evaluated. Firstly, the early and late cumulative survival rate was higher in patients receiving antiviral therapy compared with the control patients ($p<0.05$). Patients receiving sequential therapy with Peg-IFNα-2a and NAs showed a higher late cumulative survival rate and significantly reduced early and late recurrence rate, compared to those in the NA-alone group ($p<0.05$). Single NAs therapy only reduced the late recurrence rate in HCC-patients. Secondly, NAs therapy significantly increased the Child-Pugh score after five years of therapy (five-year therapy 7.03±1.50 vs. initial score 6.63±0.85; $p<0.05$), whereas the sequential therapy with Peg-IFNα-2a and NAs did not greatly alter the Child-Pugh score (6.88±1.26; $p>0.05$). Compared to the control patients, patients receiving antiviral therapy (NAs alone or sequential therapy with Peg-IFNα-2a and NAs) exhibited a significantly decreased Child-Pugh score ($p<0.05$). Compared to NAs alone, sequential therapy with Peg-IFNα-2a and NAs provided a more efficient strategy for improving both the five-year survival rate and the two-year or five-year recurrence rate in patients.

Key words: primary hepatocellular carcinoma, Peg-IFN, nucleos(t)ide analogues, antiviral therapy

Primary hepatocellular carcinoma (HCC) is a common malignant tumor in the clinic, and over 626,000 cases are diagnosed annually worldwide. HCC has ranked the fifth most malignant tumor and the cancer-related mortality of HCC ranks the third most severe with approximately 600,000 deaths every year. In China, chronic liver disease is highly prevalent. HCC develops from chronic liver disorders, which account for 55% of the worldwide disease prevalence and is the second most common cancer-related mortality. A majority of Chinese HCC patients are affected by chronic HBV infection, which is different from that of western countries [1–3]. The annual prevalence of HCC is extremely high in liver cirrhosis patients with HBV, and about one-third of these patients eventually develop HCC [4]. According to the BCLC guideline, curative resection, liver transplantation, or ablation is believed to be the most optimal strategy for the improvement of prognosis in Stage 0–1 HCC patients. However, HCC recurrence is still a major problem, which leads to poor prognosis [5–7]. It has been reported that the five-year recurrence rate in patients receiving liver resection or ablation can be as high as 50–85% [8].

The recurrence of HCC has been classified into early recurrence and late recurrence. Early recurrence, identified by HCC recurrence two years after curative resection or ablation, is predominantly associated with HCC metastasis [9]. Late recurrence, identified as HCC recurrence two years after therapy, mostly results from *de novo* tumors arising [10]. A recent study reveals that several factors contribute to HCC recurrence after curative resection, including tumor size, tumor mass number, portal vein invasion, AFP level, albumin level, and Child-Pugh score [11, 12]. In addition, high HBV DNA load is known to be an independent risk factor for HCC recurrence [13–15] and is closely associated with late HCC recurrence [16, 17]. In 2012, a nationwide cohort study in Taiwan showed that long-tern antiviral therapy using NAs significantly improved the survival rate in patients compared with control (89.4% vs. 71.7%) [18]. In addition, the six-year HCC recurrence rate in patients receiving antiviral therapy

was greatly reduced compared to control (45.6% vs. 54.6%) [18]. Shoji et al. [19] and Zimmerman et al. [20] reported that long-term antiviral therapy using LAM efficiently improved the long-term prognosis in HCC patients after curative resection and liver transplantation. The late recurrence of HCC patients receiving LAM antiviral therapy was reduced to 20% compared with a 70% five-year recurrence in control patients without antiviral therapy [19]. Nishikawa et al. [21] and Shin et al. [22] further confirmed the significance of NAs therapy such as LAM for improving the prognosis of HBV-related HCC.

A few studies have determined the association between IFN therapy and the recurrence of HBV-related HCC and shown that IFN therapy promoted the survival rate of patients by reducing early recurrence (one-year recurrence, 16.1% vs. 38.7%) [10, 23, 24]. Compared to ordinary IFN, Peg-IFN has advantages in that it is stable and retains a high plasma drug concentration, as well as giving persistent antiviral responses (3-fold increase) [25–27]. Studies in patients with chronic HBV disorders demonstrated that sequential Peg-IFN therapy with NAs significantly elevated the persistent response rate (36% vs. 14%; p=0.011) and reduced drug resistance (21% vs. 40%) compared with NAs therapy alone [28]. However, it remains unclear whether or not sequential Peg-IFN therapy with NAs promotes anti-tumor immune responses and reduces HCC recurrence in HBV-related HCC patients.

Based on this evidence, we investigated the potential improvement of long-term prognosis in HBV-related HCC patients after curative resection or ablation by long-term application of NAs antiviral therapy followed by Peg-IFN administration.

Patients and methods

Subjects. In this study, a total of 3108 primary HCC patients received curative resection or ablation in China-Japan Union Hospital, Jilin University from January 2003 to January 2013. HBV-related HCC patients with complete 5-year follow up information (n=256) were enrolled in the follow-up study. On the basis of patient willingness, patients were divided into two groups; 189 cases received antiviral therapy in the Digestive Disease Center, and 41 controls did not receive antiviral therapy. Among 189 patients receiving antiviral therapy, patients were further classified into sequential therapy with Peg-IFNα-2a and NAs (n=40) and NAs therapy alone (n=131). All patients were followed up for 5 years. The survival rate, HCC recurrence rate, Child-Pugh score, and side effects of drugs were evaluated (Figure 1). This study was conducted in accordance with the Declaration

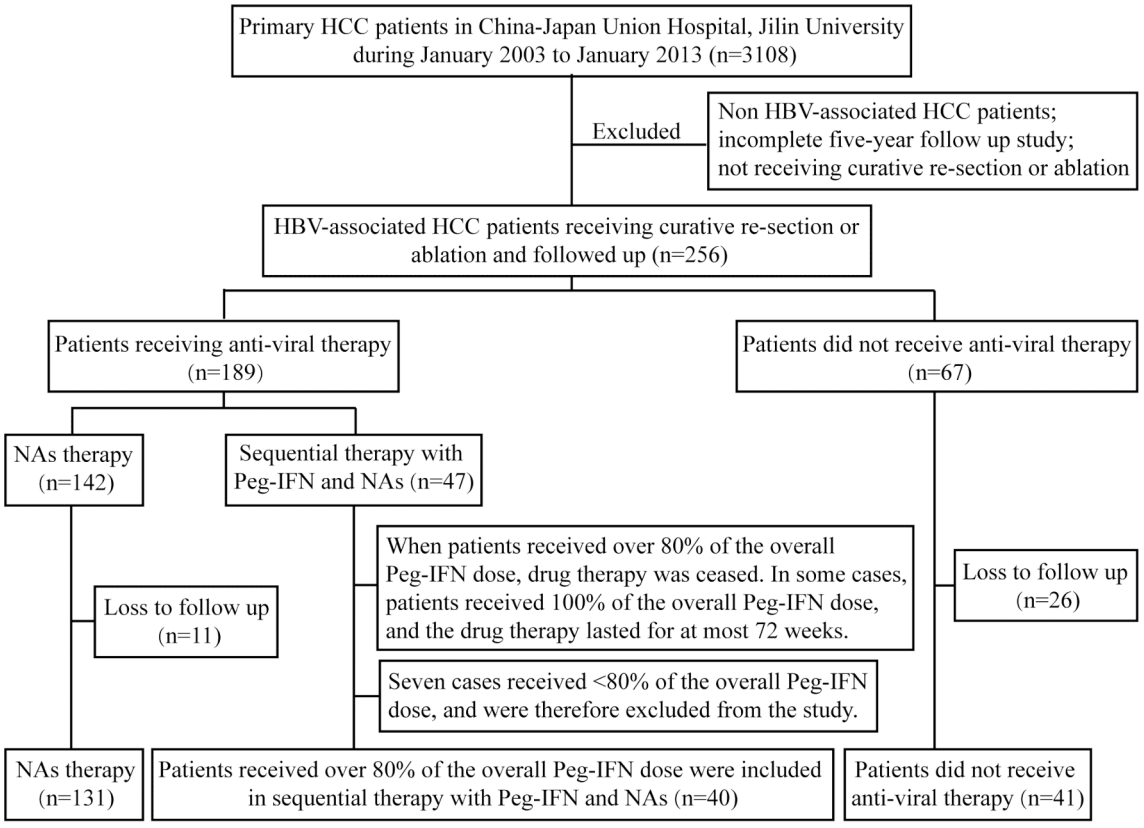

Figure 1. Flow diagram of the effects of antiviral therapy on the prognosis of HCC patients after curative resection or ablation.

of Helsinki. This study was conducted with approval from the Ethics Committee of Jinlin University. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria. Patients included in this study met the Clinical Practice Guidelines of HCC proposed by the NCCN in 2006 [29]. All patients with BCLC Stage 0–1 did not show HCC recurrence at three months following surgery. Inclusion criteria were as follows: 1) HBV DNA load $>1.0\times10^3$ copies/ml; 2) no chronic hepatitis C virus (HCV) infection or combined HIV infection determined by serological examination. Exclusion criteria were as follows: 1) patients had a history of antiviral therapy using NAs or Peg-IFNα; 2) patients received TACE therapy instead of curative resection or ablation; 3) HCC patients with residual tumor; 4) patients receiving systemic chemotherapy of Sorafenib; 5) patients with alcoholic liver disease, drug-induced liver disease, or autoimmune liver disease; 6) patients who died within three months after initial therapy.

Therapeutic strategy and experimental assignment. According to the antiviral therapy regimen, 212 patients after curative resection or ablation were classified into sequential therapy with Peg-IFNα-2a and NAs or NAs therapy alone. Patients receiving curative resection but without antiviral therapy were included as controls. All patients were followed up for 5 years.

Patients receiving sequential therapy with Peg-IFNα-2a and NAs were given Peg-IFNα-2a at an initial loading dose of 180 μg/w. If the neutrophil count was $\leq0.75\times10^9$/l or platelet count was $<50\times10^9$/l, the dose of Peg-IFNα-2a was reduced to 135 μg/w. In the case of patients being intolerant to therapy, the dose of Peg-IFNα-2a was reduced to 90 μg/w or 67.5 μg/w. Peg-IFNα-2a therapy was ceased when the neutrophil count was $\leq0.5\times10^9$/l or platelet count was $<30\times10^9$/l. When patients received over 80% of the overall Peg-IFN dose, drug therapy was ceased. In some cases, patients received 100% of the overall Peg-IFN dose and the drug therapy lasted for a maximum of 72 weeks. Patients receiving ≥80% of the overall Peg-IFN dose were included in this study. Seven cases received <80% of the overall Peg-IFN dose, and were therefore excluded from the study. After Peg-IFNα-2a withdrawal, patients were given 0.5 mg ETV (q.d.) by oral administration.

Patients in the NAs therapy alone group were given 0.5 mg ETV (q.d.) by oral administration. In cases where apparent drug resistance occurred, patients were given 0.5 mg ETV (q.d.) plus 100 mg ADV (q.d.).

Measurements. One month after initial antiviral therapy, the HBV DNA load and liver function were analyzed. Thereafter, the HBV DNA load, liver function, renal function, AFP level, blood and routine urine outputs were evaluated once every three months. The imaging examination of the liver was conducted once every three months. The above indices were examined in control patients. For those with rebound HBV DNA, drug resistance was analyzed and the NA medications were adjusted according to the drug resistance sites.

Examinations: 1) Biochemical examination: liver function, renal function, blood and routine urine outputs were evaluated using an automatic biochemical analyzer and equipped reagents (Beckmann, USA). 2) HBV DNA: The serum HBV DNA load was assessed using the Roche Cobas PCR System. The lower limit of detection was 20 copies/ml. 3) HBV drug resistance: Serum HBV drug resistance mutations were examined by Sanger sequencing.

Statistical analysis. Data were analyzed by IBM SPSS 19 software (Chicago, IL, USA). Measurement data were expressed as $\chi\pm s$. The means were compared using the student`s t test. Two-tail p-value <0.05 was considered statistically significant. χ^2 test was used for comparing the rate. Cumulative prevalence and mortality rates were analyzed using the log-rank test.

Table 1. Demographic and clinical characteristics of 3108 patients with primary HCC.

Variable	Primary HC (n=3108)
Gender (male:female)	2285:823
Age	62.7±12.8
Etiology	
Chronic HBV infection	2190 (70.5%)
Chronic HCV infection	431 (13.9%)
Alcoholic fatty liver disease	96 (3.1%)
Others (including non-alcoholic fatty liver disease, autoimmune liver disease and unknown cause)	391 (12.5%)
Therapeutic approach	
Curative resection	412 (13.3%)
Ablation	321 (10.3%)
TACE	1035 (33.3%)
Others	1340 (43.1%)

Results

Demographic and clinical characteristics. A total of 212 HCC patients were enrolled in this study. Among these patients, 171 cases received antiviral therapy and 41 cases were included as controls. There was no significant difference in the gender, age, Child-Pugh classification, percentage of HBeAg-positive patients, AFP level, ALT level, HBV DNA loads, tumor mass number, tumor size, BCLC stage between control and HCC patients receiving antiviral therapy (Tables 1, 2).

Influences of sequential therapy with Peg-IFNα-2a and NAs on the cumulative survival rate. All patients included in the five-year follow-up study were evaluated for the influence of antiviral therapy on liver disease-related mortality. Although there was no significant difference in the cumulative survival rate at two years after initial therapy between patients receiving sequential therapy with Peg-IFNα-2a and NAs, and NAs alone, patients receiving sequential therapy

Table 2. Comparison of the demographic and clinical characteristics between HCC patients receiving antiviral therapy and control.

Variable	Antiviral therapy (n=171)		Control (n=41)	p-value
	Sequential therapy with Peg-IFNα-2a and NAs (n=40)	NAs therapy alone (n=131)		
Gender (male/female)	31/9	96/35	31/10	>0.05
Age (years, mean ± SD)	51.8±5.8	54.1±6.7	55.3±7.0	>0.05
HBeAg (positive/negative)	14/26	44/87	10/31	>0.05
ALT (IU/l, mean ± SD)	54.0±42.6	54.7±64.3	54.1±53.8	>0.05
AFP (ng/ml, mean ± SD)	239.4±246.8	231.3±266.1	229.3±304.2	>0.05
HBV DNA (log_{10}copies/ml)	4.8±1.0	5.0±1.3	5.0±1.1	>0.05
HBV subtype (type B/type C)	13/27	43/88	13/28	>0.05
Liver cirrhosis	35 (87.5%)	130 (99.2%)	37 (90.2%)	>0.05
Child-Pugh stage (A/B)	15/8	52/78	13/24	
Tumor size (cm, mean ± SD)	2.4±0.5	2.5±0.5	2.6±0.4	>0.05
The number of tumor mass	6	22	6	>0.05
BCLC stage (0/1)	5/35	22/109	4/37	>0.05
Therapeutic approach	14	40	13	
Curative resection (n) Ablation (n)	26	91	28	

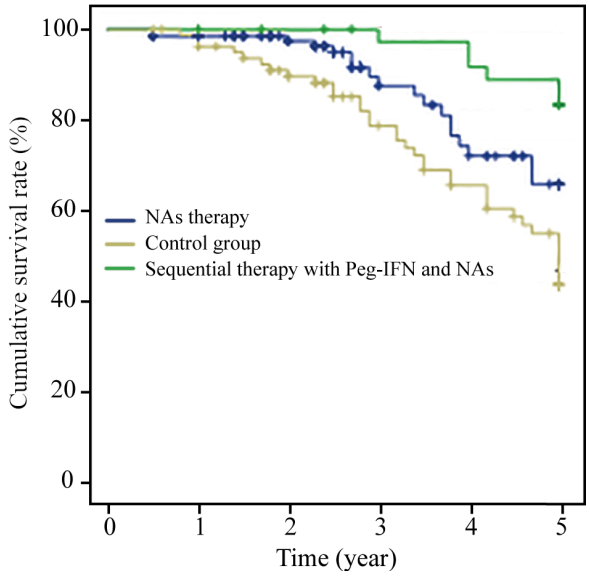

Figure 2. Influences of sequential therapy with Peg-IFN and NAs on the cumulative survival rate of HCC patients and the comparison between sequential therapy with Peg-IFN and NAs and NAs therapy alone. Two-year cumulative survival rate: Sequential therapy with Peg-IFN and NAs vs. NAs, p>0.05; NAs vs. control, p<0.05. Five-year cumulative survival rate: Sequential therapy with Peg-IFN and NAs vs. NAs, p<0.05; NAs vs. control, p<0.05.

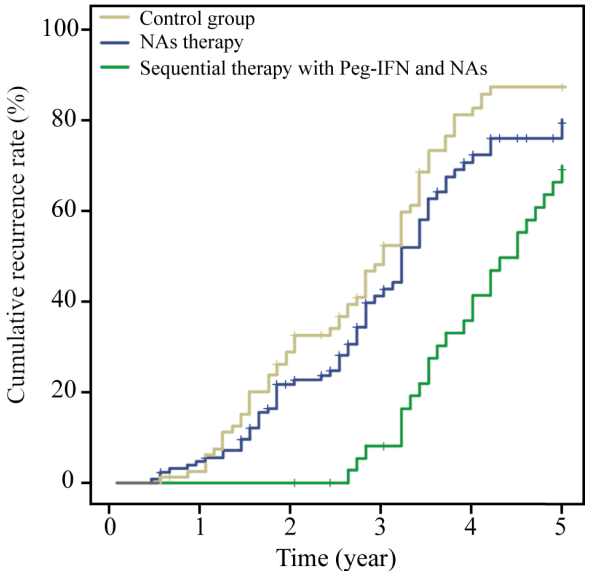

Figure 3. Influences of sequential therapy with Peg-IFN and NAs on the cumulative recurrence rate of HCC patients and the comparison between sequential therapy with Peg-IFN and NAs and NAs therapy alone. Two-year cumulative recurrence rate: Sequential therapy with Peg-IFN and NAs vs. NAs, p<0.05; NAs vs. control, p>0.05. Five-year cumulative recurrence rate: Sequential therapy with Peg-IFN and NAs vs. NAs, p<0.01; NAs vs. control, p<0.05.

with Peg-IFNα-2a and NAs had a greatly increased cumulative survival rate at five years after initial therapy compared with those receiving NAs therapy alone (p<0.05). Compared to those receiving antiviral therapy, the early and late cumulative survival rate was remarkably reduced in patients without antiviral therapy (p<0.05, Figure 2).

Influences of sequential therapy with Peg-IFNα-2a and NAs on the cumulative recurrence rate. We compared the cumulative recurrence rate in patients receiving sequential therapy with Peg-IFNα-2a and NAs versus NAs alone. Our results showed that sequential therapy with Peg-IFNα-2a and NAs contributed to significantly reduced two-year and five-year recurrence rates compared with those receiving NAs alone (p<0.05). Although there was no significant difference in the two-year recurrence rate between the NAs group and the control group, patients receiving NAs therapy had a significantly lower five-year recurrence rate than control patients (p<0.05, Figure 3).

Figure 4. Influences of antiviral therapy on the Child-Pugh score in HCC patients with liver cirrhosis.

Influences of antiviral therapy on the Child-Pugh score in HCC patients with liver cirrhosis. Among patients receiving antiviral therapy, 165 cases were identified as HCC combined liver cirrhosis, and 6 cases had no liver cirrhosis. The Child-Pugh score was not greatly altered in patients receiving sequential therapy with Peg-IFNα-2a and NAs during follow up study ($p>0.05$), whereas the Child-Pugh score was gradually elevated in the NAs group, with time. In patients receiving NAs therapy alone, there was no significantly altered Child-Pugh score at two years following initial therapy compared with that before therapy ($p>0.05$). However, the Child-Pugh score at five years following initial therapy was significantly different (7.03 ± 1.50 vs. 6.63 ± 0.85; $p<0.05$). Moreover, the Child-Pugh score at two years following initial therapy was significantly increased in patients without antiviral therapy when compared to those receiving antiviral therapy ($p<0.05$, Figure 4).

Analysis of drug resistance in patients receiving different antiviral therapy regimens. In patients receiving antiviral therapy, patients on sequential therapy with Peg-IFNα-2a and NAs were given Peg-IFN for one year followed by NAs therapy. After four years of antiviral therapy, none of the patients in this group developed drug resistance. However, in patients receiving NAs alone, two cases (4.1%) developed ETV resistant mutations (at 2.5 years and 3 years after initial antiviral therapy). No new cases of drug resistance were identified 5 years after initial therapy. DNA sequencing showed that mutation occurred on the rtM204I/V, rtL180M, and rtT184 sites. For patients with drug resistance, ADV was administrated. Drug resistance was reversed after three months and six months of ETV plus ADV therapy in these two cases.

Analysis of side effects in patients receiving different antiviral therapy regimens. Side effects of antiviral therapy using Peg-IFNα-2a included fever, influenza-like syndrome, decreased neutrophil count in peripheral blood, reduced platelet counts, and alopecia. The most common side-effect of Peg-IFNα-2a therapy was fever, which occurred in 65% of patients receiving therapy. In addition, 57.5% of patients had a reduced white blood cell count, 47.5% of patients showed a reduced platelet count, and 45% of patients felt weak with myalgia. In some cases, blood glucose fluctuation (12.5%), thyroid dysfunction (7.5%), and clinical depression (5%) were detected. No significant side-effects were noted in patients receiving NAs therapy alone.

Discussion

In China, chronic liver disease is highly prevalent. HCC develops from chronic liver disorders, which accounts for 55% of the worldwide disease prevalence and over 90% of Chinese HCC patients have chronic HBV infection [1–4]. According to the BCLC guideline, radical therapies, including curative resection, liver transplantation, or ablation, can be applied to Stage 0–1 HCC patients, whereas the five-year survival rate of these patients is between 50–70% [30]. HCC recurrence is believed to be the major cause of poor prognosis [5–7].

Previous studies reveal that long-term antiviral therapy using NAs such as LAM efficiently reduced late recurrence rate and prolonged survival time in HCC patients after curative resection and liver transplantation [19–22, 31]. IFN not only has potent antiviral activity, but also regulates multiple biological events, including immune response regulation, anti-proliferation, and anti-angiogenesis. IFN is mainly used for the adjuvant therapy of HCV-associated HCC, and there are reports regarding the use of IFN for HBV-related HCC [32]. Single drug therapy may possibly lead to the rebound or recurrence of HBV. Based on the experience of HBV management, sequential therapy with Peg-IFNα and NAs was used as adjuvant therapy for HBV-related HCC. Our results showed that, compared to NAs therapy alone, sequential therapy with Peg-IFNα-2a and NAs significantly improved the five-year survival rate (83.3%) and reduced the two-year early recurrence rate as well as the five-year late recurrence rate. Yang et al. showed that adjuvant therapy using NAs provided a 73% (59–89.7%) five-year overall survival in HBV-related HCC patients [33]. In their study, Asian HCC patients, especially in mainland China and Taiwan, received NAs adjuvant therapy after radiation excision. The characteristics of the cohorts were similar to that of our study and therefore has a certain significance for comparison. Our results demonstrated that sequential therapy with Peg-IFNα-2a and NAs significantly improved the five-year overall survival rate compared with NAs therapy alone, suggesting that sequential therapy with Peg-IFNα-2a and NAs has the ability to improve the long-term prognosis of HCC patients.

Most HBV-related HCC develops from liver cirrhosis. Despite sequential therapy with Peg-IFN and NAs being shown to improve the survival rate of patients, the impact of sequential therapy on the liver function of patients with

liver cirrhosis is still unclear. Lv et al. showed that combined administration of LAM and ADV, or LAM alone gradually reduced the Child-Pugh score at 48, 96, or 144 weeks of therapy in patients with hepatitis B virus-related decompensated cirrhosis compared with that initial score before therapy (LAM combined ADV, 1.9, 2.6, 3.1; LAM alone, 1.7, 2.2, 2.7) [34]. Nevertheless, it remains unknown whether or not similar therapeutic outcomes can be achieved using antiviral therapy for HBV-related HCC patients. In this study, we showed that there was no significant change in the Child-Pugh score in patients receiving sequential therapy with Peg-IFNα-2a and NAs during the follow-up study. However, the Child-Pugh score in patients receiving NAs therapy alone was increased at five years following initial therapy (7.03±1.50 vs. 6.63±0.85; $p<0.05$). In addition, the Child-Pugh score at two years following initial therapy was significantly increased in patients without antiviral therapy when compared to those receiving antiviral therapy (either sequential therapy with Peg-IFNα-2a and NAs group, or NAs alone group). These data indicated that antiviral therapy could not improve the Child-Pugh score in HBV-related HCC patients. However, antiviral therapy efficiently delayed liver dysfunction. Moreover, sequential therapy with Peg-IFNα-2a and NAs appears to be more efficient in controlling disease progression when compared to NAs therapy alone.

Long-term administration of antiviral agents may lead to the risk of side effects and drug resistance. In this study, seven cases (3.7%) were excluded from the study due to Peg-IFN-induced reduction of peripheral blood cells. These patients had to reduce the Peg-IFN dose or even withdraw from drug administration and received <80% of the overall Peg-IFN dose. Side-effects of antiviral therapy using Peg-IFNα-2a included fever, fatigue, myalgia, decreased neutrophils in peripheral blood, reduced platelet counts, and alopecia. The most common side effect of Peg-IFNα-2a therapy was fever, which occurred in the majority of patients receiving therapy. A significant proportion of individuals experienced the following side-effects: reduced white blood cell count, reduced platelet count, fatigue, and muscular soreness compared to that of antiviral therapy against chronic HBV infection, the side-effects of Peg-IFNα-2a therapy are relatively increased [35]. However, all patients included were closely monitored and therefore no severe side-effects were found, suggesting the safety of sequential therapy with Peg-IFNα-2a and NAs for HCC patients. Drug resistance is known to be the major problem for antiviral therapy using NAs. In order to overcome NAs resistance [36, 37], ETV, which has a high genetic barrier of resistance, was used. Our findings indicated that two cases (1.5%) developed drug resistance in the NAs therapy alone group, and none of the patients in the sequential therapy group showed drug resistance.

Considering China`s healthcare system, we could not conduct a randomized controlled trial and therefore this prospective study was performed here. The follow-up duration is relatively long and some cases were lost to follow up in patients receiving antiviral therapy or not. This is both a strength and a weakness of the study.

In summary, sequential therapy with Peg-IFNα-2a and NAs had the advantages over NAs therapy alone in the efficient improvement of the long-term survival rate, decreased recurrence, and suppressed disease progression in HCC patients with liver cirrhosis after curative resection. At present, clinical studies focus on local therapy but fail to take into account the fact that antiviral therapy is of great importance as adjuvant therapy. Hence, the study of antiviral therapy for HBV-related HCC patients strengthens the significance of antiviral therapy for HBV-related HCC and may benefit the long-term prognosis and life quality in HCC patients.

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