High percentage atypical hepatocellular carcinoma in chronic hepatitis B patients treated with nucleos(t)ide analogues

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Background/Aims: Nucleos(t)ide analogues are used for preventing liver cirrhosis in chronic hepatitis B patients, but the risk factors of hepatocellular carcinoma in these patients remain unclear. We aimed to determine the risk factors for HCC development and its presentation.

Methods: In this retrospective cohort study, patients with chronic HBV who tested HBeAg+ or HBeAg- or had a serum total bilirubin ≥2 mg/dL were treated for at least 2 years with LAM, ETV, or LdT from January 2009 to December 2010 in Taipei and Taitung Mackay Memorial Hospital. Patients were followed-up for at least 2 years to detect HCC occurrence and its presentation. The data suggested that risk factors for HCC include age, sex, HBeAg, viral load, prescription medications, liver cirrhosis, previous treatments, and liver function test results, including baseline and follow-up AST and ALT levels.

Result 1:. There are 396 patients recruited in the study, 18 developed HCC. The time from treatment to HCC was about 28.5 ± 16.7 months. The clinical characteristics in the newly developed HCC group and the no HCC group showed significant differences in age (52.8 ± 6.1 vs. 47.1 ± 12.6, p<0.01), baseline ALT levels (161.4 ± 177.3 vs. 361.7 ± 496.3, p<0.01), and baseline liver cirrhosis (72.2% vs. 29.9%, p<=0.01).

Table 1. Demographic and clinical characters of new growth hepatoma patients and no hepatoma chronic hepatitis B patients

	Hepatoma occurred (n=18)	No Hepatoma patients (n=378)	*p*
Patient related			
Male, n (%)	15 (83.3%)	285 (75.4%)	0.580
Age, mean ± SD	52.8 ± 6.1	47.1 ± 12.6	0.001
HBeAg(+/-)	7/11	164/214	0.810
Baseline ALT, mean ± SD (IU/L)	161.4 ± 177.3	361.7 ± 496.3	0.000
Baseline AST, mean ± SD (IU/L)	124.4 ± 93.0	245.4 ± 385.5	0.000
Baseline T. Bil,(mg/dL)	3.0 ± 3.7	2.4 ± 2.5	0.344
Baseline AFP,(ng/uL)	412.6 ± 1042.6	26.4 ± 79.4	0.159
The 6th month ALT	37.4 ± 17.6	36.7 ± 33.0	0.932
The 12th month ALT	45.6 ± 30.9	45.8 ± 106.4	0.992
Liver cirrhosis, n (%)	13 (72.2%)	113 (29.9%)	0.000
Baseline HBV Viral load 10^6 IU/ml	6.7 ± 130.0	150.0 ± 160.0	0.731
Treatment related			
Pretreatment	6 (33.3%)	66 (17.5%)	0.112
Tx duration (M)	57.3 ± 16.5	51.2 ± 17.4	0.141
E/L/T	5/8/5	173/160/45	0.096
Follow up period (M)	65.8 ± 11.8	65.5 ± 12.5	0.923

Result 2: In patients aged ≧45 years, the odds ratio of HCC new growth was 12.7, baseline ALT < 200 (IU/L) was 3.9, and liver cirrhosis was 5.6.

Hepatoma new growth odds ratio according to patients who was treated and follow up more than 2 years

Characteristics	Frequency of patients with HCC	Univariate analysis OR (95% CI)	p-value
Male, n (%)	300 (5.0%)	1.60 (0.47-5.41)	0.580
Age ≧45, n (%)	227 (7.5%)	12.7 (1.70-90.9)	0.001
Baseline ALT < 200(IU/L), n (%)	223 (6.7%)	3.88 (1.14-13.2)	0.026
Baseline AST < 200(IU/L), n (%)	277 (5.4%)	2.15 (0.63-7.28)	0.294
Pretreatment	72 (8.3%)	2.25 (0.87-5.78)	0.112
Liver cirrhosis, n (%)	126 (10.3%)	5.57 (2.03-15.29)	0.000

HCC, hepatoma; n (%), patient number and HCC percentage; OR, odds ratio

Results 3: Most HCC developed in the right side of the liver (14/18), singled number (13/18), tumor sized (1.9 ± 0.7 cm), and T1 staging (14/18, TNM system), and the atypical HCC occupying 93%.

Case No.	Sex	Age	L C	Time to HCC (m)	Tumor Number	Tumor Location	Tumor size cm	TMN	LI-RADS
1	M	49	+	8	1	R	1.5	T1	LR3
2	M	44	-	44	1	R	1.8	T1	LR4
3	M	53	-	50	1	R	1.9	T1	NC
4	M	45	+	46	1	R	2.5	T1	LR4
5	M	52	+	69	2	R	1.8	T2	LR4
6	M	52	+	7	1	L	2.4	T1	LR4
7	M	54	+	12	2	R	1.7	T2	LR3
8	M	60	-	21	1	L	2.1	T1	LR4
9	M	55	+	25	1	R	1.8	T1	LR3
10	M	54	+	29	1	L	1.3	T1	LR4
11	F	70	-	1	1	R	3.2	T1	LR5*
12	M	52	+	16	1	R	1.5	T1	LR3
13	M	56	+	15	3	R	1.0	T2	LR3
14	M	51	+	30	1	R	2.2	T1	LR4
15	M	48	-	38	M	R	1.0	T4	NC
16	F	58	+	35	1	R	1.6	T1	LR4
17	M	46	+	25	1	L	3.6	T1	LR5
18	F	51	+	33	M	R	1.5	T2	NC

CONCLUSION:

1. Long-term nucleos(t)ide analogue therapy recipients older than 45 years and those with baseline liver cirrhosis and low baseline ALT levels were at a high risk of HCC.
2. Careful regular AFP and image study for these patients is the gold standard for early HCC detection.
3. High percentage atypical HCC image by CT scan might disturb clinical doctors to do decision making.