Hepatocellular Carcinoma Patients May Benefit From Postoperative Huaier Aqueous Extract After Liver Transplantation

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ABSTRACT

Background. Liver transplantation has been the first choice for most early- or intermediate-stage hepatocellular carcinoma (HCC) cases. However, postoperative anti-HCC therapies remain controversial. In this study, we aimed to evaluate the safety and efficacy of Huaier aqueous extract (Jinke), when used as an adjuvant postoperative anti-HCC therapy.

Methods. We retrospectively collected the clinical and follow-up data of HCC patients who underwent liver transplantation at our center. We divided them into 2 groups: a control liver transplantation group and a Huaier treatment group. The baseline characteristics, tumor characteristics, intraoperative data, postoperative recovery, long-term overall survival rate, and tumor-free survival rate were compared between the 2 groups.

Results. Fifty-three patients were included in our study, including 28 patients who underwent postoperative Huaier therapy and 25 patients who underwent liver transplantation without postoperative Huaier therapy. The baseline and tumor characteristics were similar between the 2 groups. None of the patients in the Huaier group experienced any severe adverse events. The long-term predictive overall survival was similar between the 2 groups ($P = .202$). However, the Huaier group had a higher predictive tumor-free survival rate than the control group ($P = .029$). And the 10- and 30-month predictive tumor recurrence rates were 17.9% and 35.7% in the Huaier group, which were significantly lower than those in the control group (60% and 64%; $P < .05$).

Conclusions. HCC patients may benefit from Huaier therapy after liver transplantation, but a longer follow-up time and larger cohort study may be necessary to be sure.

HEPATOCELLULAR CARCINOMA (HCC) is the 5th leading cancer type worldwide and the 2nd leading cause of cancer-related deaths. Most of the disease burden in Asia and Africa is due to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; there are >750,000 cases diagnosed and 1 million deaths annually, and China accounts for >50% of HCC cases worldwide [1]. The radical therapies for HCC include liver transplantation (LT), hepatic resection, and radiofrequency ablation (RFA) [2]. The efficacy of RFA in HCC has been demonstrated in small cases (diameter ≤3 cm) but not in larger cases [3], even though most HCC cases were diagnosed at the intermediate or advanced stage. LT could be viewed as the optimal treatment for HCC because LT treats the tumor and the underlying liver disease [4–6]. However, even with radical LT, HCC recurrence ranges from 18.9% to 78.3% and is the leading reason for HCC morbidity [7]. Therefore, postoperative adjuvant therapies, such as TACE, systematic chemotherapy, and sorafenib, may be automatic choices for these cases. However, there is still controversy regarding these adjuvant therapies [8–10].

Some medicines, such as Huaier, have been clinically used to treat various cancers, such as hepatocellular carcinoma [11], breast cancer [12], lung cancer [13], colorectal cancers [14], and other system cancers [15]. However, the safety and efficacy of Huaier in preventing recurrence of HCC after LT are still unclear, even though some studies

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Table 1. Baseline Demographic and Tumor Characteristics of the Two Groups of Patients

Characteristic	Huaier Group (n = 28)	Control Group (n = 25)	*P* Value
Age (y)	49.9 ± 8.4	50.3 ± 10.1	.890
Sex (M/F)	27/1	25/0	.345
Weight (kg)	66.6 ± 9.8	69.5 ± 8.6	.272
Height (cm)	166.6 ± 5.6	170.4 ± 4.3	.014
BMI (kg/m^2)	23.9 ± 3.0	24.8 ± 4.2	.402
BMI <26/≥26	22/6	21/4	.617
Cirrhosis etiology (HBV/non-HBV)	28/0	23/2	.131
HBV-DNA <1,000/≥1,000	20/8	13/12	.149
Child score (A/B/C)	11/8/9	10/9/6	.680
Total bilirubin (μmol/L)	45.0 ± 26.8	46.3 ± 17.7	.299
Albumin (g/L)	31.5 ± 10.9	30.2 ± 14.9	.181
Hemoglobin (g/L)	105.2 ± 33.4	112.3 ± 29.9	.351
Creatinine (μmol/L)	77.4 ± 12.5	81.4 ± 10.2	.217
Platelet count (10^3/μL)	101.5 ± 53.1	103.2 ± 62.9	.862

Abbreviations: BMI, body mass index; HBV, hepatitis B virus.

have demonstrated the efficacy of Huaier when used as an adjuvant therapy in combination with other therapies, such as TACE [16], RFA [11], and liver resection [11]. Therefore, in the present study, we aimed to evaluate the safety and efficacy of Huaier in treating HCC as a postoperative adjuvant therapy after LT.

PATIENTS AND METHODS

We collected data on HCC patients who underwent LT from January 2009 to August 2014 at our center. The following were the inclusion criteria: age 18–70 years, HCC diagnosed by means of pathology, Child A or B liver function, Eastern Cooperative Oncology Group score of 0–1, undergoing LT, no preoperative or postoperative adjuvant therapy except Huaier, and available for follow-up after the operation. The following were the exclusion criteria: patients with impaired heart or lung function who could not tolerate LT, HCC with multiple targets that could not be treated by LT, HCC with main hepatic vein or portal vein thrombosis or extrahepatic metastasis, HCC with a postoperative diagnosis of biliary carcinoma or other mixed cell liver cancer, patients who underwent other radical therapies, such as RFA or liver resection, and patients who received other postoperative therapies, such as sorafenib. Based on the inclusion and exclusion criteria, 53 HCC patients were included in the present study. We divided them into 2 groups according to postoperative adjuvant therapy, namely, the Huaier group (28 cases) and the control group (25 cases). Then, comparisons were made between the 2 groups regarding baseline characteristics, tumor characteristics, intraoperative data, postoperative recovery, and, particularly, long-term follow-up results, including the patients' overall survival, tumor-free survival, and tumor recurrence rates.

The diagnosis of HCC in the TACE group was based on a serum hepatitis virus test, 2 imaging scans (contrast-enhanced ultrasound, double-phase helical computerized tomographic [CT] scan, or magnetic resonance imaging), and the serum alpha-fetoprotein (AFP) level. For the LT patients, HCC was retrospectively demonstrated by means of histopathologic examination. The chief physician or deputy chief physician, with >20 years of LT experience, performed the surgeries at our center. All surgical procedures were performed with the use of general anesthesia. The details of the living- or deceased-donor LT were described in our previous study [5].

All patients underwent bimonthly follow-up at the outpatient clinic for the first six months after discharge from the hospital as

Table 2. Comparison of Tumor Characteristics Between the Two Groups of Patients

Characteristic	Huaier Group (n = 28)	Control Group (n = 25)	*P* Value
AFP level (ng/mL)	984.6 ± 4,325.6	4,901.3 ± 20,416.4	.335
0–800	24	15	.036
>800	4	10	
Tumor number	1.5 ± 0.9	1.7 ± 1.2	.465
1	20	16	.546
2–3	6	6	
Multiple	2	3	
Overall tumor diameter (cm)	6.0 ± 3.3	6.7 ± 2.7	.196
Largest tumor diameter (cm)	4.9 ± 3.1	6.1 ± 2.8	.167
BCLC stage (A/B)	19/9	12/13	.147
NLR	2.7 ± 2.5	3.2 ± 3.8	.567
0–4	23	21	.859
>4	5	4	
Tumor differentiation (good/moderate/poor)	10/11/7	8/10/7	.754
Microvascular invasion (yes/no)	10/18	8/17	.778

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.