A Randomized Controlled Trial of Licartin for Preventing Hepatoma Recurrence After Liver Transplantation

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Orthotopic liver transplantation (OLT) is the only curative therapy of HCC with underlying cirrhosis, but due to HCC metastasis and recurrence, its benefit is limited to a small population who meet the strict selection criteria. We previously reported that Licartin ([131I]mAb HAb18G/CD147) was safe and effective in treating HCC patients, and its antigen, HAb18G/CD147, was closely related to HCC invasion and metastasis. Here, we reported a randomized controlled trial to assess the post-OLT antirecurrence efficacy of Licartin in advanced HCC patients. We randomized 60 post-OLT patients with HCC, who were at tumor stage 3/4 and outside the Milan criteria before OLT, into 2 groups. Three weeks after OLT, the treatment group received 15.4 MBq/kg of Licartin, while the control group received placebo intravenously for 3 times with an interval of 28 days. At 1-year follow-up, the recurrence rate significantly decreased by 30.4% \((P = 0.0174)\) and the survival rate increased by 20.6% \((P = 0.0289)\) in the treatment group, compared with those in the control group. For the control group versus the treatment group, the hazard ratio for recurrence was 3.60 (95% confidence interval [CI], 1.50-8.60) and that for death was 3.87 (95% CI, 1.23-12.21). Licartin treatment also resulted in an earlier decreased AFP level and a longer time of normal AFP level than placebo \((P = 0.0016)\). No Licartin-related toxic effects were observed. Conclusion: Licartin is a promising drug for preventing post-OLT tumor recurrence in advanced HCC patients excluded by the currently strict criteria for OLT. HAb18G/CD147 can be a good drug target. (Hepatology 2007;45:269-276.)

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Hepatocellular carcinoma is the most common type of primary liver cancer and ranks sixth among cancers as a cause of death worldwide.1 It is a highly malignant tumor characterized by rapid progression, poor prognosis, and frequent tumor recurrence. It has an annual incidence rate of 564,000 cases, and 55% of those are in China.2 The mean natural survival time was reported to be only 3-6 months due to the rapid progression of tumor, especially the spread and metastasis.3,4 Surgery is the preferred treatment, but less than 20% of patients have the chance to be treated surgically.
after diagnosis. Even then, postoperation prognosis is poor because of the high recurrence rate (3-year recurrence, 50%-70% and even higher).3,5,6 For the majority of patients with HCC with unresectable tumors, best supportive care and systemic chemotherapy are the common choices for palliative treatment. However, the prognosis for these patients is still poor.7 Orthotopic liver transplantation (OLT) is believed to be the only possible curative treatment choice, because it replaces the malignant and premalignant cirrhotic liver. Because of the poor outcome in advanced HCC patients (recurrence, 80%; 5-year survival, 30%-40%), the current OLT indications are limited to either resectable HCC combined with cirrhosis (stage 1 and 2, tumor-nodes-metastasis [TNM] classification, International Union Against Cancer), or the Milan criteria, which is a single lesion \( \leq 5 \) cm in diameter or 3 lesions all \( \leq 3 \) cm in diameter, without blood or lymphoid vessel metastasis.8-11 Most patients with HCC fail to meet these limited criteria. Even among those who can, tumor progression during the waiting time for an appropriate donor leads to a more than 20% drop out.12,13 This is especially the case in China, a region with high hepatitis risk, where at least 85% of HCCs are secondary to type B hepatitis and are accompanied by cirrhosis.1 When patients are diagnosed for the first time, their HCCs have already reached stage 3 or 4. Although some researchers have attempted to extend the limited criteria for OLT, no well-accepted drug has been reported so far to effectively decrease tumor recurrence and metastasis after transplantation.14,15

We previously developed a therapeutical anti-HCC radiolabeled monoclonal antibody (mAb), Licartin (generic name, \([\text{131I]}\)metuximab injection), which was generated by labeling of \([\text{131I}]\) with murine monoclonal antibody (mAb) fragment HAb18 F(ab')2.16-18 In our phase 1/2 trials, Licartin was found to be able to concentrate in the tumor region, and was safe and effective for the treatment of HCC.19,20 It has been approved as a new drug for clinical therapy of primary HCC by China State Food and Drug Administration (Registration No. S20050039) in April 2005. Its target HAb18G/CD147, a member of CD147 family, was defined by mAb HAb18 in our lab.21,22 HAb18G/CD147 was associated with tumor recurrence—free survival or tumor recurrence and could be used as a significant independent predictor of poor prognosis in HCC patients after tumor resection or OLT.23-25 \textit{In vitro}, it was first found that HAb18G/CD147 might be positively related to HCC invasion.25-27 Later, HAb18G/CD147 was proved to be closely related to the invasive potential of HCC cells by regulating the HCC microenvironment. Blocking HAb18G/CD147 with mAb HAb18 or Licartin resulted in a significant inhibition of HCC growth and metastasis \textit{in vivo}, whereas Licartin exhibited stronger inhibitory effects than naked mAb (Chen ZN, unpublished data). To determine the clinical efficacy of Licartin on HCC metastasis and recurrence and to evaluate the drug target of HAb18G/CD147, we performed a randomized, controlled trial in patients who were definitely diagnosed with advanced HCC and who were successfully treated with OLT. With the expectation of extending the limited criteria of OLT, this study was designed for the patients who fell out of the current OLT candidate selection criteria.

**Patients and Methods.**

**Entry and Exclusion Criteria.** Eligible subjects for this study were post-OLT patients 18-70 years of age, whose Karnofsky Performance Score performance was over 60, and who had been definitely diagnosed with stage 3 or 4 HCC (TNM classification, version 5, 1997) with tumor size outside the Milan criteria before transplantation (single lesion above 5 cm in diameter, 2 lesions above 3 cm, or multiple lesions more than 3).

Exclusion criteria included severe diseases of the heart, kidney, or blood system, bilirubin level \( >2.5 \) times the upper limit of normal value, serum albumin \(<32 \) g/l (0.48 mM) before OLT, allergic history to biologic products, pregnant or breast-feeding women, or other therapies within the previous 4 weeks of the transplantation.

**Drugs.** Licartin (Chengdu Hoist Hitech Co. Ltd., Chengdu, China; and the Fourth Military Medical University, Xi’an, China) was prepared as described.19,28,29 Briefly, HAb18 mAb (IgG1) was purified from the supernatant of the H18 hybridoma cell culture. Metuximab [HAb18 F(\text{ab}’)2] was prepared by pepsin (Sigma) digestion and purified by hydrophobic interaction chromatography (Phenyl HP, Pharmacia). The purity was more than 95% as determined by HPLC (Waters 2996 Photodiode Array detector, Waters Corp.). Radiiodination of Metuximab with Na[\text{131I}] was performed according to Mather’s method.30 The labeled product was separated with Sephadex G25 gel filtration resin (Pharmacia) and the radiochemical purity was above 95% in 24 hours. The specific activity was between 173.25-288.75 MBq/ml. The final product was tested for sterility and pyrogen content according to recommended methods by the Chinese National Institute for the Control of Pharmaceutical and Biological Products.

**Randomization.** Randomization was stratified and performed by numbered containers. Eligible patients were randomly assigned 1:1 by the doctors to receive placebo (control group) or Licartin (treatment group). Single blinding was maintained by using a matching placebo.
Those administering the interventions and those assessing the outcomes remained blinded to group assignment until the data were certified for analysis.

**Treatments.** All patients in the treatment group received Licartin 3 times at an interval of 28 days (once-course treatment) beginning from the 4th week after OLT. Lugol’s liquid was given starting 3 days before treatment to block the thyroid uptake of $^{131}$I (5-7 drops/time, 3 times/day, for 10 days). When negative response to a subcutaneous injection of Metuximab was confirmed, 15.4 MBq/kg of Licartin (the total dose to each patient contained 5 mg Metuximab) was administered intravenously. Physiological saline was used as the matching placebo in the control group and administered intravenously by the same method as that in the treatment group. The packaging of Licartin and the placebo was the same but labeled with different codes. The nurses and the patients were unaware of the treatment assignment. The study was approved by the Medical Ethics Committee, and the patients provided written informed consent for the study.

In addition to the Licartin in the treatment group and the placebo in the control group, all patients under study received the same routine immunosuppression regimen of FK506/cyclosporin A, mycophenolate mofetil, and prednisone. The hepatitis B infection was treated with the same regimen of lamivudine and hepatitis B immunoglobulin. Adefovir was also used for the patients with YMDD and YIDD mutation.

**Evaluation.** Before treatment, the patients’ complete medical history was recorded and physical examination, complete blood count, hepatic and renal tests, and $\alpha$-fetoprotein (AFP) level determination were performed. Abdominal ultrasonography and whole-body computer tomography scans were also performed, with bone scintigraphy and other tests as indicated. During the treatment, patients were evaluated mainly by AFP level once every month, ultrasonograph every 2 weeks, and whole-body CT scans every month. After the treatment, the examination of AFP level and ultrasonograph were conducted the same as during the treatment but the whole-body CT scans were performed every 3 months if there was no suspect symptoms or physical signs and no abnormal results of AFP and ultrasonograph examination, and taken at any time as indicated. HCC recurrence was diagnosed mainly by (1) abnormal AFP value, that is, the pretreatment high AFP value did not decrease to the normal level or increased again after became normal, and (2) new lesions found in the CT scans. Patients in whom HCC recurrence was suspected were biopsied for histological confirmation of the recurrence. Bone scintigraphy was performed if necessary.

Complete blood count and hepatic and renal tests were conducted before and after treatment to determine toxic effects. All adverse events reported by the patients or observed by the investigators and abnormal laboratory findings were recorded and graded according to the World Health Organization toxicity scale. All adverse events and serious adverse events were recorded by the investigators whether or not they were considered drug-related. The human anti-mouse antibody was detected at the 14th day after each administration. In the event of intolerable side effects, treatment was stopped.

**Immunohistochemistry.** The expression of HAb18G/CD147 in the pretransplant HCC tissues of the patients was examined with HAb18 mAb (1:500 diluted) using Histostain-SP kits (Zymed Laboratories) according to manufacturer instructions. The negative control was established by substituting the primary antibody with mouse immunoglobulin G.

**Statistical Analysis.** The aim of this trial was to compare the recurrence rate and overall survival rate in the Licartin treatment group with those in the placebo control group. The sample size was calculated by the formula (power = 0.8) according to preliminary test data. Clinical efficacy was analyzed using the CMH chi-square test, Kaplan-Meier method, log-rank test, and multiple factor Cox regression analysis (death for nontumorous reason was considered as censor). The primary endpoint was tumor recurrence. The secondary endpoint was survival defined as the time from the first administration (3 weeks after OLT) to clinical death or to the most recent follow-up visit. Recurrence rates and survival curves of the patients were compared using the Kaplan-Meier method and analyzed using the log-rank test. All the statistical tests were 2-sided and $P < 0.05$ was considered statistically significant. The Cox regression analysis was used to assess each treatment-by-subgroup interaction. Toxic effects were evaluated with the CMH chi-square test and the Student $t$ test. The above analyses were performed using SAS 6.12 statistical software (SAS Inc., Cary, NC).

**Results**

**Study Population.** Between July 2004 and November 2004, a total of 60 eligible Chinese patients were enrolled and randomly assigned to receive placebo or 15.4 MBq/kg of Licartin intravenously 3 weeks after OLT when negative response to a subcutaneous injection of Metuximab was confirmed. All patients had stage 3 (40%) or stage 4 (60%) HCC with cirrhosis before transplantation and had undergone successful OLT (donor livers were from cadaver donors who voluntarily donated). No organs were obtained from executed prisoners. About half of the patients had portal vein
cancer thrombi. All the patients had either a single pretransplantation tumor lesion above 5 cm diameter, or 2 lesions above 3 cm diameter, or multiple lesions more than 3. A single tumor lesion was found in 8 patients of the control group (tumor size: mean $\pm$ SD 9.25 $\pm$ 2.38 cm, range 5.9 to 13 cm), and 9 patients of the treatment group (8.89 $\pm$ 1.98 cm, 6 to 12 cm). Double lesions were found in 8 patients of the control group (5 $\pm$ 1.39 cm, 3 to 7 cm; total tumor size: 7.94 $\pm$ 1.72 cm, range 5.5 to 10 cm), and 11 patients of the treatment group (4.45 $\pm$ 1.01 cm, 3 to 6.5 cm; total: 6.75 $\pm$ 1.74 cm, 5 to 11 cm). Presence of more than 3 lesions was found in 14 patients of the control group and 10 patients of the treatment group. No significant differences in the tumor size were found between the 2 arms ($P = 0.9933$). Comparison of the clinical and demographic characteristics of the patients in the 2 arms also revealed no statistically significant differences (Table 1). All the patients had a positive HAb18G/CD147 expression in their pretransplant HCC tissues by immunohistochemical analysis (Fig. 1). None of the patients dropped out, but in the control group, 1 patient died of infection 3 months after transplantation and was considered as censor (Fig. 2).

**HCC Recurrence.** Median follow-up time was 12.3 months (range = 2 to 13 months, mean = 10.99 months). Forty-four patients achieved 1-year follow-up, comprising 18 from the control group and 26 from the treatment group. At the 1-year follow-up, a total of 17 patients in the control group suffered HCC recurrence: 5 had intrahepatic recurrence, 8 had pulmonary metastasis, 3 had both, and 1 had osseous metastasis. Of 8 patients in the treatment group who suffered recurrence, 3 had intrahepatic recurrence, 4 had pulmonary metastasis, and 1 had both. By the Kaplan-Meier method, the 3-month, 6-month, 9-month, and 12-month recurrence rates in the control group were 21.3%, 46.4%, 53.5%, and 57.1%, respectively, while those in the treatment group were 10%, 23.3%, 23.3%, and 26.7%, respectively. Log-rank test showed a significant difference in the recurrence rate between the 2 arms ($P = 0.0174$) (Fig. 3). Taking into account the pretransplantation clinical stages (stage 3 or

| Table 1. Baseline Characteristics |
|-----------------------------------|
| Characteristic                     | Treatment Group (N = 30) | Control Group (N = 30) | $P$ Value* |
| Age, years                         |                           |                         |            |
| Mean $\pm$ SD                      | 44.9 $\pm$ 7.77          | 45.07 $\pm$ 8.57        | 0.9374     |
| Median                            | 44.5                      | 42.5                    |            |
| Range                             | 33-62                     | 32-62                   |            |
| Sex, no. of patients (%)           |                           |                         |            |
| Male                              | 27 (90)                   | 27 (90)                 | 1.0000     |
| Female                            | 3 (10)                    | 3 (10)                  |            |
| Type B hepatitis history, n (%)    |                           |                         |            |
| Yes                               | 26 (86.7)                 | 27 (90)                 | 0.6876     |
| No                                | 4 (13.3)                  | 3 (10)                  |            |
| Hepatic cirrhosis, n (%)           |                           |                         |            |
| Yes                               | 30 (100)                  | 30 (100)                | 1.0000     |
| No                                | 17 (56.7)                 | 16 (53.3)               |            |
| AFP (µg/l), n (%)                  |                           |                         |            |
| $\leq$20                          | 8 (26.7)                  | 8 (26.7)                | 1.0000     |
| $>$20                             | 22 (73.3)                 | 22 (73.3)               |            |
| Tumor size, n (%)                  |                           |                         |            |
| Single lesion, d $>$ 5 cm          | 22 (73.3)                 | 21 (70)                 | 0.7745     |
| Multiple lesion, d $>$ 3 cm        | 8 (26.7)                  | 9 (30)                  |            |
| TNM stage, n (%)                   |                           |                         |            |
| Stage 3                           | 12 (40)                   | 12 (40)                 | 1.0000     |
| Stage 4                           | 18 (60)                   | 18 (60)                 |            |
| Child-Pugh grading, n (%)          |                           |                         |            |
| A                                 | 14 (46.7)                 | 12 (40)                 | 0.7174     |
| B                                 | 13 (43.3)                 | 16 (53.3)               |            |
| C                                 | 3 (10)                    | 2 (6.7)                 |            |

*The treatment group was compared with the control group for differences in age of the patients using Student $t$ test of significance, while for differences in other baseline characteristics using chi-square tests. All statistical tests were 2-sided, and $P < 0.05$ were considered statistically significant. Abbreviations: PVAT, portal vein cancer thrombi; AFP, $\alpha$-fetoprotein; d, diameter of the lesion; TNM, tumor-nodes-metastasis classification.
4) and AFP levels (20-500; ≥500 µg/l), multiple factor Cox regression analysis also showed a significant difference of recurrence rate between the 2 arms (P = 0.004). The hazard ratio for recurrence was 3.60 [95% confidence interval (CI) = 1.50 to 8.60] for the control group versus the treatment group. High AFP level was associated with high recurrence risk (hazard ratio = 4.37; 95% CI = 1.90 to 10.05; P = 0.0005).

Survival. At the 1-year follow-up, total 11 patients in the control group and 4 patients in the treatment group died of HCC recurrence or metastasis. With Kaplan-Meier method, the 3, 6, 9, and 12-month overall survival rates in the control group were 93.1%, 75.9%, 69.0%, and 61.9%, respectively, while those in the treatment group were 100%, 96.7%, 90%, and 82.5%, respectively. Log-rank test showed a significant difference in the survival rate between the 2 arms (P = 0.0289) (Fig. 4). Taking into account the pretransplantation clinical stages and AFP levels, multiple factor Cox regression analysis also showed a significant difference of survival rate (P = 0.0211). The hazard ratio for death was 3.87 (95% CI = 1.23 to 12.21) for the control group versus the treatment group. A higher pretransplantation AFP level was associated with poorer survival (hazard ratio = 3.55; 95% CI = 1.26 to 10.04; P = 0.0169).

AFP Level. AFP level is an important predictor of HCC prognosis. In this study, the pretransplantation AFP level was found to be associated with both HCC recurrence and survival. After the treatment, the elevated AFP value (>20 µg/l) in the treatment group decreased to normal level sooner than that in the control group (Fig. 5). Log-rank test showed a significant difference in the negative maintenance rate (defined as the maintenance time after the elevated AFP level became normal) between the 2 arms (P = 0.0016). The 1-year negative maintenance rate of control and treatment groups was 44.08% and 87.82%, respectively, with Kaplan-Meier method. These data suggest a better prognosis for the patients in the treatment group than those in the control group.

Toxicity Profiles. After treatment, no adverse events were reported or observed, including fever, nausea, vomiting, anorexia, stomach ache, or diarrhea. One patient in the control group died of infection after OLT, which was reported as a serious adverse event. Considering the basically abnormal levels of the laboratory tests after OLT, we graded the values of these parameters obtained from each patient before and after treatment by World Health Organization criteria and compared them between the 2 arms. The compared parameters included the count of white blood cells, neutrophils, and platelets, and the levels of ALT, AST, alkaline phosphatase, direct bilirubin (DBIL), total bilirubin, albumin, urea nitrogen, and cre-
aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

was observed in this study. effects, death, or human anti-mouse antibody response was found. Altogether, no treatment-related toxic in the control (Tables 3 and 4). During the whole obser-

vantinine. Except for DBIL and albumin, there were no significant differences between the 2 arms in the grades of these parameters either before or after treatment, or in individual patient changes of grades (pretreatment grade minus posttreatment grade, Table 2). For DBIL and albumin, significant differences were found in pretreatment ($P_{DBIL} = 0.0249$) or posttreatment grade ($P_{albumin} = 0.0000$) and in the individual patient changes of grade ($P_{DBIL} = 0.0089, P_{albumin} = 0.0003$), together with the descriptive data, suggesting a more significantly improved DBIL and albumin level in the treatment group than that in the control (Tables 3 and 4). During the whole observation term, no positive human anti-mouse antibody response was found. Altogether, no treatment-related toxic effects, death, or human anti-mouse antibody response was observed in this study.

Discussion

Our preclinical work and phase 1/2 trials have demonstrated that Licartin can accumulate in HCC lesions and is safe and effective in the treatment of HCC.17-20,32,33 In the present study, Licartin was well tolerated and effective in decreasing the recurrence of HCC and prolonging the survival of patients with advanced HCC after OLT. Compared with that of the control group, 1 course treatment of Licartin significantly reduced the 1-year recurrence rate by 30.4%, and significantly increased the 1-year survival rate by 20.6%. The pretransplantation AFP level was found to be associated with both recurrence and survival. The patients in the treatment group obtained an earlier decrease of the basal abnormal AFP level and a longer period of normal AFP level than the patients in the control group, suggesting a better prognosis.

OLT is believed to be the only possible curative therapeutic option for unresectable HCC with underlying cirrhosis. But some discouraging experiences and the lack of donor liver grafts require the medical community to accurately define the patient population or to develop some multimodality therapy, such as pretransplant loco-regional treatment, pretransplant, intratransplant, and posttransplant systemic chemotherapy, and immunosuppressive protocol.34 Pretransplant loco-regional treatment has to some extent prevented tumor progression in pa-

| Table 2. Number of Patients With Individual Changes of Grades* Regardless of Drug Related |
|-----------------------------------------------|
| Treatment Group | Control Group |
| (N = 30) | (N = 30) |
| Parameters | Pretreatment | Posttreatment | Pretreatment | Posttreatment |
| | + | 0 | −1 | −2 | −3 | + | 0 | −1 | −2 | −3 |
| White blood cell | 2 | 23 | 3 | 2 | 0 | 2 | 24 | 3 | 1 | 0 |
| Neutrophil | 1 | 25 | 4 | 0 | 0 | 1 | 27 | 2 | 0 | 0 |
| Platelet | 9 | 16 | 5 | 5 | 0 | 4 | 19 | 4 | 0 | 3 |
| ALP | 17 | 9 | 4 | 0 | 0 | 21 | 9 | 0 | 0 | 0 |
| AST | 5 | 20 | 4 | 1 | 0 | 5 | 22 | 3 | 0 | 0 |
| Total bilirubin | 14 | 14 | 2 | 0 | 0 | 9 | 17 | 4 | 0 | 1 |
| Direct bilirubin | 22 | 8 | 0 | 0 | 0 | 15 | 10 | 4 | 0 | 1 |
| Creatinine | 0 | 30 | 0 | 0 | 0 | 2 | 26 | 2 | 0 | 0 |
| Urea nitrogen | 1 | 26 | 3 | 0 | 0 | 1 | 23 | 5 | 1 | 0 |

*The individual patient changes of grades were calculated as pretreatment grade subtracting posttreatment grade. +, grade improved; 0, no changes; −1, −2 and −3, grade aggravated by 1, 2 and 3 grades. Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

| Table 3. Group Comparison of Direct Bilirubin (DBIL) Level |
|----------------------------------------------------------|
| WHO Grade of DBIL Level | Treatment Group | Control Group | P Value* |
| | (n = 30) | (n = 30) | |
| Pretreatment grade, n (%) | 0 | 6 (20) | 14 (46.7) | 0.0249 |
| I | 9 (30) | 8 (26.7) | |
| II | 7 (23.3) | 4 (13.3) | |
| III and IV | 8 (26.7) | 4 (13.3) | |
| Posttreatment grade, n (%) | 0 | 24 (80) | 23 (76.7) | 0.6144 |
| I | 5 (16.7) | 3 (10) | |
| II | 1 (3.3) | 2 (6.7) | |
| III and IV | 0 (0) | 2 (6.7) | |
| Individual patient changes of grades† n (%) | −3 | 0 (0) | 1 (3.3) | 0.0089 |
| −1 | 0 (0) | 4 (13.3) | |
| 0 | 8 (26.7) | 10 (33.3) | |
| 1 | 8 (26.7) | 10 (33.3) | |
| 2 | 10 (33.3) | 3 (10) | |
| 3 | 4 (13.3) | 2 (6.7) | |

*The treatment group was compared with the control group for differences in WHO grade of DBIL level of the patients using CMH chi-square tests of significance. All statistical tests were 2-sided, and P values < 0.05 were considered statistically significant. †Individual patient changes of grades = pretreatment grade − posttreatment grade.

| Table 4. Group Comparison of Albumin Level |
|-------------------------------------------|
| Albumin Level (g/l) | Treatment Group | Control Group | P Value* |
| | (N = 30) | (N = 30) | |
| Pretreatment level | Mean ± SD | 39.15 ± 5.14 | 39.84 ± 3.52 | 0.5428 |
| | Median | 38.85 | 39.5 | |
| | Min, Max | 31.4, 51.5 | 32.9, 48 | |
| Posttreatment level | Mean ± SD | 46.41 ± 4.75 | 40.46 ± 5.18 | 0.0000 |
| | Median | 45.95 | 41.15 | |
| | Min, Max | 37.4, 57.5 | 26.8, 51.5 | |
| Individual patient changes of levels‡ | Mean ± SD | −7.26 ± 7.38 | −0.61 ± 5.78 | 0.0003 |
| | Median | −7.65 | −0.95 | |
| | Min, Max | −25.4, 11.7 | −13, 12.7 | |

*Treatment group was compared with control group for differences in albumin level of the patients, using the Student t test of significance. All statistical tests were 2-sided, and P < 0.05 was considered statistically significant. ‡Individual patient changes of levels = pretreatment grade − posttreatment grade.
tients on the waiting list for transplantation, other multimodality protocols have either fallen out of favor or need further randomized controlled trials to confirm their effects, with the emphasis on preventing recurrence by imposing strict selection criteria. Milan criteria were widely used and warranted good outcome in a strictly selected but small group of patients with HCC. At present, about 10% recurrence was seen in those patients meeting the Milan criteria, while rates as high as 50% were reported in those patients with tumors more than 5 cm in size and with portal vein invasion. In the present study, the 1-year recurrence rate in control-group was 57.1%, which was similar to that reported previously (50%), while that in the treatment group was 26.7%, which was significantly decreased compared with that in the control group.

For a patient with HCC treated by transplantation, 1-year survival rates of 77%-80% could be expected when the Milan criteria is met. Recently, some researchers have questioned whether the criteria might be safely extended. Using extended criteria (single tumor less than 6.5 cm in size, or more than 3 tumors, the largest less than 4.5 cm, and a total diameter for all tumors less than 8 cm), Yao et al. reached a 1-year survival of 90%. But in China, it was reported that all the patients with stage 3 or 4 HCC suffered recurrence in 3-6 months after OLT, and the average survival time was 4.5 months. In this study, all the patients had stage 3 or 4 HCCs and large-size tumors or more lesions. Posttransplant Licartin treatment achieved the 1-year survival rate of 82.5%, which was similar to the current expected 1-year survival rate for a patient with HCC who has been transplanted (77%-80%).

To our knowledge, the present study is the first prospective randomized controlled trial to evaluate the clinical efficacy of antibody targeting radioimmunotherapy in preventing tumor recurrence and prolonging survival after OLT in patients with advanced HCC with larger tumor size and more tumor lesions than that in Milan criteria or in some reported expanded criteria. The clinical efficacy of Licartin may be attributed to 2 possible mechanisms. HAb18G/CD147, the target antigen, was recently found to be involved in HCC invasion and metastasis in vitro and in vivo. Licartin could specifically bind to HAb18G/CD147 and effectively inhibit HCC metastasis (Chen ZN, unpublished data). In the present work, Licartin may exert its effect by blocking the function of HAb18G/CD147. Furthermore, it may also function through its high affinity and specific binding to HAb18G/CD147 on HCC cells and the carried radionuclide. It is generally believed that the high risk factor for HCC metastasis and recurrence is the escaped tumor cells in the circulation. Licartin may efficiently target and bind to the escaped HCC cells in the circulation or homing cells to liver by the antigen-antibody specific recognition and thus allow the carried radionuclide to destroy the target site and to kill the cells.

In this study, the 1-year recurrence in the treatment group (26.7%) is still higher than that seen with Milan criteria (10%), but the 1-year survival in the treatment group (82.5%) is comparable with that seen with Milan criteria (77%-80%). Because most patients with HCC fail to meet Milan criteria, this study provides information about whether they can benefit from OLT when they have no other better therapeutic choices and have a suitable donor liver. The combination of Licartin with other treatments, such as chemotherapy, may also be a promising direction in antirecurrence therapy of advanced HCC after OLT. If this evidence is confirmed, the current strict selection criteria may be safely expanded so that more HCC patients could benefit from OLT and enjoy a prolonged life.

In conclusion, we show that HAb18G/CD147 can be a good drug target and Licartin is a promising new anti-metastasis and recurrence agent for treating advanced HCC after OLT.

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