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Hepatic artery injection of ^{131}I-metuximab combined with transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: a prospective non-randomized, multicenter clinical trial

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Running title: A clinical trial of TACE+^{131}I-metuximab

ABSTRACT

This prospective non-randomized, multicenter clinical trial was performed to investigate efficacy and safety of ^{131}I-labeled metuximab in adjuvant treatment of unresectable hepatocellular carcinoma.

Methods: Patients were assigned to treatment with transcatheter arterial chemoembolization (TACE) combined with ^{131}I-metuximab or TACE alone. The primary outcome was overall tumor recurrence. The secondary outcomes were safety and overall survival.

Results: The median time to tumor recurrence was 6 months in the TACE+^{131}I-metuximab group (n = 160) and 3 months in the TACE group (n = 160) (hazard ratio, 0.55; 95% confidence interval, 0.43 to 0.70; $P < 0.001$). The median overall survival was 28 months in the TACE+^{131}I-metuximab group and 19 months in the TACE group (hazard ratio, 0.62; 95% confidence interval, 0.47 to 0.82; $P = 0.001$).

Conclusions: TACE+^{131}I-metuximab showed a greater anti-recurrence benefit, significantly improved the 5-year survival of patients with advanced hepatocellular carcinoma, and was well tolerated by patients.

Keywords: ^{131}I-labeled metuximab; transcatheter arterial chemoembolization; hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related death worldwide (*1*). Systematic treatment for advanced HCC remains of great concern (*2*). Although transcatheter arterial chemoembolization (TACE) is frequently used for the treatment of HCC, it fails to lead to a complete response in most patients, especially in the middle or late stage when the tumor is larger than 5 cm. ^{131}I-metuximab is a radioimmunoconjugate generated by labeling metuximab directed against CD147 which is associated with hepatocarcinogenesis and tumor metastasis (*3*,*4*). Previous studies have shown the beneficial treatment effects of ^{131}I-metuximab combined with TACE in patients with HCC, and no severe toxicities were reported in these studies (*5,6*). In this study, we conducted a prospective clinical trial to evaluate the therapeutic efficacy of ^{131}I-metuximab combined with TACE in patients with unresectable HCC.

MATERIALS AND METHODS

Patient Population and Study Design

Between November 2, 2011 and December 31, 2015, a prospective, non-randomized concurrent controlled, multicenter, open-label clinical trial was performed in patients with unresectable HCC at four medical centers in China. Patients diagnosed with unresectable HCC according to the guidelines of the American Association for the Study of Liver Diseases were assigned to the TACE+^{131}I-metuximab or TACE group (*7*). To minimize bias, we matched patients between the two groups based on age, sex, Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh class, and Eastern Cooperative Oncology Group (ECOG) score. The Medicine Ethics Committee of Peking University Cancer Hospital approved this study and all subjects signed a written informed consent. The study was registered at http://www.chictr.org (ChiCTR-ONRC-11001664).

Inclusion and Exclusion Criteria

The eligibility criteria included men and women aged 18 to 80 years, with confirmed HCC according to the criteria of the American Association for the Study of Liver Diseases, BCLC classification of stage B or C, ECOG performance status ≤ 2, Child-Pugh liver function class A or B, platelet count ≥ 70×10^9 per liter, white blood cell count ≥ 3×10^9 per liter, no organ dysfunction, and a life expectancy of ≥ 3 months. Patients who were allergic to biological products, pregnant, or lactating or had thyroid hypofunction, brain metastases, or a positive initial skin test for metuximab were excluded. The selection criteria and algorithm used to determine patient grouping were completely and strictly consistent across different centers.

Drugs and Treatments

The patients in both groups underwent standard TACE treatment according to the Clinical Guidelines for the Diagnosis and Treatment of Primary Liver Cancer, China 2011. For TACE administration, a catheter was placed into the proper hepatic artery through the femoral artery using the Seldinger technique. For hepatic lesions with a rich blood supply, hepatic arterial chemoembolization (pharmorubicin [40] mg and ultra-fluid lipiodol [3-20 mL] were administered according to the tumor size) was conducted first. After embolization, 750 mg diluted 5-fluorouracil was perfused via a 2.4-F microcatheter. In the TACE+^{131}I-metuximab group, patients were transferred to the nuclear medicine ward after TACE, and 27.75 MBq/kg of ^{131}I-metuximab was administered into the proper hepatic artery (*8*).

Sample Size

According to our previous research, the assumptions were a 1-year recurrence rate of 50% in the TACE+^{131}I-metuximab group and 69.5% in the TACE group. We needed 141 patients in each group (power of 90%,

two-sided significance level of 5%, 1:1 allocation) to detect a 19.5% difference in recurrence rate between groups. We also estimated and added 10% to account for patients who might have been lost to follow-up. Based on these calculations, we estimated that we needed to enroll at least 155 patients.

Outcomes and Evaluation

The primary outcome was overall tumor recurrence, which was measured from the date of the first TACE after allocation until the first documented tumor recurrence event and based on the assessment criteria of the modified Response Evaluation Criteria in Solid Tumors. The secondary outcomes were safety and overall survival. Safety was assessed according to the National Cancer Institute's Common Terminology Criteria for adverse effects (version 4.0).

Statistical Analysis

The analyses of overall recurrence and overall survival were performed using the Kaplan-Meier method and a log-rank test using a two-sided overall alpha level of 0.05. *P* values were two-sided and less than 0.05 considered statistically significant. Statistical analyses were performed using SPSS software (version 16.0; IBM Corp., Armonk, NY, USA).

RESULTS

We evaluated 441 Chinese patients with a confirmed diagnosis of HCC. Based on the inclusion and exclusion criteria, 320 patients were enrolled in our study, with 160 (50%) patients assigned to the TACE+^{131}I-metuximab group and 160 (50%) patients assigned to the TACE group (Fig. 1). Baseline patient characteristics was

showed in Supplemental Table 1 and Supplemental Table2.

The study was completed on March 30, 2020. The median follow-up period was 17 months (Interquartile Range, 8–30 months). At that time, 121 (76%) patients in the TACE+^{131}I-metuximab group and 151 (94%) patients in the TACE therapy group had developed tumor recurrence. In the TACE+^{131}I-metuximab group, 100 (63%) patients had new intrahepatic recurrence, 102 (64%) patients had intrahepatic residual recurrence, and 52 (33%) patients had extrahepatic metastasis, compared with 128 (80%), 130 (81%), and 98 (61%) patients in the TACE group, respectively, which was significantly different between the two groups (Supplemental Table 3). The median time to overall tumor recurrence was significantly longer in the TACE+^{131}I-metuximab group than in the TACE group (6 months vs. 3 months; hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.43 to 0.70; $P < 0.001$). The log-rank test revealed a significant difference in the recurrence rates between the two groups ($P < 0.001$) (Fig. 2A). The significant anti-recurrence benefits represented a relative reduction of 23% in tumor recurrence at 12 months (Supplemental Table 4). An exploratory multivariate analysis using the Cox proportional hazards model identified seven baseline characteristics that were prognostic indicators of overall tumor recurrence. After adjusting for these prognostic factors, the effect of ^{131}I-metuximab on overall recurrence remained significant (HR, 0.46; 95% CI, 0.35 to 0.61; $P < 0.001$). A pre-specified subgroup analysis showed an anti-recurrence benefit for TACE+^{131}I-metuximab over TACE alone in most of the subgroups analyzed (Fig. 3A).

At the time of the final analysis, 93 (58%) patients in the TACE+^{131}I-metuximab group and 113 (71%) patients in the TACE group had died. The median overall survival was significantly longer in the TACE+^{131}I-metuximab group than in the TACE group (28 *vs*. 19 months; HR 0.62; 95% CI, 0.47 to 0.82; $P = 0.001$). The log-rank test revealed a significant difference in survival rate between the two groups ($P = 0.001$) (Fig. 2B). The survival rates were shown in Supplemental Table 4. An exploratory multivariate analysis using the Cox proportional hazards

model identified seven baseline characteristics that were prognostic indicators of overall survival. After adjusting for these prognostic factors, the effect of TACE+^{131}I-metuximab on overall survival was significantly different from that of TACE alone (HR, 0.55; 95% CI, 0.41 to 0.74; $P < 0.001$). A pre-specified subgroup analysis showed a survival benefit for TACE+^{131}I-metuximab over TACE alone in the BCLC stage C, Child–Pugh class A, ECOG score 0, extrahepatic spread (no), macroscopic vascular invasion (no), size range of tumor, No. of tumors (single), and previous therapy (no) subgroups (Fig. 3B).

The reported adverse effects for patients receiving TACE+^{131}I-metuximab were predominantly grade 1 or 2 in constitutional symptoms and gastrointestinal events, such as fever, pain, vomiting, and fatigue (Supplemental Table 5). Grade 3 laboratory abnormalities included a decrease in white blood cell count (5% in the TACE+^{131}I-metuximab group *vs*. 0.6% in the TACE group, $P = 0.04$). No serious adverse effects and treatment-related deaths were observed. Taken together the descriptive data suggested that ^{131}I-metuximab as a radioimmunotherapeutic agent did not pose a hazard to hepatic function in the TACE+^{131}I-metuximab group.

At the time of analysis, 206 (64%) patients in the two groups had died. A total of 93 (58%) patients in the TACE+^{131}I-metuximab group died, and 113 (71%) patients in the TACE group died. The causes of death were shown in Supplemental Table 6. The chi-square test showed a significant difference between the two groups ($P = 0.018$).

DISCUSSION

TACE is still an important therapy for unresectable HCC, but the median recurrence time is reported to be 3 months (*9*). Our study indicated that ^{131}I-metuximab combined with TACE delayed tumor recurrence by 3 months in patients with unresectable HCC and preserved liver function compared with TACE alone. The results also demonstrated that the TACE group had a higher risk of recurrence and extrahepatic metastasis, and especially early

recurrence relative to the TACE+^{131}I-metuximab group, which suggested that TACE alone could manage the existing intrahepatic tumor and ^{131}I-metuximab could inhibit tumor recurrence and metastasis.

In this study, tumor parenchyma was embolized with lipiodol instead of particles, while the main tumor supplying artery was preserved. Therefore the formation of tumor tortuous blood circulation was relatively less, which was conducive to subsequent interventional therapy. We did not use ^{131}I-metuximab alone for comparison based on ethical considerations. Because of the radioactivity of the drug, we could not perform a double-blind study for the safety of patients and doctors. This study had several limitations, including mixed populations of previously treated and untreated individuals, a lack of double blinding and randomization, which may result in a subjective bias. In addition, when recurrence was detected, the patients were treated with various treatments which may affect the results of overall survival. Nevertheless, caution should be exercised when analyzing the results of a non-randomized concurrent control trial; well-designed, prospective randomized controlled trials remain necessary.

CONCLUSION

The combination of TACE and ^{131}I-metuximab represents a logical, new, and encouraging approach for neoadjuvant therapy for advanced HCC. ^{131}I-metuximab is associated with a significant reduction in the risk of recurrence and death and is well tolerated in patients with unresectable HCC. The combination of TACE and ^{131}I-metuximab using the present regimen may postpone relapse in a selected group of patients with unresectable HCC and is an effective palliative treatment option.

DISCLOSURES

This work was supported by a grant from the National Science and Technology Major Project (2012ZX10002-015), State Key Laboratory of Cancer Biology (CBSKL2019ZZ16), and Natural Science Foundation of Shaanxi Province (2020SF-252). No other potential conflicts of interest relevant to this article are reported.

KEY POINTS

QUESTION:

Can ^{131}I-metuximab combined with TACE be used as an effective palliative therapy in patients with unresectable HCC?

PERTINENT FINDINGS:

^{131}I-metuximab combined with TACE showed a greater anti-recurrence benefit and significantly improved the 5-year survival of patients with advanced HCC over TACE alone and was well tolerated.

IMPLICATIONS FOR PATIENT CARE:

The combination of TACE and ^{131}I-metuximab using the present regimen postpones relapse in a selected group of patients with unresectable HCC and is an effective palliative treatment option.

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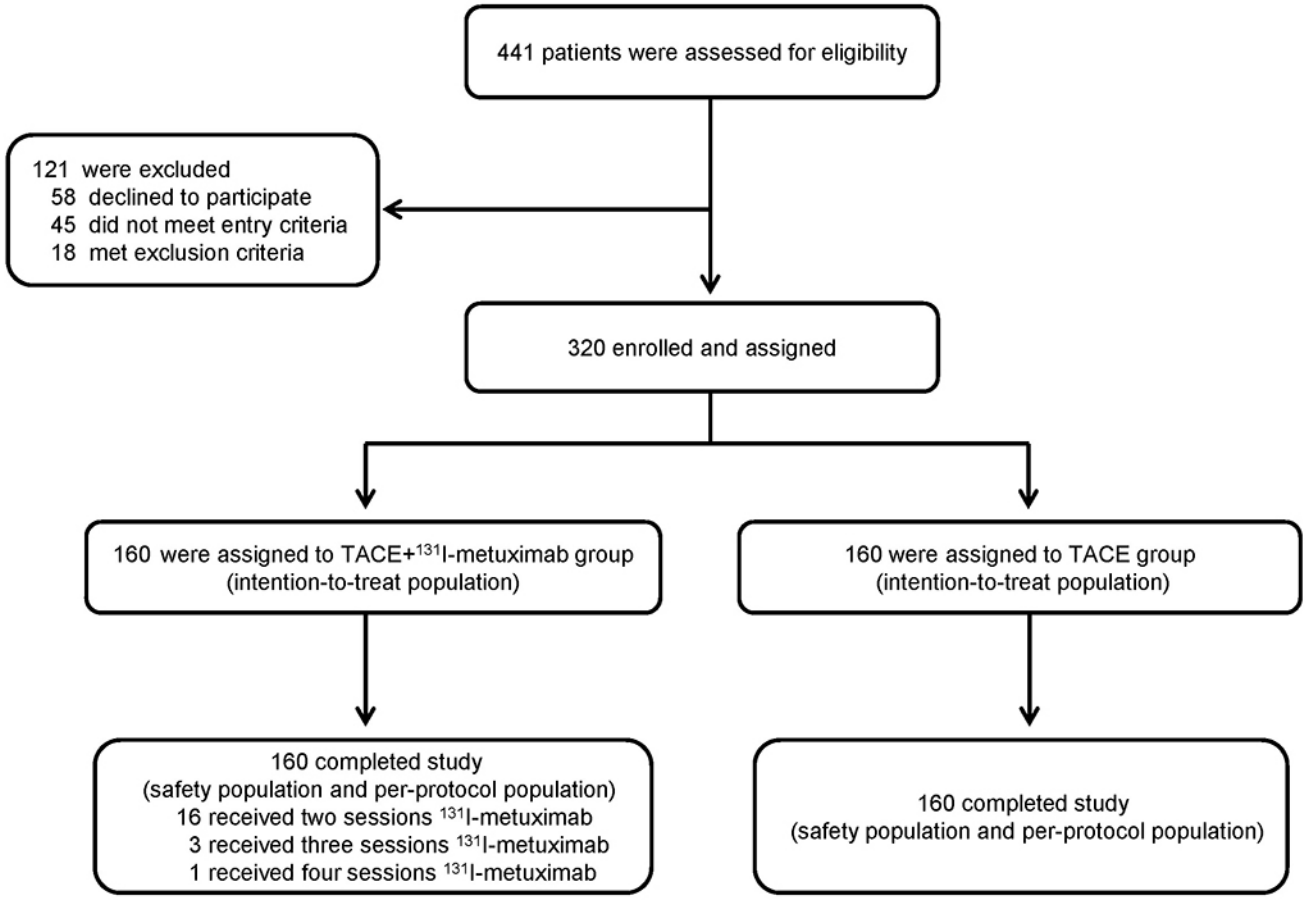
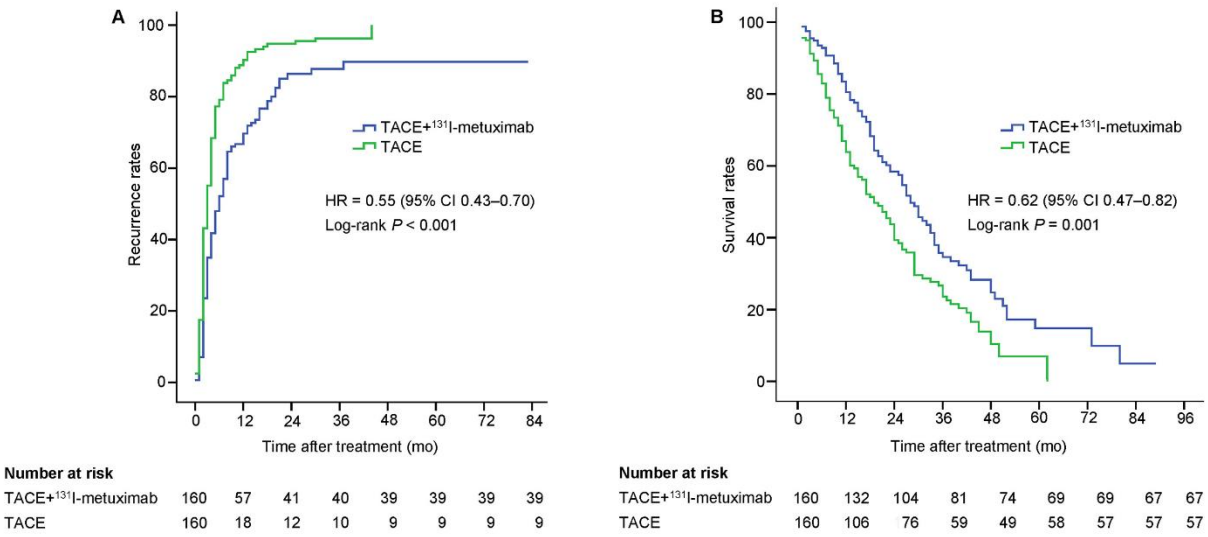
FIGURE 1. Trial profile



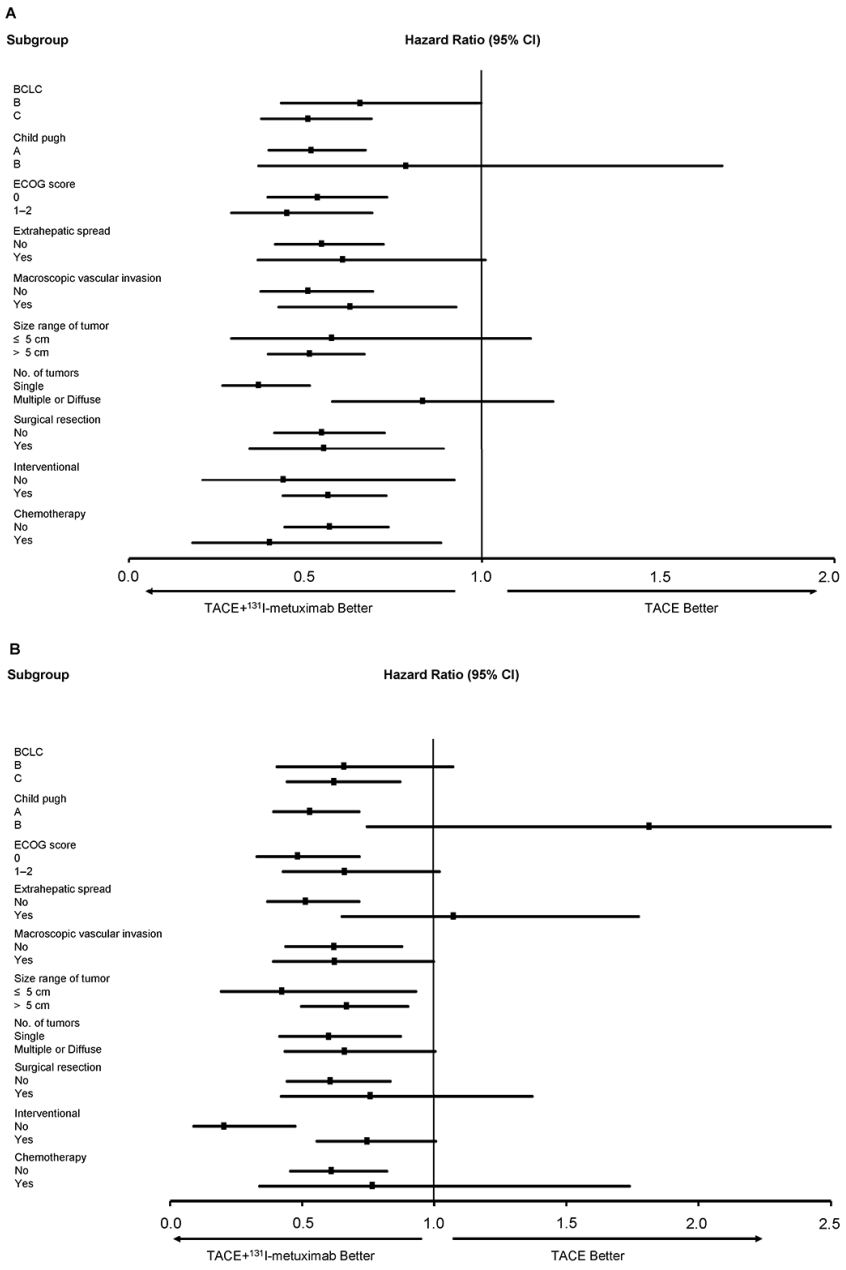
Enrollment and outcomes.

FIGURE 2. Overall recurrence and overall survival



Overall recurrence (A) and overall survival (B). Data were analyzed using the Kaplan-Meier method and log-rank test. HR = hazard ratio. CI = confidence interval.

FIGURE 3. Analysis of selected subgroups



Overall recurrence (A) and overall survival (B) of the selected subgroups according to baseline prognostic factors.

Subgroup analyses for recurrence and survival were performed using the Cox regression models.

Graphical Abstract

A prospective non-randomized concurrent controlled, multicenter open-label clinical trial with 320 patients investigated efficacy and safety of ^{131}I-labeled metuximab in adjuvant treatment of unresectable HCC