Efficacy and Safety of Transarterial Chemoembolization Combined With Anlotinib for Unresectable Hepatocellular Carcinoma: A Retrospective Study

Wenbo Guo, MD\textsuperscript{1}, Song Chen, MM\textsuperscript{1}, Zhiqiang Wu, MM\textsuperscript{1}, Wenquan Zhuang, BD\textsuperscript{1}, and Jianyong Yang, MD\textsuperscript{1}

Abstract

Objective: This study aimed to explore the efficacy and safety of using transarterial chemoembolization (TACE) combined with anlotinib in patients with unresectable hepatocellular carcinoma, compared with TACE alone. Methods: This was a single-center study, retrospectively recruited 82 unresectable HCC patients who received either TACE alone (TA group; n = 46) or TACE combined with anlotinib (TC group; n = 36) between Jan 2018 and Jan 2019. The primary outcomes were progression-free survival (PFS) and overall survival (OS). While the secondary outcomes were the objective response rate (ORR), the disease control rate (DCR), and main complications. Log-rank test and Kaplan–Meier method was used to calculate the survival difference. All statistical tests were 2-sided and P value <0.05 were taken as statistically significant. Results: Patients in TC group had a significant higher PFS than those in TA group (7.35 months vs. 5.54 months, p = 0.035). Although 3-month survival rate in the 2 groups was not statistically different (97.2% vs. 93.5%, p = 0.627), the survival rate at 6 months and 1 year were strongly higher in TC group (83.3% vs. 56.5%, p = 0.016; 66.7% vs. 19.6%, respectively, p < 0.05). Furthermore, there was a significantly higher ORR in TC group, while no statistical difference existed in DCR. Neither treatment-related mortality nor grade 4 adverse events (AEs) occurred. However, 2 patients in TC group had grade 3 AEs (one suffered with erythra, and the other with hand-foot-skin reaction), which disappeared after prompt treatment. Conclusion: TACE combined with anlotinib is safe and may improve outcomes for unresectable HCC patients comparing with TACE alone. Randomized controlled trials are warranted to further evaluate treatment effects of anlotinib in HCC.

Keywords
hepatocellular carcinoma, anlotinib, transarterial chemoembolization, progression-free survival, overall survival, objective response rate

Introduction

Hepatocellular carcinoma (HCC), which composes about 65% of all liver cancers, is among one of the leading causes of cancer-related death.\textsuperscript{1-3} Together with lung cancer, HCC is the most common cancer happened in Chinese population.\textsuperscript{4} There are a variety of treatment options for HCC, including surgery, liver transplantation, molecular-targeted therapy, local-regional therapies, and immunotherapy.\textsuperscript{5} Traditionally, only surgery and transplantation are taken as curative options for HCC patients. However, curative resection or transplantation was not suitable for the majority of HCC patients when diagnosed, considering the tumor size, number, location, vascular involvement, extrahepatic metastases, liver function, and patients’ general condition.\textsuperscript{6-8} Therefore, it is extremely urgent to develop an effective therapy for unresectable HCC.

In recent years, local-regional therapies, including transarterial chemoembolization (TACE) and radiofrequency ablation

\textsuperscript{1} The First Affiliated Hospital of Sun Yat-sen University, Guangdong, China

Corresponding Authors:
Wenbo Guo and Song Chen, Department of Interventional Radiology, The First Affiliated Hospital of Sun Yat-sen University, No. 58, Zhongshan Second Road, Yuexiu District, Guangzhou, Guangdong 510080, China. Emails: suyan20200428@163.com; topi9597419du@163.com

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have been regarded as optimal therapies for HCC patients. TACE has been generally recommended as the standard palliative therapeutic regimen by guidelines and expert consensus for unresectable HCC. However, comparing with the other treatment options, such as chemotherapy, molecular targeted therapy or immunotherapy, TACE displays limited benefits. Two main reasons may contribute to the unsatisfactory effects. First, TACE, especially after incomplete embolization, may lead to the regaining of vascular supply of nutrients and oxygen to residual tumors. Second, TACE can’t prevent recurrence and metastasis of the tumor effectively. After interdicting the blood supply of tumor, the increased level of HIF (hypoxia-inducible factor) will promote the release of VEGFR sequentially, which may facilitate the recurrence and metastasis of tumor.

A multidisciplinary approach is needed for HCC patients to obtain optimal outcomes. Therefore, TACE should be combined with other treatment regimens to improve clinical efficacy. It has been reported that TACE combined with tyrosine kinase inhibitors (TKIs), for example, sorafenib or lenvatinib can be applied in patients with unresectable HCC. Anlotinib, a novel TKI, is used as a third-line treatment agent for patients with advanced non-small cell lung cancer, approved by Chinese Food and Drug Administration (CFDA) on May, 2018. However, the treatment efficacy and safety of anlotinib in HCC patients is still undetermined.

Based on the above findings, the study aimed to evaluate the efficacy and safety of using TACE combined with anlotinib in unresectable HCC patients, comparing to TACE alone.

Methods

Patients

We recruited unresectable HCC patients who underwent either TACE alone or a combination of TACE and anlotinib through January 2018 to January 2019 at the First Affiliated Hospital, Sun Yat-sen University, retrospectively. The Unresectable HCC includes one or more aspects as following: i) residual liver volume is insufficient, ii) distant metastasis or great vascular invasion, iii) liver function or physical condition is poor, iv) resection is highly risky assessed by 2 experienced surgeons. Among 82 patients included, 46 received TACE alone (TA group), while 36 received TACE combined with anlotinib (TC group). The eligibility of each participant was confirmed, using the following inclusion criteria: (1) Diagnosed HCC using noninvasive criteria, which is consistent with the European Association/American Association guidelines for Liver Disease or pathological diagnosis; (2) HCC deemed to be unresectable or incurable after multidisciplinary treatments; (3) Liver function, class A or B of Child-Pugh; (4) Performance score of Eastern Cooperative Oncology Group (ECOG) ≤2; (5) Available of complete medical records, including imaging (enhanced computed tomography [CT] and/or magnetic resonance imaging [MRI]), and prognostic data. Exclusion criteria were prior therapy or contraindicated to receive TACE or targeted therapy. The study had obtained approval from the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. And written informed consent was obtained from all recruited patients.

Efficacy and Safety Assessments

The modified Response Evaluation Criteria in Solid Tumors (RECIST23) was used to explore the response to the treatments. The target lesions for each patient were independently evaluated by 2 radiologists and 1 interventional clinician. Any disagreement would be resolved to reach an agreement after reviewing the contrast-enhanced CT and/or MRI images.

Progression-free survival (PFS) was estimated according to the time duration between initial therapy and progression. Overall survival (OS) was defined as time length from initial therapy to death, or last hospital visit data. The objective response rate (ORR) was calculated as the percentage of both complete and partial response, maintained for at least 8 weeks among all cases. The disease-control rate (DCR) was the percentage of patients with stable disease, or complete/partial response. PFS and OS (including survival rate at 3-month, 6-month, and 1-year) between TC group and TA group were compared. Besides, the overall response rate including ORR and DCR was evaluated as well.

Safety was evaluated by physical examination, vital signs, clinical laboratory results, and AEs.
statistical analysis

Student test was used to compare the continuous data, and Chi-square test was used for categorical variables. The results were presented with mean ± standard deviation (SD) or median (interval). A life-table method was used to calculate PFS, with the Mantel-Cox test for further comparison. Log-rank test and Kaplan–Meier method was used to calculate the survival difference. All statistical tests were 2-sided and \( P \) value <0.05 were taken as statistically significant. Statistical analyses were conducted with SPSS 20.0.

results

patient characteristics

Among all the 82 patients, the baseline characteristics in the 2 groups had no significant difference, as showing in Table 1. In this study, the median follow-up time was 13.76 months, ranging from 2 to 20 months. A total of 54 patients (65.9%) died during follow-up time.

| Table 1. Baseline Demographics, Disease Characteristics and Treatment. |
|---------------------------------------------------------------|
| Treatment | TC Group (n=36) | TA group (n=46) | \( P \) |
|-----------|-----------------|-----------------|------|
| Age (yr)  | 56.41 ± 12.44   | 56.28 ± 11.66   | 0.730|
| Gender    |                 |                 |      |
| Male      | 29              | 38              | 0.811|
| Female    | 7               | 8               |      |
| BCLC stage|                 |                 | 0.427|
| A         | 3               | 1               |      |
| B         | 16              | 23              |      |
| C         | 17              | 22              |      |
| Portal vein thrombosis |     |                 | 0.35 |
| Present   | 12              | 20              |      |
| Absent    | 24              | 26              |      |
| PVTT type |                 |                 |      |
| I         | 3               | 1               |      |
| II        | 6               | 11              |      |
| III       | 3               | 8               |      |
| Extrahepatic metastasis |     |                 | 0.405|
| Present   | 8               | 14              |      |
| Absent    | 28              | 32              |      |
| Child-pugh class |   |                 | 0.382|
| A         | 26              | 37              |      |
| B         | 10              | 9               |      |
| Large tumor size (mm) | 90.37 ± 46.89 | 90.44 ± 31.97 | 0.943|
| Number of tumors |             |                 | 0.423|
| Single    | 14              | 14              |      |
| Multiple  | 22              | 32              |      |
| Hepatitis |                 |                 | 0.707|
| B         | 35              | 44              |      |
| C         | 1               | 2               |      |
| AFP       |                 |                 | 0.082|
| >400      | 9               | 20              |      |
| ≤400      | 27              | 26              |      |

BCLC: Barcelona Clinic Liver Cancer; PVTT: portal venous tumor thrombus.

Figure 1. Progression-survival in unresectable HCC patients treated with TACE combined and anlotinib (TC group) and TACE alone (TA group).

| Table 2. 3 Month, 6 Month and 1 Year Month Survival Rate in TC and TA Group. |
|---------------------------------------------------------------|
| OS (month) | TC (n=36) | TA (n=46) | \( P \) |
|------------|-----------|-----------|------|
| 3          | 35 (97.20%) | 43 (93.50%) | 0.627|
| 6          | 30 (83.30%) | 26 (56.50%) | 0.016|
| 12         | 24 (66.70%) | 9 (19.60%) | <0.01|

OS: Overall survival.

pfs and os

Comparing with TA group, patients in TC group had a significant longer PFS (7.35 vs. 5.54 months, \( P = 0.035 \); Figure 1). Although no significant difference on 3-month survival rate (97.2% vs. 93.5%, \( P = 0.627 \); Table 2), the survival rates at both 6 months and 1 year in TC group were strongly higher than those in TA group (83.3% vs. 56.5%, \( P = 0.016 \); 66.7% vs. 19.6%, \( P < 0.01 \); Table 2).

Overall Response to Treatment

Regarding to the overall response to treatments, complete response, partial response, stable disease, and progressive disease were 5 (13.9%), 23 (63.9%), 6 (16.6%), and 2 (5.6%), respectively in TC group, and 5 (10.9%), 10 (21.7%), 23 (50.0%), and 8 (17.4%) in TA group. In addition, ORR in TC group was significantly higher than TA group (77.8% vs. 32.6%, \( P < 0.01 \); Table 3). While, the 2 groups showed no statistical difference in DCR (94.4% vs. 82.6%, \( P = 0.17 \); Table 3).

adverse events (aes)

AEs related to treatment in TC group were as followings: hand-foot-skin reaction (n = 17, 47.2%), hypertension (n = 10,
Table 3. Overall Response to Treatment in TC and TA Group.

| Response | TC (n = 36) | TA (n = 46) | P  |
|----------|-------------|-------------|----|
| CR       | 5 (13.9%)   | 5 (10.9%)   | /  |
| PR       | 23 (63.9%)  | 10 (21.7%)  | /  |
| SD       | 6 (16.7%)   | 23 (50.0%)  | /  |
| PD       | 2 (5.6%)    | 8 (17.4%)   | /  |
| ORR      | 28 (77.8%)  | 15 (32.6%)  | <0.05 |
| DCR      | 34 (94.4%)  | 38 (82.6%)  | 0.17 |

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; DCR: disease control rate; ORR: objective response rate; TACE: transarterial chemoembolization.

Although the management of HCC has been greatly improved in recent years,24 curative therapies including surgery and liver transplantation can only be used in less than 30% of HCC patients.25,26 As the change of concept and progress of treatment method, the first-line therapy for unresectable HCC includes TACE, targeted monotherapy or combination therapy.27–29 In recent years, TACE combined with targeted therapy are more extensively applied in clinical practice. One of reasons is that the side effects of TACE, combined with anlotinib were no more severe than those with lenvatinib or sorafenib. Considering a cheaper cost, comparing to other MTAs, anlotinib might be more cost-effective to Chinese HCC patients. Thus, TACE combined with anlotinib might be used as an alternative treatment modality for unresectable HCC. Randomized controlled trials with large sample size are warranted to further confirm the findings.

In summary, the combination of TACE and anlotinib was effective and safe for unresectable HCC patients. Furthermore, the side effects of TACE, combined with anlotinib were no more severe than those with lenvatinib or sorafenib. Considering a cheaper cost, comparing to other MTAs, anlotinib may be more cost-effective to Chinese HCC patients. Thus, TACE combined with anlotinib might be used as an alternative treatment modality for unresectable HCC. Randomized controlled trials with large sample size are warranted to further confirm the findings.

Authors’ Note
The study had obtained approval from the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. {(2019)239}.

Declaration of Conflicting Interests
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ORCID iD
Wenbo Guo [https://orcid.org/0000-0002-8767-9401]
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