Research Paper

Study on the Effect of Atezolizumab Combined with Bevacizumab after Radical Resection in the Treatment of Hepatocellular Carcinoma

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To investigate the efficacy of the addition of atezolizumab combined with bevacizumab after radical resection in the treatment of hepatocellular carcinoma. This was a randomized controlled trial in which 84 patients with hepatocellular carcinoma treated with radical resection were enrolled. 43 patients were randomly assigned to receive trans catheter arterial chemoembolization and were classified as the control group (group C); the other 41 patients were randomly assigned to receive atezolizumab combined with bevacizumab treatment and were classified as research group (group R). Overall survival, recurrence-free survival, objective response rate, and the incidence of adverse events were compared between the two groups. In group R and group C, the median follow-up period was 8.6 mo and 8.2 mo, respectively. In comparison to group C, group R had significantly higher overall survival, recurrence-free survival, and risk ratio ($p<0.05$). The rate of negative reactions was greater in group R compared to group C ($p<0.05$). After radical resection of hepatocellular carcinoma, the addition of atezolizumab in combination with bevacizumab to transcatheter arterial chemoembolization significantly improves patients overall survival and recurrence-free survival with a high objective remission rate; however, this dosing regimen leads to a higher number of adverse effects, which need to be paid attention to.

Key words: Hepatocellular carcinoma, radical resection, atezolizumab, bevacizumab

90 % of primary liver cancers are Hepatocellular Carcinoma (HCC), which are also the 3rd greatest cause of cancer-related fatalities[1,2]. The pathogenesis of HCC is closely related to chronic liver disease, and is mainly due to Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), or non-viral causes such as alcoholism and non-alcoholic fatty liver disease. There is some variability in the global incidence of HCC, with >50 % of HCC occurring in China[3]. According to data from the World Health Organization's International Agency for Research on Cancer (IARC) Global Cancer Burden 2020 report, there were 830 000 deaths and 906 000 new cases of primary liver cancer in 2020. China accounted for 42.5 % of the world's liver cancer cases during the previous 5 y with an annual average of 423 000 new cases[4]. Patients with early-stage HCC with a good liver function reserve should undergo surgical resection as their preferred treatment option[5]. Some studies have shown that patients with advanced HCC undergoing radical resection have a more favorable prognosis compared to alternative therapies such as Transcatheter Arterial Chemoembolization (TACE) [6,7]. However, the Barcelona Clinic Liver Cancer (BCLC) criteria recognized in the West limit, the scope of radical resection to patients with very early or early stage (BCLC0 or A) HCC, which may prevent patients who could benefit from radical resection from receiving effective treatment[1]. One of the main causes for restricting the scope of radical resection in the West is the high postoperative recurrence rate. The failure of radical therapy is primarily because to the high rate of recurrence following drastic resection. Previous studies have reported that the recurrence rate of HCC is >40 % within 2 y and >70 % within 5 y after radical resection[8]. Recurrence following radical resection of HCC is frequently defined as occurring 2 y after resection, with early recurrence defined as occurring

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within 2 y of surgery and late recurrence defined as occurring after 2 y. Early recurrence accounts for >70 % of postoperative HCC recurrences[9]. Studies have concluded that recurrence at different periods is caused by different risk factors. Early recurrence is mainly driven by aggressive features of the primary tumor, such as tumor size, vascular invasion, and high serum Alpha Fetoprotein Test (AFP) levels[10]. In contrast, late recurrence is mainly due to changes in the hepatic oncologic field caused by underlying liver disease and cirrhotic lesions[11]. The number of risk variables present at the time of surgery affects the prognosis of patients with recurrence[12]. Therefore, effective adjuvant therapy is urgently required to reduce postoperative recurrence and thereby enhance the prognosis of HCC patients who have recurrence risk factors[13].

Radiation therapy, systemic chemotherapy, TACE and anti-allogeneic viral hepatitis therapy are frequently utilized as adjuvant therapies for HCC following surgery[14,15]. Among them, TACE is an effective strategy to prevent HCC recurrence. Some studies have reported that postoperative TACE can improve the Recurrence-Free Survival (RFS) and Overall Survival (OS) of HCC patients[16,17]. Meanwhile, postoperative adjuvant therapy for HCC with immunotherapy has encouraging outcomes. Expression of the immune checkpoint molecule Programmed Cell Death Ligand 1 (PD-L1) on tumor cells or tumor-infiltrating immune cells suppresses antitumor immunity. Anti-PD-L1 reduces T cell proliferation and effector capabilities when it binds to its receptor, PD-1 on T cells. Atezolizumab targets PD-L1 specifically to stop it from interacting with PD-1 receptor, reversing T cell suppression[18]. HCC development is also tightly linked to Vascular Endothelial Growth Factor (VEGF) overexpression. By reversing VEGF-mediated immunosuppression and encouraging T-cell infiltration in tumors, anti-VEGF therapy decreases VEGF-mediated immunosuppression in tumors and their microenvironment[19,20] and strengthens the role of anti-PD-1 and PD-L1[21,22]. Angiogenesis and tumor growth are inhibited by the monoclonal antibody bevacizumab, which has previously shown to have great anti-HCC action and good remission rates[23,24] .

Therefore, immune checkpoint inhibitor junctions may improve the translational therapy of unrespectable HCC by converting unrespectable HCC into respectable HCC, thus improving the outcome of HCC[25]. The therapies of atezolizumab and bevacizumab after radical resection of HCC have been confirmed by several studies[26,27], but there is a lack of sufficient clinical trial data to support the efficacy of this regimen, and none of these studies occurred in China. Therefore, we hypothesized that the addition of atezolizumab in combination with bevacizumab after radical resection could enhance postoperative recovery in patients with HCC. We conducted a randomized controlled trial in China to test our hypothesis.

MATERIALS AND METHODS

Study design:

A total of 84 patients with HCC who underwent radical resection at a tertiary care hospital in China between January 2018 and December 2021 were included in this study, which was a randomized controlled trial. Of those patients, 41 were assigned at random to receive atezolizumab along with bevacizumab postoperatively and were referred to as the research group (group R). The remaining 43 patients were divided into a control group (group C) and given TACE following surgery. Informed consent was signed by patients in both groups. Under the permission number, the ethics committee gave approval to this study.

Inclusion and exclusion criteria:

Inclusion criteria: Diagnosis of HCC and treatment with radical resection; complete clinical data and follow-up data and ≥18 y of age[28].

Exclusion criteria: Patients with comorbidities of other malignancies; patients with comorbidities of autoimmune diseases; patients with comorbidities of infectious diseases and patients with risk of bleeding.

Treatment:

Patients in both groups were treated with TACE within 2 mo after surgery. Group C was treated with atezolizumab and bevacizumab in addition to TACE. After assessing the patient's normal liver function, atezolizumab 1200 mg and bevacizumab 15 mg/kg were administered intravenously in a 21 d course. If patients did not develop serious complications, they were treated continuously for 6 mo.

During the treatment period, all patients were followed up by telephone and outpatient follow-up visits every 3 mo. Follow-up ended on March 31, 2023 (24 mo) or when the patient died.

Outcomes:

The time from the start of treatment till death from any cause refers to OS. The interval between the start of treatment and the recurrence of the disease refers to PFS. In objective remission rate, treatment efficacy was assessed by solid tumor efficacy criteria[29]. In Complete Remission (CR), the target lesion is gone. A 30 % reduction in the total of the long diameters of the underlying lesions is considered Partial Remission (PR). Stable Disease (SD) is defined as a decrease in the total number of baseline lesion without a corresponding increase in PR or PD. PD is the emergence of new lesions or a cumulative rise of baseline lesion of >20 %.

Objective Response Rate (ORR)=(CR+PR)/ Total×100 %

Incidence of adverse events: Safety and side effect profiles were assessed using the National Cancer Institute (NCI) common terminology criteria for adverse events, version 4.0, to determine the nature, frequency and severity of adverse events occurring in both groups.

Study endpoint: The primary endpoints were OS and RFS. The secondary focus was the objective remission rate.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) 21.0, statistical software for social sciences, was used to analyze the data. The Chi-square (χ^2) test was used to compare counts, which were presented as n (%). The Kolmogorov-Smirnov test was used to determine whether the data had a normal distribution, the median and quartiles were used to express non-normally distributed measures, the Mann-Whitney U test was used to compare groups, and all measures that followed a normal distribution were expressed as ($\bar{x}\pm s$), and comparisons were made using the t-test, Analysis of Variance (ANOVA), and Least Significant Difference (LSD) test. At $p<0.05$, differences were declared statistically significant.

RESULTS AND DISCUSSION

As depicted in fig. 1, 102 HCC patients who underwent radical resection were included in the study; 7 patients failed to meet the requirements, and 3 patients declined to take part. With 46 patients apiece, the remaining 92 patients were randomly divided into groups R and C. One patient in group C and two patients in group R refused to receive the prescribed treatment, respectively. Two patients in group C and three in group R failed to show up for follow-up, respectively. No patients in either group were excluded at the analysis stage.

According to Table 1, there were no differences in the two groups' demographic and baseline data ($p>0.05$). As of March 31st 2023, the median follow-up times of group R and group C were 8.6 mo and 8.2 mo, respectively. As shown in fig. 2 and fig. 3, OS and Progression-Free Survival (PFS) were significantly longer in group R than in group C ($p<0.05$). According to Table 2, group R had a greater ORR than group C ($p<0.05$). The incidence of negative reactions was higher in group R than in group C ($p<0.05$), as indicated in Table 3.

The results of this study showed that postoperative adjuvant therapy with atezolizumab and bevacizumab combined with TACE after radical resection can effectively prolong OS and RFS with high objective remission rate in HCC patients compared with TACE alone, but such postoperative adjuvant therapy regimen can cause more adverse effects and needs to be paid attention.

Although current strategies for the radical treatment of HCC are gradually improving, the 5 y recurrence rate after treatment such as surgery or ablation is still 40 % to 70 %[30] . Some studies have tried to use sorafenib as an adjuvant therapy after hepatic resection or ablation therapy, but the results showed no significant benefit[31]. Additionally, there was no discernible effect from using nivolumab or anlotinib as adjuvant therapy for HCC following surgery[32,33]. Adjuvant use of TACE in radical resection has been shown to eliminate the blood supply to the tumor, thereby inducing growth arrest and even death of HCC cells[34], but the results are still unsatisfactory when used alone. Theoretically, molecularly targeted therapies could reduce recurrence after radical resection by inhibiting tumor angiogenesis and proliferation[35]. HCC cells evade immune detection through activation of PD-1 cell conductance, and immune checkpoint molecule inhibitors prevent immune escape and activate T cells to suppress HCC cells[36]. Atezolizumab in combination with bevacizumab is considered to be the most promising combination of immunotherapy and targeted therapy available for the treatment of HCC[37]. The group R patients in this study were treated with atezolizumab, bevacizumab and TACE after radical resection, and group C received TACE alone, and after a median follow-up of 8.2 mo and 8.6 mo, the OS rate, RFS

rate, and ORR of group R were 75.61 %, 65.85 %, and 41.46 %, respectively OS rate of group C was 46.51 %, 41.86 %, and 20.93 %, suggesting that the addition of atezolizumab in combination with bevacizumab to TACE after radical resection can improve OS and RFS in patients with HCC, which is consistent with the results of the phase IB GO30140 trial[24]. Such results are promising. It somewhat reaffirms atezolizumab and bevacizumab efficacy and viability as adjuvant therapies for HCC following radical resection in China.

However, the results of this study suggest that atezolizumab in combination with bevacizumab leads to more serious adverse reactions. The occurrence of adverse reactions may be related to the patient's underlying disease and the known safety profile of the drug[23]. Adverse reactions induced by atezolizumab in combination with bevacizumab are predominantly grade 1-2 and grade 3-4, and are mainly characterized by hypertension, proteinuria, malaise, and bleeding. Atezolizumab, as an immune checkpoint inhibitor, can mainly lead to immune-like adverse reactions represented by pruritus. Bevacizumab is a targeted angiogenic drug, and its adverse reactions can involve multiple systems and organs throughout the body, leading to proteinuria, fatigue, skin toxicity, liver toxicity, etc.,[38]. How to prevent and control the adverse reactions caused by these two drugs is a key concern to improve their clinical efficacy and needs to be further studied.

This research has several restrictions. For example, the small number of study subjects will reduce the credibility of the findings to some extent. The follow-up time of the patients was short, and longer-term survival data could not be obtained. Meanwhile, the causes of adverse reactions, prevention and treatment measures were not deeply explored. All these limitations will be improved in future studies.

Atezolizumab combined with bevacizumab brings more choices for adjuvant treatment of HCC after radical resection, which can significantly improve OS and RFS, with high objective remission rate and good clinical benefits for patients. However, treatment-related adverse reactions still need to be emphasized, and the timely development and management of adverse reactions is a necessary strategy to improve the effect of atezolizumab combined with bevacizumab treatment and save patients' lives.

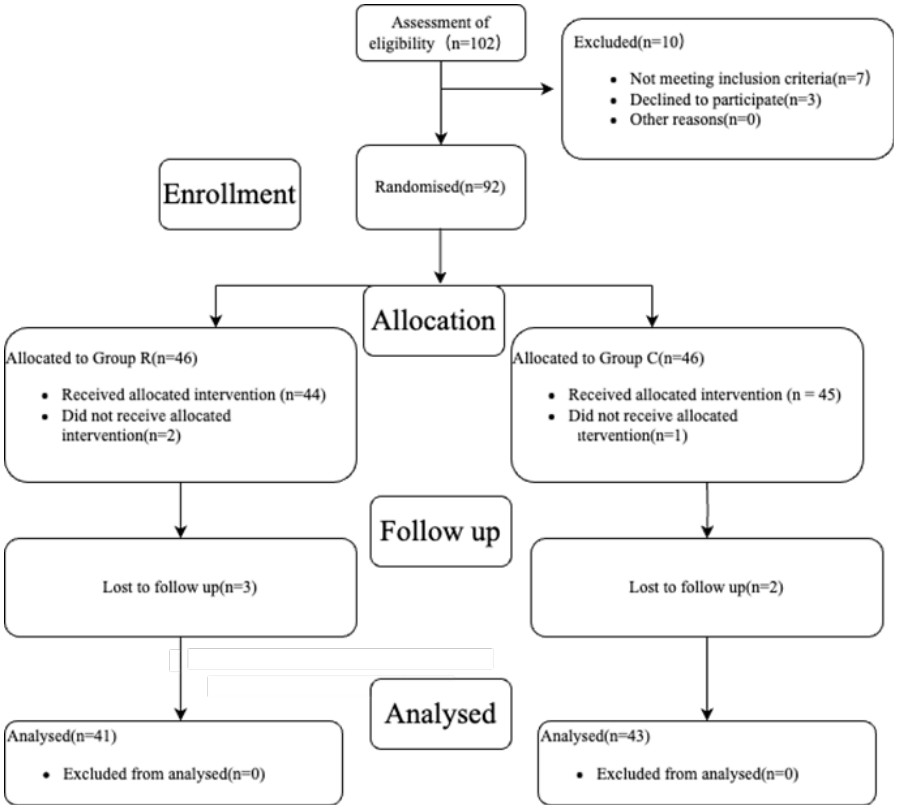

Fig. 1: Study subject inclusion process

TABLE 1: DEMOGRAPHIC AND BASELINE INFORMATION OF THE TWO GROUPS

Variable	Group R (n=41)	Group C (n=43)	p
Age (years, mean±SD)	64.35±2.71	64.31±2.69	0.947
Male/female, n (%)	31 (75.61)/10 (24.39)	30 (69.77)/13 (30.23)	0.548
Cause of hepatocellular carcinoma			0.776
Hepatitis B	21 (51.22)	20 (46.51)	
Hepatitis C	7 (17.07)	10 (23.26)	
Nonviral	13 (31.71)	13 (30.23)	
Alpha-fetoprotein ≥400 ng/ml, n (%)	15 (36.59)	16 (37.21)	0.953
Barcelona clinic liver cancer stage, n (%)			0.704
A	2 (4.88)	4 (9.30)	
B	8 (19.51)	7 (16.28)	
C	31 (75.61)	32 (74.42)	
Proliferation, n (%)			0.612
Macrovascular invasion	12 (29.27)	11 (26.83)	
Extrahepatic spread	17 (41.46)	15 (34.88)	
Macrovascular and extrahepatic	12 (29.27)	17 (39.53)	

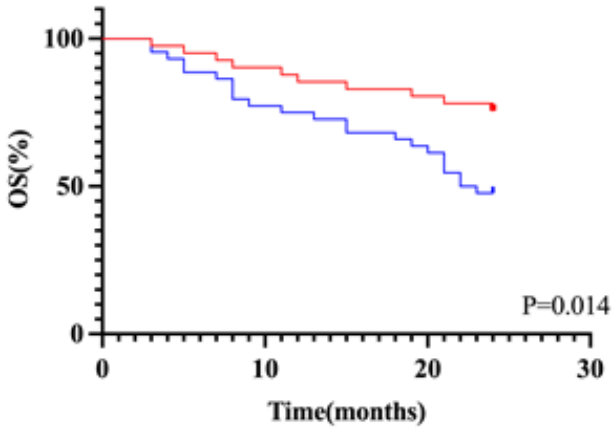

Fig. 2: OS median follow-up times
Note: ( ): Group R and ( ): Group C

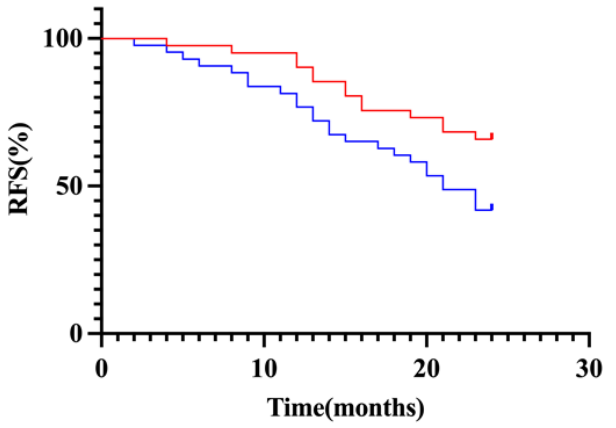

Fig. 3: PFS median follow-up times
Note: ( ): Group R and ( ): Group C

TABLE 2: OBJECTIVE REMISSION RATE n (%)

Variable	Group R (n=41)	Group C (n=43)	χ^2	p
CR	7 (17.07)	4 (9.30)		
PR	10 (24.39)	5 (11.63)		
SD	14 (34.14)	20 (46.51)		
PD	10 (24.39)	14 (32.56)		
RR	17 (41.46)	9 (20.93)	4.140	0.042

TABLE 3: INCIDENCE OF ADVERSE REACTIONS n (%)

Variable	Group R (n=41)	Group C (n=43)	χ^2	p
Grade 1 or 2 event	8	4		
Grade 3 or 4 event	6	4		
Grade 5	3 (12.20)	1 (6.98)		
Total	18 (43.90)	9 (20.93)	5.078	0.024

Author's contributions:

Xuemei Wang and Beilei Su have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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