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ORIGINAL RESEARCH

The Combination of D-TACE-HAIC, Lenvatinib, and PD-1 Inhibitors Shows Significant Clinical Efficacy in Patients with Unresectable Hepatocellular Carcinoma

Yintao Wu*, Jianyong Zhu*, Hong Zhang, Nianxin Xia

Senior Department of Hepato-Pancreato-Biliary Surgery, the First Medical Center of PLA General Hospital, Beijing, 100853, People's Republic of China

*These authors contributed equally to this work

Correspondence: Nianxin Xia, Senior Department of Hepato-Pancreato-Biliary Surgery, the First Medical Center of PLA General Hospital, Beijing, 100853, People's Republic of China, Email doctorxnx@163.com

Purpose: This study was developed to compare the efficacy of combined D-TACE-HAIC + lenvatinib + PD-1 inhibitor treatment to that of TACE + sorafenib treatment for patients with intermediate and advanced HCC.

Patients and Methods: Here, a retrospective analysis of patients with unresectable HCC who underwent transarterial chemoembolization (TACE) from March 2018 to March 2022 at the our hospital was conducted. In total, 60 patients underwent treatment with drug-eluting beads-TACE-hepatic arterial infusion chemotherapy (D-TACE-HAIC) combined with lenvatinib and PD-1 inhibitors (Group A), while 21 underwent combined TACE and sorafenib treatment (Group B).

Results: In this study cohort, the rate of surgical conversion in Group A was significantly higher than that in Group B (33.3% vs 9.5%). As per the Revised Evaluation Criteria for Clinical Efficacy in Solid Tumors (mRECIST) criteria, the objective remission rate in Group A was significantly higher than that in Group B (86.6% vs 33.4%). Group A also exhibited significantly higher rates of overall adverse events including hypertension, abdominal pain, leukopenia, thrombocytopenia, and hypoproteinemia as compared to Group B, although the incidence of hand-foot syndrome in Group A was significantly reduced as compared to Group B (13.3% vs 42.8%). The median progression-free and overall survival (PFS and OS) of patients in Group A were 13.2 and 28.8 months, with both being significantly higher than the corresponding intervals in Group B (5.7 and 10.8 months, respectively). Cox multivariate analyses identified combination D-TACE-HAIC + lenvatinib+ PD-1 inhibitor treatment as being independently associated with patient PFS and OS.

Conclusion: In summary, D-TACE-HAIC + lenvatinib + PD-1 inhibitor treatment exhibits a favorable safety profile, outperforming TACE + sorafenib treatment for unresectable HCC patients while improving overall rates of translational efficacy, increasing rates of surgical conversion, prolonging patient survival, and conferring long-term survival benefits.

Keywords: unresectable hepatocellular carcinomas, drug-eluting beads-transarterial chemoembolization-hepatic arterial infusion chemotherapy, clinical efficacy, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third leading cause of tumor-related death worldwide. Based on the GLOBOCAN 2020 statistics, approximately 910,000 new cases are diagnosed with HCC annually and it is also claiming the lives of around 830,000 individuals each year.[1] HCC remains the fourth most common and second deadliest malignancy in China, with the Chinese HCC incidence and mortality rates accounting for more than half of the global total, representing a major threat to public health.[2] HCC tumors tend to be highly malignant, with an insidious onset lacking any signs or symptoms during the early stages of disease together with a tendency to progress rapidly. As a majority of patients are diagnosed with moderately advanced or advanced disease, just 20–30% are eligible for radical surgery. Patients may ultimately be unable to undergo surgery for reasons including the present or

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large lesions, multiple lesions, intrahepatic or extrahepatic metastases, hepatic insufficiency, a lack of sufficient residual liver volume, and/or vascular invasion.[3–5] Per the HCC Diagnosis and Treatment Guidelines, various treatments, including interventional therapy, radiofrequency ablation therapy, radiotherapy, and systemic treatment can be deployed for patients with intermediate or advanced disease.[6] Given the context of systemic therapy, patients are not only afforded extended survival advantages but also provided with the potential for down-staging conversion and the facilitation of sequential surgical procedures in the management of advanced hepatocellular carcinoma.

Transarterial chemoembolization (TACE) remains a standard approach to managing HCC in China, but in HCC patients exhibiting tumors more than 10 cm long, TACE tends to yield unsatisfactory efficacy as evidenced by a disease control rate of under 50% and a surgical conversion rate of roughly 10%.[7–10] Hepatic arterial infusion chemotherapy (HAIC) together with an oxaliplatin plus fluorouracil and leucovorin (FOLFOX) regimen for HCC patients with locally advanced disease has been demonstrated to give rise to improved tumor response rates, including higher rates of conversion to surgery and a superior safety profile. Combining HAIC and targeted immunotherapy can thus be an efficacious and safe means of achieving high rates of surgical conversion in cases of locally advanced, potentially resectable HCC.[11–15] At present, traditional monotherapeutic treatments tend to yield unsatisfactory efficacy such that a growing number of studies have been conducted in recent years highlighting the promising synergistic efficacy of various treatment combinations.

This study was developed to compare the efficacy of combined D-TACE-HAIC + lenvatinib + PD-1 inhibitor treatment to that of TACE + sorafenib treatment for patients with intermediate and advanced HCC. In the D-TACE-HAIC + lenvatinib + PD-1 inhibitor group, the rates of surgical conversion (33.3%) and objective remission (86.6%) were both higher than those in the TACE + sorafenib group, with patients in the former group exhibiting median PFS and OS intervals of 13.2 and 28.8 months, respectively. Cox multivariate analyses revealed that D-TACE-HAIC + lenvatinib + PD-1 inhibitor treatment was independently associated with patient OS and PFS.

Materials and Methods

Study Population

This study entailed the retrospective analysis of patients with unresectable HCC who underwent TACE between March 2018 and March 2022 at the senior Department of Hepato-Pancreato-Biliary Surgery, the First Medical Center of PLA General Hospital. In total, 60 patients underwent combination D-TACE-HAIC, lenvatinib, and PD-1 inhibitor treatment (Group A), while 21 underwent combination TACE and sorafenib treatment (Group B). The Medical Ethics Committee of the senior Department of Hepato-Pancreato-Biliary Surgery, the First Medical Center of PLA General Hospital approved this study, with all patients having provided written informed consent.

Patient Inclusion and Exclusion

Eligible patients were those individuals who (1) were diagnosed with HCC as per the Diagnostic and Therapeutic Guidelines for HCC of the China Healthcare Commission (2022 edition), or those with pathologically confirmed disease; (2) patients with stage Ib, IIa, or IIb disease who were not eligible for radical surgical treatment owing to severe cirrhosis or insufficient residual functional liver volume, or those with stage IIIa or IIIb disease; (3) patients with Child-Pugh classifications of A or B; (4) patients with an ECOG physical status of 0–1; and (5) patients with good organ function who were not receiving any antitumor targeted immunotherapies. Patients were excluded if they had received a pathologic diagnosis of fibrous platysmal or sarcomatoid HCC, exhibited disease with a cholangiocarcinoma component, had a Child-Pugh classification of C, were in poor general condition, exhibited serious cardiopulmonary disease, or were unable to tolerate targeted immunotherapy.

Therapy

Group A treatment: Patients < 60 kg and ≥ 60 kg were respectively treated with oral lenvatinib at doses of 8 mg/day and 12 mg/day. Patients were administered intravenous PD-1 inhibitors and underwent D-TACE-HAIC treatment every 3 weeks. D-TACE-HAIC was performed with the Seldinger technique, in which a percutaneous femoral artery was cannulated for

abdominal arteriography, inserting a catheter to conduct arteriography in the celiac trunk and superior mesenteric artery. Based on the arterial blood supply for the target tumor, a microcatheter was inserted at the end of the tumor blood-supplying artery, with the peripheral and distal tumor blood supply then being embolized using drug-loaded microspheres that had been mixed with oxaliplatin (50 mg) without complete devascularization. After embolization, the microcatheter was allowed to remain in the main trunk of the tumor blood-supplying artery or the left/right hepatic artery, and aqueous heparin (10 mL; 1,000 U, diluted 1:1,000) was injected to protect against any microcatheter-associated coagulation. The area exposed to the catheter was covered using sterile medical gauze and secured to the skin of the groin and lower abdomen. This microcatheter was connected to a micro-pump which was used to continuously infuse oxaliplatin (85 mg/m^2) for 2 h, calcium folinate (400 mg/m^2) for 2h, 5-fluorouracil (400 mg/m^2) for 15 min, and 5-fluorouracil (2400 mg/m^2) for 46 h.

Group B treatment: Patients in Group B received oral sorafenib 400 mg twice per day and underwent TACE treatment every 3–4 weeks based on the physical condition and liver function of each patient. TACE was performed with the Seldinger technique, with percutaneous femoral artery puncture intubation to abdominal arteriography. After tumor vessels and blood-supplying arteries had been defined, pirorubicin (40 mg) emulsified with iodine oil (10–20 mL) was administered for vein chemoembolization.

Adverse Event Management

Drug-related adverse events (AEs) were assessed using the common terminology criteria for adverse events 5.0 (CTCAE 5.0). In cases where the side effects of lenvatinib or sorafenib were intolerable for patients, treatment was discontinued to await recovery, after which the corresponding drugs were administered as per relevant guidelines with delayed treatment or reduced dosages.[16,17] Treatment was interrupted if patients exhibited tumor progression or experienced excessive toxic side effects.

Evaluation of Clinical Efficacy

Patients in both groups underwent routine blood testing, tumor marker analyses, and tests of liver and kidney function prior to each 3-week treatment cycle. Tumors were evaluated every two cycles via CT or MRI with enhancement. Portal and hepatic vein thrombosis staining was performed in accordance with the Japanese Liver Cancer Study Group.[18] In cases where radical surgery or radiofrequency was feasible, PD-1 inhibitor treatment and lenvatinib treatment were respectively discontinued three and one weeks before surgery. Adjuvant therapy was initiated 2–3 weeks post-surgery, with the treatment regimen being selected as per the degree of pathological remission for a given patient. PD-1 inhibitor treatment alone was administered for 6 months when patients achieved a pathologic complete response (pCR). Treatment was continued for 12 months using the original regimen but discontinuing D-TACE-HAIC or TACE when patients did not achieve pCR. D-TACE-AIC or TACE were discontinued in cases of stenosis or occlusion of the artery supplying blood to the tumor as a result of repeated D-TACE-HAIC or TACE treatment, the loss of blood supply to the extrahepatic side branches, or loss of an intratumoral blood supply. Tumor responses were assessed as per the modified response evaluation criteria in solid tumor (mRECIST) criteria, and were classified into cases of complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). In addition, patient progression-free and overall survival (PFS and OS) as well as objective response rate (ORR) and disease control rate (DCR) were evaluated.[19,20] Outpatient or telephone-based follow-up were performed through March 2023.

Statistical Analysis

Data were analyzed with SPSS 20.0. Categorical data are reported as cases (%) and were compared with chi-square and Fisher's exact test. The Kaplan-Meier method was used for survival curve construction, while survival comparisons were made with the Log rank test. Cox regression models were used to identify factors associated with survival. $P < 0.05$ served as the significance threshold.

Results

Clinicopathological Characteristics

Of the patients enrolled in this study, 95.1% were HBsAg positive, while 66.7% exhibited alpha-fetoprotein (AFP) levels exceeding 400 ug/L (Table 1). Liver function tests indicated that the total bilirubin (TB) and glutamic pyruvic

Table 1 The Clinicopathological Characteristics of the Enrolled Hepatocellular Carcinomas Patients

Characteristics	Group A	Group B	χ^2	*P*
Gender			2.905	0.088
Man	52	14		
Women	8	7		
Age (yr)			0.006	0.940
≤50	28	10		
>50	32	11		
ECOG Score			0.001	0.970
0	26	9		
1	34	12		
Child-Pugh Categorization			0.103	0.748
A	45	15		
B	15	6		
HbsAg			0.294	0.588
Positive	57	20		
Negative	3	1		
AFP (ug/L)			0.289	0.591
≤400	19	8		
>400	41	13		
TB (umol/L)			0.131	0.717
≤20	55	18		
>20	5	3		
ALT (U/L)			0.008	0.931
≤60	50	17		
>60	10	4		
ALB (g/L)			0.886	0.347
≥40	5	4		
<40	55	17		
Tumor size (cm)			0.230	0.650
≤10	28	11		
>10	32	10		
Portal vein cancer embolus			0.009	0.924
Positive	35	12		
Negative	25	9		
Hepatic vein cancer embolus			0.230	0.632
Positive	14	6		
Negative	46	15		

Abbreviations: AFP, alpha fetoprotein; TB, total bilirubin; ALT, glutamic pyruvic transaminase; ALB, albumin.

transaminase (ALT) levels were reduced in both groups (Table 1), with a significant decrease in albumin (ALB) levels. Imaging results suggested that portal vein tumor thrombosis was more common than hepatic vein tumor thrombosis in this study cohort.

Surgical Conversion

The median number of D-TACE-HAIC treatment cycles in Group A was 2 (2–40, while the median number of TACE cycles in Group B was 2 (1–3). Radical hepatectomy was successfully performed after treatment for 20 patients in Group A but just 2 patients in Group B. The rate of surgical conversion in Group A of 33.3% (20/60) was significantly higher than the Group B rate of 9.5% (2/21) ($\chi 2=5.181$, $P < 0.05$). Three patients in Group A and none in Group B achieved postoperative pathologic CR.

Clinical Efficacy

Per the mRECIST criteria, significantly higher PR and OR rates were observed for patients in Group A relative to Group B, whereas SD rates in Group A were significantly lower than in Group B ($P < 0.05$, Table 2). There was no significant difference between these groups in DCR.

Adverse Reactions

With respect to overall AEs, rates of hypertension, abdominal pain, leukopenia, thrombocytopenia, and hypoproteinemia in Group A were significantly higher than those in Group B. With respect to Grade 3–4 AEs, abdominal pain, leukopenia, and thrombocytopenia rates in Group A were significantly higher than those in Group B (Table 3). There were no significant differences in the incidence rates for any other AEs between these groups, nor did either group exhibit any instances of treatment-associated death.

Prognosis

Enrolled patients were followed for a median 15.3 (range: 7.5–30.4) month interval. In total, 43 and 4 patients in Group A and Group B, respectively, survived. The median PFS in Group A was 13.2 months (95% CI: 10.32–15.34) as

Table 2 Assessment of Clinical Efficacy of Hepatocellular Carcinoma Patients in Two Groups

Clinical Efficacy	RECIST				mRECIST			
	Group A	Group B	χ^2	*P*	Group A	Group B	χ^2	*P*
CR	0	0	/	/	5 (8.3)	1 (4.8)	0.003	0.957
PR	12 (20)	4 (19)	0.050	0.823	47 (78.3)	6 (28.6)	17.030	0.000
SD	45 (75)	14 (66.7)	0.546	0.460	6 (6)	12 (57.1)	17.367	0.000
PD	3 (5)	3 (14.3)	0.836	0.361	2 (3.4)	2 (9.5)	0.294	0.588
DCR	57 (95)	18 (85.7)	0.836	0.361	58 (96.6)	19 (90.4)	0.294	0.588
ORR	12 (20)	4 (19)	0.050	0.823	52 (86.6)	7 (33.4)	22.365	0.000

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; ORR, objective remission rate.

Table 3 Adverse Reactions Statistics in Two Groups

AEs	Overall				3–4 grade			
	Group A	Group B	χ^2	*P*	Group A	Group B	χ^2	*P*
Weaken	20 (33.3)	4 (19.0)	1.532	0.217	4 (6.6)	1 (1.6)	0.064	0.830
Weight loss	25 (41.7)	4 (19.0)	3.463	0.063	5 (8.3)	1 (1.6)	0.003	0.957
Nausea	15 (25.0)	6 (28.5)	0.103	0.748	3 (5.0)	1 (1.6)	0.294	0.588
Emesis	10 (16.7)	5 (23.8)	0.159	0.690	3 (5.0)	1 (1.6)	0.294	0.588
Diarrhea	8 (13.3)	7 (33.3)	2.905	0.088	3 (5.0)	1 (1.6)	0.294	0.588
Abdominal pain	28 (46.7)	3 (14.2)	6.904	0.009	13 (21.6)	0 (0.0)	3.931	0.047
Hypertension	35 (58.3)	2 (9.5)	14.935	0.000	4 (6.6)	1 (1.6)	0.046	0.830
Erythra	20 (33.3)	0 (0.0)	9.295	0.002	3 (5.0)	0 (0.0)	0.000	0.564
Peripheral neuropathy	12 (20.0)	3 (14.3)	0.064	0.800	2 (3.3)	0 (0.0)	0.000	1.000
Hand-foot syndrome	8 (13.3)	9 (42.8)	6.493	0.011	2 (3.3)	0 (0.0)	0.000	1.000
Leukopenia	35 (58.3)	4 (19.0)	9.616	0.002	19 (31.6)	2 (9.5)	3.971	0.046
Thrombocytopenia	35 (58.3)	4 (19.0)	9.616	0.002	19 (31.6)	1 (4.7)	6.056	0.014
Elevated ALT	20 (33.3)	9 (42.8)	0.614	0.433	6 (10.0)	2 (3.3)	0.131	0.717
Hyperbilirubinemia	8 (13.3)	3 (14.3)	0.068	0.795	2 (3.3)	0 (0.0)	0.000	1.000
Hypoproteinemia	23 (38.3)	2 (9.5)	6.051	0.014	2 (3.3)	0 (0.0)	0.000	1.000

Abbreviations: AEs, adverse events; ALT, glutamic pyruvic transaminase.

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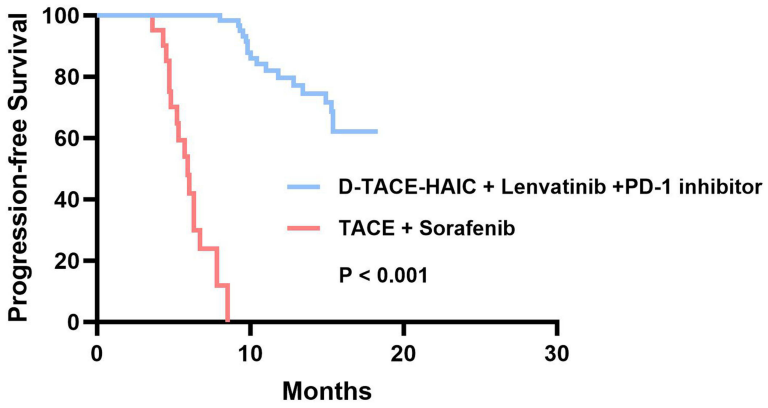

Figure 1 HCC patient progression-free survival in the two study groups.

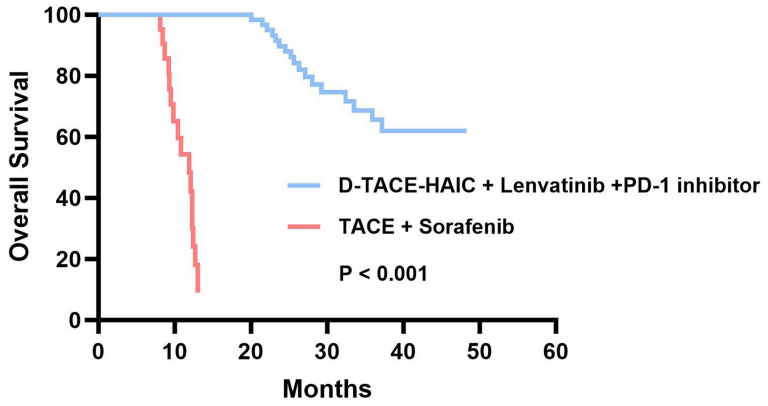

Figure 2 HCC patient overall survival in the two study groups.

compared to 5.7 months (95% CI: 4.58–6.23) in Group B (Figure 1). The median OS of patients in Group A was 28.8 months (95% CI: 14.28–44.63) as compared to 10.8 months (95% CI: 9.32–12.37) in Group B (Figure 2). Significant differences were observed between these groups with respect to both PFS ($\chi 2=31.324$, $P<0.05$) and OS ($\chi 2=67.349$, $P<0.05$). In Cox multivariate analyses, combined treatment with D-TACE-HAIC, lenvatinib, and PD-1 inhibitors was independently associated with patient PFS and OS (HR=0.248, 0.487; $p<0.05$).

Discussion

Per current consensus guidelines, technically unresectable HCC (stage Ia, Ib, IIa) and oncologically unresectable HCC (stage IIb, IIIa) are classified as cases of junctional resectable HCC. Efforts to actively explore transformative preoperative treatments are encouraged for these patients with the aim of improving overall prognostic outcomes. In some patients with technically unresectable stage IIb and IIIa HCC, the combination of aggressive systemic and local treatment can improve overall surgical accessibility.[21] Preoperative TACE and radiotherapy in cases of unresectable HCC can potentially lead to tumor downstaging, thereby providing patients with the opportunity to undergo surgery. In past studies, conventional TACE treatment strategies have been shown to be effective but suboptimal.[22–25] The increasingly common application of targeted immunotherapies and combination D-TACE, HAIC, radiotherapy, and radiofrequency-based treatment strategies has contributed to increasingly encouraging treatment efficacy for HCC patients in the clinic.[26,27] In HCC patients exhibiting a large tumor burden, an abundant tumor blood supply, and portal vein tumor thrombosis, D-TACE of the distal and peripheral tumor blood supply can provide an effective means of preserving the

overall blood supply without complete devascularization. This approach, together with subsequent HAIC treatment, can significantly reduce the total chemotherapeutic drug doses used while prolonging the duration of efficacy for highly concentrated chemotherapeutic drugs, improving the overall therapeutic efficacy.[28,29] Lenvatinib can also selectively bind to inhibit TACE-induced VEGF generation.[30,31] Regulatory T cells (Tregs) are key immunosuppressive effectors, and TACE treatment can reduce the overall proportion of Tregs, thereby improving immune function and enhancing overall immunotherapeutic efficacy.[9,32,33]

The present results revealed that when treating cases of unresectable HCC, D-TACE-HAIC combined with lenvatinib and PD-1 significantly outperformed the combination of TACE and sorafenib with respect to the surgical conversion rate, median OS, PFS, and ORR of treated patients. In total, 20 patients from the combination D-TACE-HAIC group were able to undergo subsequent radical surgery, of whom 3 achieved postoperative pathologic CR. In contrast, just 2 of the patients from the combined TACE and sorafenib treatment group had the opportunity to undergo radical surgery, and neither achieved pathologic CR. Per the mRECIST criteria, the objective remission rate in the combination D-TACE-HAIC + lenvatinib + PD-1 inhibitor group was significantly higher than that in the TACE + sorafenib group (86.6% vs 33.4%). The D-TACE-HAIC + lenvatinib + PD-1 inhibitor regimen thus provides HCC patients with a greater potential for conversion to radical surgery. Even in cases when this combined regimen did not lead to radical surgical treatment, it did effectively arrest tumor progression, prolonging patient survival and increasing the odds of long-term survival such that the treated HCC patients can be regarded as having a chronic disease.

With respect to AEs, the combined D-TACE-HAIC + lenvatinib + PD-1 inhibitor regimen was associated with significantly higher rates of hypertension, abdominal pain, leukopenia, thrombocytopenia, and hypoproteinemia relative to TACE + sorafenib treatment, while the rate of hand-foot syndrome was significantly reduced relative to that in the TACE + sorafenib group. The D-TACE-HAIC + lenvatinib + PD-1 inhibitor group also presented with higher rates of grade 3–4 AEs including abdominal pain, leukopenia, and thrombocytopenia, while there were no significant differences between these two groups with respect to other grade 3–4 AEs. This difference is presumably related to the fact that the former regimen entails the combination of several different therapies, thereby incurring a greater risk of AE incidence. Fortunately, the majority of patients were able to tolerate these treatment-related AEs, with symptomatic treatment coinciding with significant reductions in tumor size and no instances of treatment-related mortality. The most common treatment-related AEs were leukopenia and thrombocytopenia, which were largely managed successfully through the administration of granulocyte-stimulating factor and thrombopoietin. In patients experiencing severe myelosuppression, the dose of chemotherapeutic drugs including oxaliplatin can be reduced as needed. Abdominal pain in both groups was primarily associated with vasospasm and necrosis following tumor embolization as a result of oxaliplatin infusion. These symptoms can be rapidly relieved by slowing or arresting the oxaliplatin infusion and administering appropriate analgesic or antispasmodic drugs. Rashes were primarily associated with oral lenvatinib and sorafenib administration, and were resolved in patients following dose reductions or suspension. Hypertension was primarily associated with oral lenvatinib administration and can be alleviated through symptomatic antihypertensive management. These results thus suggest that combining D-TACE-HAIC with lenvatinib and PD-1 inhibitors can effectively achieve high levels of translational efficacy without causing any serious immune-related AEs.

Conclusions

In summary, relative to combination TACE plus sorafenib treatment, the management of unresectable HCC using a combination of D-TACE-HAIC, lenvatinib, and PD-1 inhibitors is associated with a more favorable safety profile, shortening the cycle of translational therapy, improving overall translational therapeutic efficacy, increasing rates of surgical conversion, prolonging patient survival, and affording long-term survival benefits.

Ethical Statement

All patients submitted their informed consent before enrolment. This study was approved by the Medical Ethics Committee of the senior Department of Hepato-Pancreato-Biliary Surgery, the First Medical Center of PLA General Hospital. The research was performed following the World Medical Association Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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