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Donafenib versus sorafenib in triple therapy for unresectable hepatocellular carcinoma: a propensity score-matched multicenter analysis

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Abstract

Background In recent years, triple therapy (molecular targeted agent + PD-1 inhibitor + transarterial therapy) has emerged as a promising strategy for unresectable hepatocellular carcinoma (uHCC). However, the optimal molecular targeted agent choice within triple therapy remains unclear. Donafenib is currently the only targeted drug with superior survival benefits compared with sorafenib monotherapy. This study aimed to compare donafenib-based versus sorafenib-based triple therapy in patients with uHCC, providing preliminary evidence to guide molecular targeted agent selection in this emerging treatment paradigm.

Methods This retrospective study enrolled 106 patients with initially uHCC who received triple therapy combining either donafenib or sorafenib with PD-1 inhibitors and transarterial therapies. A 1:2 nearest neighbour propensity score matching was used to minimize selection bias. The primary endpoints were overall survival (OS) and progression-free survival (PFS) based on Kaplan-Meier analysis. The secondary endpoints included objective response rate (ORR), surgical conversion rate and adverse events (AEs). Statistical comparisons used Cox regression for survival data and chi-squared/ t-tests for other metrics, with $p < 0.05$ indicating significance.

Results After matching, 30 patients received sorafenib-based triple therapy (Sor-P-T/H group) and 50 patients received donafenib-based triple therapy (Don-P-T/H group). Although the median OS was not attained, the Don-P-T/H regimen demonstrated a statistically significant survival advantage (HR = 0.317, $P = 0.004$). Moreover, the Don-P-

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T/H group demonstrated significantly higher median PFS (9.00 vs. 4.62 months, $P=0.005$), ORR (64% vs. 40%, $P=0.037$) and surgical conversion rate (26.0% vs. 3.3%, $P=0.01$) compared to the Sor-P-T/H group. The two groups showed no notable difference in the overall severity of adverse events but the Don-P-T/H group demonstrated less liver impairment.

Conclusion Donafenib may be more advantageous than sorafenib in triple therapy for patients with uHCC.

Keywords Hepatocellular carcinoma, Molecular targeted agent, Transarterial therapy, PD-1 inhibitor, Triple therapy

Introduction

Primary liver cancer is the sixth leading malignant tumor as well as the third leading cause of cancer-related deaths worldwide [1]. Hepatocellular carcinoma (HCC), the most common pathological type of primary liver cancer, is discussed in this study. Currently, surgical resection remains the primary treatment for patients with HCC to achieve long-term survival. However, most patients with HCC are diagnosed at unresectable status initially and surgical resection is feasible in less than 30% of patients in China [2]. Therefore, the treatment of HCC requires enhancing the objective remission rate of uHCC, prolonging the survival of uHCC patients, and raising the conversion resection rate to achieve complete eradication.

In recent years, with the rapid development of targeted therapy and immunotherapy, triple therapy (molecular targeted agent + PD-1 inhibitor + transarterial therapy) has emerged as a key strategy for the conversion treatment of unresectable hepatocellular carcinoma (uHCC). Many clinical studies have explored the triple therapy strategy of molecular targeted agents combined with PD-1 inhibitors plus transarterial therapy and demonstrated desirable positive results [3–5]. This triple therapy strategy exerts stronger anti-tumour effects through the synergistic action of multiple mechanisms. It has been reported that targeted drugs can improve the tumor immune microenvironment by normalizing blood vessels, thereby improving the therapeutic effect of immune checkpoint inhibitors [6–8]. Meanwhile, immunosuppressants can activate $CD4^+$ and $CD8^+$ T cells to promote the restoration of tumor blood vessels [6, 9]. Moreover, transarterial therapy can diminish tumor load and stimulate the immune system through tumor neoantigens and inflammatory factors [10, 11]. However, due to the diversity of targeted agents, PD-1 inhibitors, and interventional drugs, direct comparison of all possible triple combinations is neither realistic nor feasible, resulting in a lack of uniform dosing criteria and clinicians relying on personal experience to select drugs. In addition, existing studies mostly focus on comparing triple therapy to dual therapy to confirm the efficacy of triple therapy, but this approach could not adequately address the clinical needs of uHCC patients for an optimized triple therapy regimen.

Therefore, we attempted to use a stepwise optimisation research method, first identifying the optimal targeted drug within the framework of triple therapy. Compared to existing literature, our study was the first to directly compare two triple therapy regimens for uHCC. Sorafenib, the first-line standard of care for over a decade, has been used in combination with PD-1 inhibitors and transarterial therapy recently and shown improved efficacy [12–14]. After numerous failed head to head studies, donafenib became the only molecular targeted agent that was superior to sorafenib in terms of overall survival (OS) as the first-line treatment of advanced HCC (median OS, 12.1 vs. 10.3 months; HR: 0.831; 95% CI: 0.699–0.988; $P=0.0245$) [15]. Donafenib differs from sorafenib in that all the hydrogen atoms on the rightmost aminomethane are replaced with deuterium atoms. This deuteration can alter drug metabolism, improve pharmacokinetics, reduce the rate of drug metabolism, prolong half-life, and reduce toxicity [16–18]. Currently, the Chinese guidelines recommend the use of donafenib for the first-line treatment of uHCC in patients who have not received prior systemic antitumor therapy [19]. Based on these findings, we previously further investigated the efficacy and safety of triple therapy combining donafenib, PD-1 inhibitors, and transarterial therapy in patients with uHCC. The preliminary results, demonstrating an objective response rate (ORR) of 59.3% and a disease control rate (DCR) of 92.6%, were presented at the 2023 ASCO Annual Meeting (Abstract e16135) [20]. Moreover, some clinical studies have demonstrated that donafenib-based triple therapy has better benefits than dual therapy for patients with uHCC [21–22]. Therefore, the aim of this study was to compare the efficacy and safety of donafenib with sorafenib in triple therapy to provide a clinical rationale for optimising treatment options for patients with unresectable hepatocellular carcinoma.

Methods

Population and study design

We collected and organized the clinically relevant data of initially uHCC patients treated with triple therapy (either donafenib + PD-1 inhibitor + transarterial therapy or sorafenib + PD-1 inhibitor + transarterial therapy) from May 2021 to September 2023 at Zhujiang Hospital of Southern Medical University and The First Affiliated

Hospital of Hunan Normal University retrospectively. The main inclusion criteria were as follows: (1) Diagnosis of HCC based on the Chinese clinical diagnostic criteria of HCC according to the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition); (2) Consideration of initially uHCC from surgical or oncological perspectives; (3) At least one measurable target lesion according to the Response Evaluation Criteria in Solid Tumors, including RECIST v1.1 and mRECIST; (4) Age 18 or older; (5) Child-Pugh class A or B; (6) Eastern Cooperative Oncology Group performance status (ECOG-PS) score 0–1; (7) No severe cardiac, pulmonary or renal dysfunction. The main exclusion criteria were as follows: (1) Other concomitant active malignancies; (2) Other anti-tumour treatments before triple therapy; (3) Contraindications to donafenib/sorafenib, PD-1 inhibitors, or transarterial therapy; and (4) Incomplete follow-up data.

The study was registered at ClinicalTrials.gov (identifier: NCT05638438). The trial protocol was approved by the institutional review board of all participating hospitals.

Therapeutic regimens

Patients in the Don-P-T/H group received oral donafenib 0.2 g twice daily, while those in the Sor-P-T/H group were administered oral sorafenib 0.4 g twice daily. PD-1 inhibitors such as tislelizumab, camrelizumab, and sintilimab were administered intravenously on a tri-weekly schedule.

Transarterial therapy, comprising transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), was administered every 4 weeks. TACE: Following local anesthesia, the right femoral artery was accessed via the Seldinger technique, and a 5 F catheter sheath was inserted using an exchange guidewire. The catheter was intubated into the abdominal artery for the purpose of imaging to determine the extent, size, location, and blood supply of the tumor. Microcatheters were inserted into the tumor-supplying artery, followed by the injection of 10 mL of superliquefied iodine oil and embolization with microspheres (100–300 μm) into the artery's main branch. The catheter was retained in the hepatic artery for subsequent perfusion chemotherapy. Chemotherapeutic drugs include raltitrexed, doxorubicin, and lopressors. Following local infiltration, the right femoral artery was punctured using the Seldinger technique. Angiography was performed by sequentially inserting catheters into the abdominal and hepatic arteries to assess the tumor's scope, size, location, and blood supply. The catheter was retained in the hepatic artery for subsequent perfusion chemotherapy. Chemotherapeutic drugs include raltitrexed, doxorubicin, and lopressors. HAIC: After local infiltration, the right femoral artery was punctured using the Seldinger technique, and the abdominal and hepatic arteries were inserted sequentially for angiography to determine the scope of the tumor, its size, location, and blood supply. The catheter was then super-selected to the tumor's blood vessel, and then the catheter was retained in the main trunk of the right or left hepatic artery or its branches (based on the tumor's location) and fixed in vitro, sealed with heparin saline. The catheter was fixed, sealed with heparin saline, and connected to a syringe pump for the continuous infusion of chemotherapeutic agents. The FOLFOX chemotherapy regimen involved an arterial infusion of oxaliplatin (130 mg/m^2) for 2 hours, calcium folinate (400 mg/m^2) for 1.5 h, and 5-fluorouracil (400 mg/m^2) for 2 hours, followed by a continuous arterial infusion of 5-fluorouracil (2,400 mg/m^2) over 46 h.

Collection of baseline and follow-up data

We collected and analyzed clinical baseline and follow-up data from eligible patients, including relevant clinical information such as age, sex, BCLC stage, hepatitis B virus (HBV) infection status, cirrhosis status, number of tumors, tumor size, portal vein tumor thrombus, extrahepatic metastasis, Child-Pugh classification, and relevant test indices such as alpha-fetoprotein (AFP), total bilirubin (TBIL), aspartate aminotransferase (AST) and so on. Tumor response was assessed by imaging evaluations based on mRECIST, which were performed by specialized radiologists every 4 weeks. The follow-up data were recorded until disease progression or death or to the follow-up cut-off date (December 15, 2023).

Evaluation indicators

The primary endpoints were OS and PFS. OS was defined as the duration from the start of combination therapy to death from any cause. PFS was the time from the start of combination therapy to disease progression or death. The Secondary endpoints included the ORR, surgical conversion rate and AEs. ORR was the total proportions of complete response (CR) and partial response (PR). Disease control rate (DCR) was the sum of CR, PR, and stable disease(SD). Surgical conversion rate was referred to proportion of patients with uHCC accepted surgical resection after conversion therapy. Adverse events (AEs) were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0).

Statistical analysis

All statistical analyses were performed using R4.3 software. Chi-square tests were used for categorical variables, while t-tests were applied to continuous variables. Fisher's exact test was applied for sample sizes under 40 or when the expected frequency was below 1.The

Kaplan-Meier method was used to analyze OS and PFS, while Cox univariate and multivariate regressions were utilized to estimate prognostic factors for both OS and PFS. A *p*-value threshold of 0.05 was used to determine statistical significance.

To reduce confounders and selection bias, we performed propensity score matching (PSM). The covariates in the analysis included sex, age, viral hepatitis, Child-Pugh score, AFP level, BCLC stage, ECOG-PS score, tumor number, tumor size, portal vein tumor thrombus (PVTT), extrahepatic metastases, liver cirrhosis, and times of receiving TACE/HAIC. A 1:2 nearest neighbour matching was used with a caliper width of 0.2. Due to limitations in the matching algorithm and sample size, the final matched patient numbers may not perfectly align with this ratio to ensure the quality of matching.

Results

Clinical characteristics

A total of 106 patients with uHCC were included from 2 hospitals in China according to the following criteria: 70 received donafenib + PD-1 inhibitor + TACE/HAIC, and 36 received sorafenib + PD-1 inhibitor + TACE/HAIC. After propensity score matching (1:2), 30 patients in the Sor-P-T/H group were matched to 50 patients in the Don-P-T/H group. In general, the two groups in matched cohorts had balanced baseline characteristics (Supplemental Table 1). There were 72 (90%) men and 8 (10%) women in the analysis. HBV infection was present in 64 patients (39[78%] in the Don-P-T/H group and 25[83%] in the Sor-P-T/H group). There were 34 patients (68%) presented with BCLC stages C in the don-P-T/H group and 23 patients (77%) presented with BCLC stages C in the Sor-P-T/H group. All patients in this study received more than two cycles of combination therapy, with a mean of 3.00 cycles of transarterial therapy (TACE/HAIC).

Efficacy

The main observational objectives of this study were to evaluate OS and PFS. After matching, the median OS was not reached in the Don-P-T/H group, and the median OS in the Sor-P-T/H group was 12.90 months (95% CI: 8.80–NA). Compared with the Sor-P-T/H group, the Don-P-T/H group exhibited a remarkable improvement in overall survival ($P = 0.004$, HR = 0.317) (Fig. 1a). The Don-P-T/H group exhibited a significantly higher median PFS of 9.00 months (95% CI: 6.07–NA) compared to 4.62 months (95% CI: 2.57–8.20) in the Sor-P-T/H group ($P = 0.005$, HR = 0.470) (Fig. 1b). Stratified analysis revealed that when stratified by AFP levels (AFP < 400 μg/L vs. AFP ≥ 400 μg/L), both OS and PFS were significantly higher in the Don-P-T/H group than in the Sor-P-T/H group if AFP was ≥ 400 μg/L (Fig. 2a, b). In addition, the surgical conversion rate of the Don-P-T/H group was significantly higher than the Sor-P-T/H group (26.0% vs. 3.3%; $P = 0.01$) (Fig. 3).

The secondary observational objective included the ORR based on mRECIST. After matching, the ORR was 64% and 40% in the Don-P-T/H and Sor-P-T/H groups with significant difference ($P = 0.037$). Moreover, the DCR in the Don-P-T/H group was 96%, significantly surpassing the 80% observed in the Sor-P-T/H group ($P = 0.047$) (Table 1). In patients with AFP levels ≥ 400 μg/L, the Don-P-T/H group exhibited a significantly higher ORR compared to the Sor-P-T/H group (Table 2).

Prognostic factor analysis

Cox regression models were used for univariate and multivariate analyses to identify independent prognostic

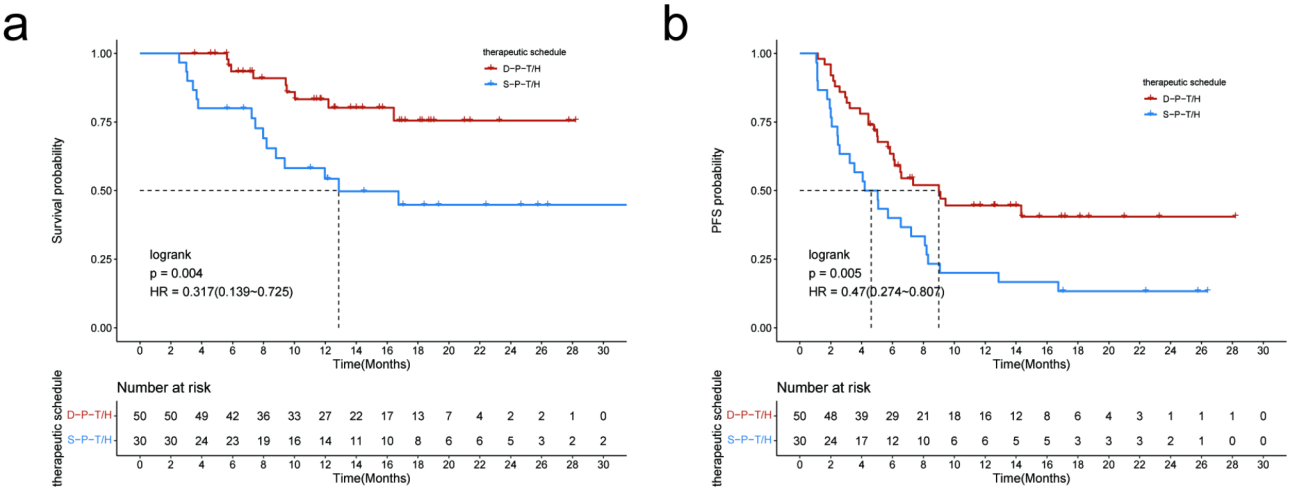

Fig. 1 OS and PFS with different therapeutic schedules. (**a**) OS in the Don-P-T/H group and the Sor-P-T/H group. (**b**) PFS in the Don-P-T/H group and the Sor-P-T/H group

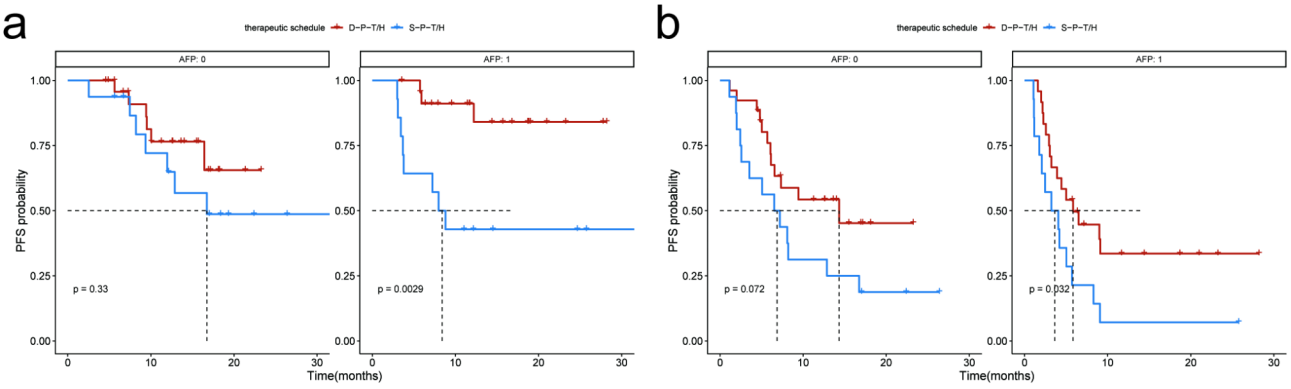

Fig. 2 Subgroup analysis for OS and PFS stratified by AFP levels. ("0" represents AFP < 400 μg/L and "1" represents AFP ≥ 400 μg/L) (**a**) OS in the Don-P-T/H group and the Sor-P-T/H group stratified by AFP level. (**b**) PFS in the Don-P-T/H group and the Sor-P-T/H group stratified by AFP level

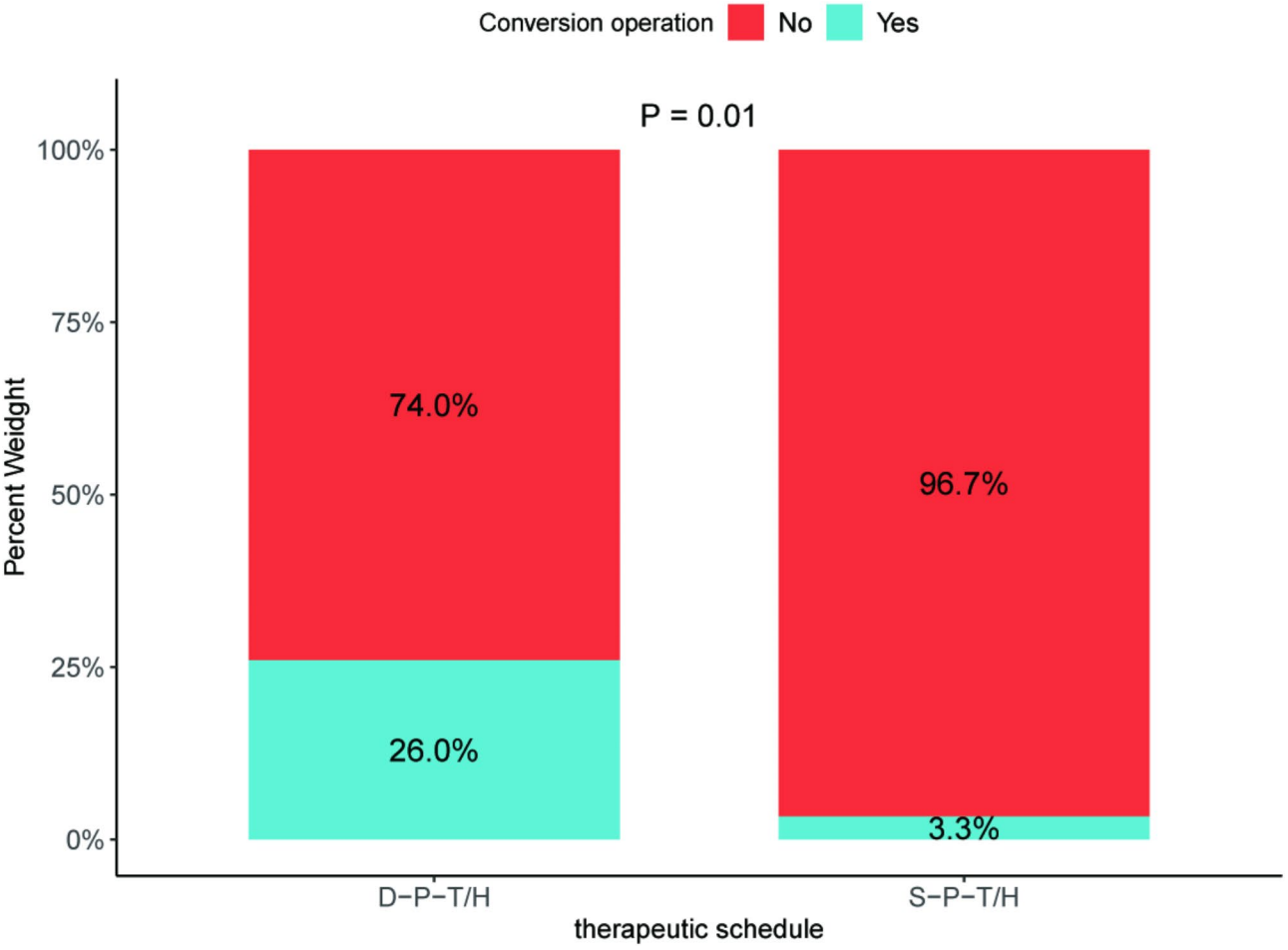

Fig. 3 Comparison of surgical conversion rates between the Don-P-T/H group and the Sor-P-T/H group. (green column displays the conversion success rate and the red column displays the conversion failure rate)

factors for OS and PFS. In the univariate analysis (Fig. 4a, b), OS was associated with therapeutic schedule and Child-Pugh score, while PFS was associated with therapeutic schedule, ECOG score, Child-Pugh score, extrahepatic metastasis, and tumor size. The multivariate analysis (Fig. 4c, d) revealed that treatment with Don-P-T/H compared to Sor-P-T/H was an independent prognostic factor for both OS (HR = 0.341, 95% CI: 0.168–0.690, $p = 0.003$) and PFS (HR = 0.469, 95% CI: 0.285–0.771, $p = 0.003$). Additionally, tumor size and extrahepatic metastasis were identified as independent prognostic factors for PFS in the multivariate analysis.

Table 1 Best tumor response according to the mRECIST

Characteristic	D-P-T/H, $N=50$[1]	S-P-T/H, $N=30$[1]	*p*-value[2]
Best tumor response			0.041
CR	4 (8%)	0 (0%)	
PR	28 (56%)	12 (40%)	
SD	16 (32%)	12 (40%)	
PD	2 (4%)	6 (20%)	
ORR	32 (64%)	12 (40%)	0.037
DCR	48 (96%)	24 (80%)	0.047

[1] *n* (%)

[2] Fisher's exact test; Pearson's Chi-squared test

ORR: Objective response rate; DCR: Disease control rate; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease

Table 2 Therapeutic efficacy in patients stratified by AFP level

Characteristic	AFP level(ug/L) < 400, $N=42$			AFP level(ug/L) ≥ 400, $N=38$		
	D-P-T/H, $N=26$[1]	S-P-T/H, $N=16$[1]	*p*-value[2]	D-P-T/H, $N=24$[1]	S-P-T/H, $N=14$[1]	*p*-value[2]
mRECIST			0.482			0.052
CR	3 (12%)	0 (0%)		1 (4%)	0 (0%)	
PR	15 (58%)	9 (56%)		13 (54%)	3(21%)	
SD	7 (27%)	5 (31%)		9 (38%)	7 (50%)	
PD	1 (3%)	2 (13%)		1 (4%)	4 (29%)	
ORR	18 (69%)	9 (56%)	0.394	14 (58%)	3 (21%)	0.027
DCR	25 (96%)	14 (88%)	0.547	23 (96%)	10 (71%)	0.052

[1] *n* (%)

[2] Fisher's exact test; Pearson's Chi-squared test

ORR: Objective response rate; DCR: Disease control rate; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease

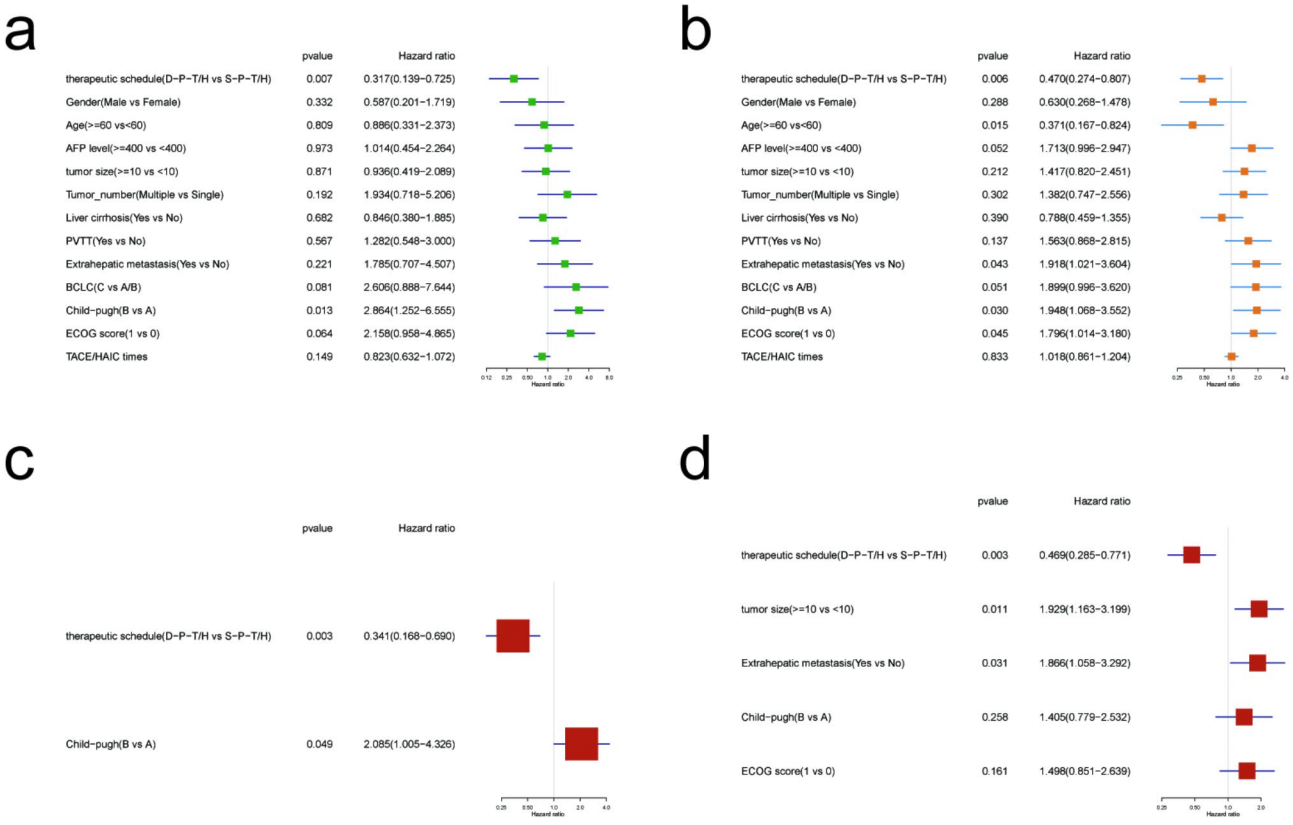

Fig. 4 Univariate and multivariable Cox regression analysis for OS and PFS. (**a**) Univariate Cox regression analysis for OS. (**b**) Univariate Cox regression analysis for PFS. (**c**) Multivariable Cox regression analysis for OS. (**d**) Multivariable Cox regression analysis for PFS

Table 3 Treatment-related adverse events

Characteristic	Overall, $N=80$[1]	D-P-T/H, $N=50$[1]	S-P-T/H, $N=30$[1]	*p*-value[2]
Fever	29.0 (36.3%)	16.0 (32.0%)	13.0 (43.3%)	0.307
Abdominal pain	29.0 (36.3%)	18.0 (36.0%)	11.0 (36.7%)	0.952
Nausea	20.0 (25.0%)	17.0 (34.0%)	3.0 (10.0%)	0.016
Vomiting	15.0 (18.8%)	12.0 (24.0%)	3.0 (10.0%)	0.120
Hand-foot skin reaction	22.0 (27.5%)	17.0 (34.0%)	5.0 (16.7%)	0.093
Diarrhea	14.0 (17.5%)	11.0 (22.0%)	3.0 (10.0%)	0.171
Hypertension	17.0 (21.3%)	13.0 (26.0%)	4.0 (13.3%)	0.180
Decreased appetite	8.0 (10.0%)	6.0 (12.0%)	2.0 (6.7%)	0.703
Decreased weight	13.0 (16.3%)	10.0 (20.0%)	3.0 (10.0%)	0.351
Fatigue	9.0 (11.3%)	4.0 (8.0%)	5.0 (16.7%)	0.284
Proteinuria	5.0 (6.3%)	2.0 (4.0%)	3.0 (10.0%)	0.358
Leukocytopenia	14.0 (17.5%)	9.0 (18.0%)	5.0 (16.7%)	0.879
Thrombocytopenia	26.0 (32.5%)	15.0 (30.0%)	11.0 (36.7%)	0.538
Elevated ALT	31.0 (38.8%)	15.0 (30.0%)	16.0 (53.3%)	0.038
Elevated AST	41.0 (51.3%)	20.0 (40.0%)	21.0 (70.0%)	0.009
Elevated TBIL	18.0 (22.5%)	4.0 (8.0%)	14.0 (46.7%)	< 0.001

[1] *n* (%)

[2] Pearson's Chi-squared test; Fisher's exact test

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin

Safety

The most common conditions among patients were elevated AST (51.3%), elevated ALT (38.8%), fever (36.3%), and abdominal pain (36.3%). The overall severity of adverse events did not significantly differ between the two groups ($P=0.84$) (Supplemental Fig. 1). Differences in certain types of AEs were observed between the two groups (Table 3). Nausea was more prevalent in the Don-P-T/H group compared to the Sor-P-T/H group (34.0% vs. 10.0%; $P=0.016$). The proportion of grade 1–3 ALT (30.0% vs. 53.3%, $P=0.038$), AST (40.0% vs. 70.0%, $P=0.009$), and serum bilirubin elevation (8.0% vs. 46.7%, $P<0.001$) in the Donafenib group were lower than Sorafenib group, respectively. All adverse events resolved post-treatment, with no grade 4–5 adverse events or treatment-related fatalities occured in the study.

Discussion

The study showed that uHCC patients treated with donafenib-based triple therapy had better survival results than those treated with sorafenib-based triple therapy. Moreover, all reported treatment-related AEs were manageable, indicating their therapeutic safety. The Don-P-T/H group showed significant improvements in PFS (9.00 vs. 4.62 months, $P=0.005$) and conversion success rates (26.0% vs. 3.3%, $P=0.01$). The Don-P-T/H group exhibited significantly better OS than the Sor-P-T/H group (HR = 0.317, $P=0.004$), with 12-month OS rates of 83.3% versus 54.3%.

The rapid advancement of targeted drugs and immune checkpoint inhibitors has significantly enhanced prognosis of uHCC patients in recent years. The atezolizumab plus bevacizumab regimen used in the IMbrave 150 study demonstrated improved ORR in patients (27.3%) [23], leading to its approval as the preferred first-line treatment for advanced HCC by the BCLC guidelines. A regimen of pembrolizumab plus lenvatinib used in the LEAP-002 study further improved the ORR to 40.8% [24]. These findings indicate that combining systemic and local therapy is a standard approach for treating intermediate to advanced HCC. In our study, the Don-P-T/H group demonstrated a statistically significant survival advantage. This could be attributed to the improved surgical conversion rate achieved using the Don-P-T/H treatment regimen. The surgical conversion rate was 26.0%, notably surpassing that of the Sor-P-T/H group. Conversion therapy, essential for the long-term survival of uHCC patients, reduces tumor size and stage to facilitate surgical resection. The achievement of surgical conversion is usually based on obtaining a high ORR. The ORR in the Don-P-T/H group was 64.0%, which is consistent with the results of previous combination therapy studies [25, 26]. The higher ORR and DCR of Don-P-T/H group suggested it was more effective in reducing tumor burden and controlling disease progression, which was consistent with its better conversion success rate, PFS, and OS. We analyzed OS, PFS, and ORR across different AFP levels and found that when AFP was ≥ 400 μg/L, the Don-P-T/H group had higher OS, PFS, and ORR than the Sor-P-T/H group. AFP is a widely used serum biomarker in HCC treatment. AFP levels are associated with cancer phenotypes such as cirrhosis, vascular invasion, tumor burden, and physical status [27, 28]; higher AFP levels are predictors of poor survival [29, 30]. The Don-P-T/H regimen showed greater efficacy in patients with AFP levels

of 400 μg/L or higher, suggesting its potential benefit for treating HCC patients with elevated AFP.

Cox multivariate analysis identified independent factors linked to OS and PFS, finding therapeutic schedule and Child-Pugh score associated with OS, and therapeutic schedule, tumor size, and extrahepatic metastasis associated with PFS. Both Cox multivariate analysis of OS and PFS confirmed that therapeutic schedule was an independent prognostic factor, with the Don-P-T/H regimen improving the survival benefits for uHCC patients. Although initial evidence suggests that combination therapy can be safely administered in patients with uHCC outside strict Child-Pugh A criteria [31], patients with good Child-Pugh have sufficient stamina to tolerate combination therapy generally which results in better survival benefits. Furthermore, tumor size, in addition to correlating with tumor burden, is an important parameter for assessing the possibility of surgical resection and prognosis [32], especially for patients with isolated tumors, because the smaller the tumor, the better the patient prognosis [33, 34]. According to our findings, extrahepatic spread was the major independent risk factor for survival in patients with uHCC, consistent with previous reports [35, 36].

In this study, AST elevation was the most common treatment-related AE. The Don-P-T/H group had lower proportions for AST elevation, ALT elevation, and serum bilirubin elevation than the Sor-P-T/H group, indicating a lower likelihood of hepatic impairment. This might be due to the deuterated nature of donafenib, which may reduce drug-induced hepatocyte damage. Liver function plays a crucial role in affecting the prognosis of patients with advanced HCC, regardless of whether surgical treatment or systemic treatment is used [29, 37, 38]. Good liver function is crucial for tolerating systemic treatments and qualifying for surgical resection, particularly in uHCC patients. To achieve surgical resection, patients must maintain good liver function after combination therapy. The Don-P-T/H regimen, with its lower hepatotoxicity, can increase the conversion resection rate and is preferable for uHCC patients.

Our study had some limitations. First, this was a retrospective study with a limited number of patients, which might have introduced a selection bias. Second, variations in PD-1 inhibitors and transarterial therapy regimens may introduce heterogeneity and potentially confound the observed benefits of the therapeutic schedules. While propensity score matching was used to reduce selection bias and adjust for known confounders, residual heterogeneity related to treatment protocols can not be entirely eliminated. Future studies with standardized treatment protocols are warranted to further clarify these findings and minimize potential confounding effects. Third, the study had a limited follow-up period and involved a small number of research centers. Therefore, more prospective randomized clinical trials are required to validate our findings. Forth, since HBV is a major cause of HCC in China, 80% (64/80) of the population after propensity score matching in this study were HBV-related uHCC. We should be prudent in applying our conclusions to non-HBV uHCC. International multicenter clinical studies are necessary to validate our findings. Fifth, while our analysis identified key prognostic factors, the observational variables remained incomplete. Future multicenter studies should expand the scope of covariates, such as previous anti-HBV therapy history and so on.

It's worth noting that we fully endorse the authority of the atilizumab + bevacizumab regimen or sorafenib monotherapy as first-line treatment for advanced hepatocellular carcinoma. However, the aim of this study was not to directly challenge the existing gold standard, but to focus on exploring the internal optimisation of the emerging strategy of triple therapy for uHCC. Specifically, we aimed to answer the following question: is donafenib a more suitable component of triple therapy than sorafenib in patients who have opted for a triple therapy strategy? The answer to this question could provide a reference for clinicians' drug selection within the framework of triple therapy. We will conduct prospective studies to validate our current conclusions and mechanistic studies to explore the underlying molecular mechanisms. We also plan to conduct a head-to-head comparative study with the gold standard once we have completed the internal optimisation of triple therapy. The current study is fundamental to this long-term goal.

In summary, donafenib may be more advantageous than sorafenib in triple therapy for patients with uHCC, but this conclusion needs to be validated in a larger prospective study. The findings may provide a promising treatment alternative for uHCC patients, particularly those who may benefit from more aggressive combination strategies.

Abbreviations

HCC	Hepatocellular carcinoma
uHCC	Unresectable hepatocellular carcinoma
TACE	Transarterial chemoembolization
HAIC	Hepatic arterial infusion chemotherapy
ORR	Objective response rate
DCR	Disease control rate
PD	Progressive disease
PR	Partial response
SD	Stable disease
OS	Overall survival
PFS	Progression-free survival
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Tb	Total bilirubin
AFP	Alpha-fetoprotein
PVTT	Portal vein tumor thrombus

BCLC Barcelona Clinic Liver Cancer
ECOG-PS Eastern Cooperative Oncology Group performance status

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03767-5.

Supplemental Table 1: Baseline characteristics of the patients

Supplemental Figure 1: Comparison of severity of adverse events between the Don-P-T/H group and the Sor-P-T/H group

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(I) Conception and design: M Pan, S Liu, L Cai, Y Wen, S Zhou, Y Xu; (II) Administrative support: M Pan, S Liu; (III) Provision of study materials or patients: M Pan, S Liu, L Cai, Y Wen, S Zhou, Y Xu, C Zhang, L Wang; (IV) Collection and assembly of data: Y Wen, S Zhou, C Zhang, Y Song, B Ding, C Peng, H Tan, C Wang, J Feng; (V) Data analysis and interpretation: Y Wen, Y Xu, G He, S Fu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
The study was approved by the ethical institutional review board of Zhujiang Hospital of Southern Medical University (*Number: 2022-KY-180-01*) and the Ethics Committee of Hunan Provincial People's Hospital/The First Affiliated Hospital of Hunan Normal University (*Number: 2023 – 50.1*).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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