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Transarterial Chemoembolization Combined With Tyrosine Kinase Inhibitors for Intermediate-Stage Hepatocellular Carcinoma, What Else Can We Do?

Jun Deng and Feng Wen *

Department of Radiology, Shengjing Hospital of China Medical University, Shenyang, China

Transarterial chemoembolization (TACE) has been considered the standard treatment for intermediate-stage hepatocellular carcinoma (HCC). However, intermediate-stage HCC is highly heterogeneous with a broad population with varying tumour burdens, liver function. This suggests that TACE monotherapy treatment might not be suitable for all patients with intermediate-stage HCC. The administration of tyrosine kinase inhibitors (TKIs) has become an important treatment option for improving the prognosis of patients with advanced HCC. Over the years, several trials have been conducted to explore the effects of TACE combined with TKIs for intermediate-stage HCC. However, the clinical efficacy is still controversial, and its potential clinical utility needs to be confirmed. This review will focus on the recent progress of TACE combined TKIs for intermediate-stage HCC.

Keywords: hepatocellular carcinoma, intermediate stage, tyrosine kinase inhibitors, transarterial chemoembolization, combination therapy

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***Correspondence:**
Feng Wen
fwen@cmu.edu.cn

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths worldwide, and the prognosis of unresectable HCC is poor (1, 2). Chronic liver disease caused by hepatitis B and C viral infections is an important pathogenic factor for HCC (3, 4). However, with the anti-viral treatment in recent years, most HCC patients developed from hepatitis virus infection have decreased. In addition, non-alcoholic fatty liver disease (NAFLD) has gradually become prominent with increasing numbers of patients with diabetes mellitus, obesity, and hyperlipidemia (5–8). Approximately 20-30% of patients with NAFLD develop non-alcoholic steatohepatitis (NASH), and 10-20% of that develop cirrhosis (9, 10). Additional HCC patients are expected worldwide with the advances in surveillance programs and early diagnosis. The patients with intermediate-stage HCC do not often benefit from the transarterial chemoembolization (TACE) procedure due to its heterogeneity (11, 12). More and more physicians realize the importance of intermediate-stage HCC substaging. According to the 2022 Barcelona Clinic Liver Cancer (BCLC) version stratifies, TACE is only suitable for patients with well-defined nodules, preserved portal flow, and selective access (13). In addition, incomplete TACE embolization can

induce the overproduction of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which may promote tumor recurrence or metastasis (14, 15). Since most HCC patients have typically developed advanced stages with inferior prognosis, it is essential to prolong the patient's duration in the intermediate-stage HCC. The Food and Drug Administration (FDA) approves tyrosine kinase inhibitors (TKIs) for the treatment of advanced HCC because they can suppress tumor angiogenesis *via* the inhibition of multiple receptor (16). Recently, the combination of TACE with TKIs, such as sorafenib, has been confirmed to be a feasible and safe treatment (17–19). This review will attempt to analyze the present status of TACE combined TKIs for intermediate-stage HCC.

TACE

The operative approach of conventional-TACE (cTACE) is to infuse a chemotherapy agent and lipiodol emulsions into the tumor-feeding arteries through a catheter under the guidance of medical imaging technology, followed by an injection of gelatin sponge particles to embolize the blood vessels (20). There are studies indicating that cTACE may significantly prolong survival in cases of intermediate-stage HCC compared with supportive care (21, 22). Some studies have shown that patients who respond to cTACE have a better prognosis and long-term survival (23, 24).

Although cTACE has been proven to have survival benefits for patients with intermediate-stage HCC, no optimal technique has been established (25). Due to the operator's instability, the patient's prognosis may also differ to a certain extent (26, 27). Drug-eluting beads transarterial chemoembolization (DEB-TACE) is to load chemotherapy drugs onto drug-loaded microsphere and then deliver them to the feeding artery of the hepatic tumor (28). This technology can achieve the sustained release of the chemotherapy drugs in the local tumor and reduce systemic exposure (29–31). Compared with the intra-arterial injection of chemotherapeutic drugs with or without lipiodol, DEB-TACE significantly reduces plasma concentrations of chemotherapeutic agents (32). Meanwhile, a previous study investigated serum VEGF level response after TACE with different embolic agents in patients with HCC and reported cTACE group had a more extraordinary rise in the circulating plasma levels of VEGF compared to the DEB-TACE group for 24-hour post-TACE and during the 4-week follow-up (114% vs. 164%, p=0.01; 123% vs. 170%, p=0.03) (33). This result indicates that DEB-TACE may better control tumors' local recurrence and metastasis. However, many studies have compared the effectiveness of cTACE and DEB-TACE, and the results show that there is no statistical difference in the median overall survival (mOS) (34–37). For adverse events, DEB-TACE does not seem to perform better than cTACE. In the PRESCISION V study, there is no statistical difference (p=0.86) between cTACE (19.4%) and DEB-TACE (20.4%) in serious adverse events within 30 days after TACE (34). Recently, Zhang et al. showed that DEB-TACE caused more hepatobiliary injuries and severe abdominal pain (38).

Different sizes of DEBs may also influence the therapeutic effect of HCC patients. There are currently numerous bead sizes for clinical use. Some studies demonstrated that smaller DEBs enable more distal embolization, greater penetration, and tumor necrosis (39–41). Previously, multiple studies have demonstrated the effectiveness and safety of small-size DEBs for HCC patients, indicating that small-size DEBs have better application prospects for HCC patients (42–47).

The current clinical evidence was not sufficient to prove the superiority of DEB-TACE over cTACE. Thus, more high-quality clinical studies are certainly needed. The development of DEBs and the update of embolization technology also provide new options for the local treatment of intermediate-stage HCC.

TKIs

Most HCC nodules are supplied by the hepatic artery. Angiogenesis plays a vital role in tumor occurrence, development, invasion, and metastasis (48). Angiogenesis of HCC is predominantly related to the out-of-control information transmission of cells in the tumor. The main pathway included epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), HGF/C-Met and fibroblast growth factor receptor (FGFR). These receptors' activation further triggers the cascade of intracellular RAS/RAF/MEK/ERK protein kinase signaling, leading to an imbalance between pro and anti-angiogenesis (4, 49). In an animal study, researchers prepared the iodine 124-labeled iodoazomycin galactopyranoside as a PET tracer for imaging and found that the oxygen content in the tumor was significantly lower than that of normal liver cells in the mouse (50). This finding may indicate that liver tumor cells are in a hypoxic microenvironment, and hypoxia can strongly stimulate tumor angiogenesis (51–53). The generated abnormal tumor blood vessels can interfere with the treatment of HCC. Therefore, we can improve the treatment efficacy of HCC through improving hypoxic microenvironment of tumor cells and normalizing the tumor vasculature. VEGF is widely considered an essential regulator of HCC tumor-induced angiogenesis. Overexpression of VEGF can cause uneven blood flow distribution and oxygen delivery in tumor blood vessels (54, 55). TKIs drugs can act on different kinase receptors. For example, sorafenib, which was first approved for the treatment of advanced HCC, can act on receptors such as VEGFR1-3, PDGFR-β, C-kit, RET, and PLT3, and extending the survival of patients with advanced HCC by blocking the information transmission of tumor cells, inhibiting tumor angiogenesis, promoting the normalization of tumor blood vessels (56, 57).

INTERMEDIATE-STAGE HCC (BCLC STAGE B)

Intermediate-stage HCC is highly heterogeneous with a broad population. The differences were mainly reflected in the clinical characteristics, liver function, performance status, and tumor

burden. For long times, TACE has been the standard and effective therapy for intermediate-stage HCC. However, this treatment is not suitable for all patients with intermediate-stage HCC (12). TACE is suitable for some patients with a small tumor burden and well-preserved liver function (58, 59). Previous randomized studies have shown that in selected patients with good liver function, the three-year survival rate of the TACE group is only 30% (60). Many patients require repeated TACE treatment because of incomplete embolization, which may deteriorate hepatic function and poor outcomes (61, 62).

The screening and stratification of the suitable population for TACE is essential. Some studies have performed the subclassification of the intermediate-stage group and the design of treatment strategies. In 2012, a panel of experts first divided stage B HCC patients into stages B1-B4 and proposed the "beyond Milan" and the "within up-to-7" to guide clinical practice (63). A study by Ha et al. conducted a survival analysis and evaluation of this subclassification system with additional improvements in which B3 and B4 subclasses were merged as BIII. There are significant differences in the mOS of the three subclassifications (41.0 vs. 22.1 vs. 16.6 months, $p \leq 0.001$) (64). In 2016, Kudo et al. updated Bolondi's subclassification modified for intermediate-stage HCC (Kinki Criteria). This subclassification divides intermediate-stage HCC into B1,B2,B3 mainly based on the Child-pugh score, beyond Milan and within up-to-7 (65). A subsequent study validated the Kinki Criteria and showed a statistically significant difference in mOS among the three substages (40.5 vs. 28.1 vs. 13.0 months, $p \leq 0.001$) (66). The seven-eleven criteria proposed by Hung et al. recently divided intermediate-stage HCC into low tumor burden, intermediate tumor burden, and high tumor burden. The results show that this substage has significant discriminative power for mOS in three subgroups (33.1 vs. 22.3 vs. 11.9 months, $p \leq 0.001$) (67). At present, many subclassifications of stage B HCC have been proposed, and several clinical studies have verified (68–73) (**Table 1**). The subclassification of BCLC stage B HCC is of significant value for the evaluation of patient prognosis as well as the selection of treatment protocols. Only patients who are suitable for TACE treatment can obtain the ideal survival benefit.

COMBINATION OF TACE AND TKIs

Although TACE is the standard treatment for intermediate-stage HCC, TACE is unlikely to bring long-term clinical benefits to all patients with intermediate-stage HCC. Furthermore, TACE causes the hypoxic microenvironment, leading to the upregulation of hypoxia-inducible factor-1α (HIF-1α). Increased HIF-1α then upregulates the expression of VEGF and PDGF and increases tumor angiogenesis (14, 15, 74). For intermediate-stage HCC, TACE treatment needs to be further

TABLE 1 | Some substaging systems of intermediate stage HCC.

Criteria	Reference indicators	BCLC sub-stage	Number of patiens	mOS (months)	1st treatment option	Alternative treatment
Borondi et al. (63)*	CPT score	B1	101	41.0	TACE	LT/TACE+ablation
	Beyond MC and	B2	232	22.1	TACE or TARE	Sorafenib
	within Ut7	B3	35	14.1	-	Research trials/TACE/
	ECOG	B4	98	17.2	BSC	sorafenib
						LT
Kudo et al, (65)	CPT score	B1	158	46.8	LR/Ablation/Superselective cTACE	DEB-TACE (large, C-P 7)
	Beyond MC and	B2	236	30.0	DEB-TACE(>6cm)/HAIC(>6tumors)/	B-TACE
	within Ut7	B3:B3a	31	13.2	Sorafenib (CP-A)	cTACE
		B3b			LT/ Ablation /Superselective cTACE	DEB-TACE/B-TACE/HAIC
					HAIC/Selective DEB-TACE	BSC
Hung et al. (67)	7-11	Low TB	185	33.1	–	–
		Intermediate	224	22.3		
		TB	223	11.9		
		High TB				
Yamakado et al. (68)	CPT score	B1	139	40.5	–	–
	4-of-7	B2	180	28.1		
		B3	12	13.0		
Hiroka et al. (71)	ALBI grade	B1	94	63.5	LR/RFA/TACE	–
	Beyond MC and	B2	175	38.1	RFA/TACE	
	within Ut7	B3	452	28.0	TACE/HAIC/sorafenib (CP-A)	
		B4	33	12.5	TACE/HAIC/BSC/LT	
Hu et al. (72)	CPT socre	B1	165	29.0	TACE+LR.LT/RFA	–
	Ut7	B2	671	19.0	TACE	
		B3	190	10.0	TACE+systemic therapies	
Kim et al. (73)	CPT socre	B1	410	44.8	TACE	–
	Ut11	B2	364	21.5	TACE	
	ECOG	B3	47	11.3	Sorafenib/HAIC	

*MC, Milan criteria; Ut7/Ut11, maximum tumor diameter plus tumor number less than 7/11; 7-11, the sum of maximum tumor diameter and tumor number; 4-of-7, the four tumors of 7 cm criterion; LR, liver resection; LT, liver transplantation; HAIC, hepatic artery infusion chemotherapy; BSC, best supportive care; RFA, radiofrequency ablation; *the OS date from a study by Ha et al. (64).*

optimized to improve the response rate, protect liver function, and prolong survival. TKIs can act on multiple kinase receptors to block the information transmission of tumor cells and inhibit tumor angiogenesis. TACE monotherapy often fails to bring good clinical outcomes to patients. Since TKIs came into the treatment field of HCC, the clinical researches of TACE combined with TKIs for the treatment of intermediate-stage HCC is continuously being explored and improved (**Table 2**).

Combination of TACE and Sorafenib

In phase I clinical study of TACE combined with sorafenib in the treatment of HCC, Dufour et al. confirmed that the adverse effects of the combination therapy are equivalent to those of sorafenib monotherapy. After the combination therapy, VEGF concentrations in serum decreased from 93 ng/l to 67 ng/l, and this suggests that the combined regimen may reduce the overexpression of VEGF in the blood and inhibit the recurrence and metastasis of tumors (19). The way of administration in this study may impact the outcome of the HCC patients, which uses continuous administration (i.e., dose-escalation, and without drug discontinuation post-TACE and pre-TACE). Kudo et al. reported a phase III multi-center randomized controlled study (Post-TACE) that included Korean and Japanese patients of TACE combined with sorafenib for unresectable HCC (18). Patients with an objective response after the last TACE were given oral sorafenib within 1-3 months based on their liver function. However, the final results of the Post-TACE trial showed no significant difference in time to progression (TTP) between combination and control groups, which may be related to the low therapeutic dose of sorafenib (386mg) of the combination therapy. In this study, 60% of patients have delayed administration for more than nine weeks before randomization. The peak of the VEGF concentration in the circulating blood reached on the first day after TACE (14), so the interval between sorafenib administration before and after TACE should not be too long. In the exploratory analysis of this study, it was found that Korean patients had a better TTP hazard ratio (HR, 0.38 vs. 0.94) compared with Japanese patients, which may be related to the longer median duration of sorafenib (31 weeks vs. 16 weeks).

At the same time, Llovet et al. carried out a phase II, randomized, double-blind clinical study (SPACE) (76). Sorafenib was administrated for pre-treatment 3-7 days before the first TACE in the combined therapy group to promote the normalization of tumor blood vessels. Time to untraceable progression (TTUP), as the secondary endpoint, was proposed for the first time in this study. It is defined as a nodule receiving treatment that fails to achieve objective response after at least two TACE treatments or has contraindications for chemotherapy regimens, including macrovascular invasion (VMI), extrahepatic spread (EHS), persistent ascites, and liver function Child-Pugh B grade or ECOG PS> 2 or platelet count $\leq 60\times10^9$/L. However, no statistically significant difference was observed in TTP between the combination and the monotherapy group in this study, which may be related to the restrictive definition of TTUP. Because there will be transient liver function abnormalities and blood biochemical parameters change after TACE, it may be inappropriate to be defined as disease progression at this time. In addition, the TACE procedure in this study was performed at fixed intervals. When intrahepatic lesions respond well to TACE, unnecessary repeated TACE may impair liver function or increase the side effects of sorafenib (81). Although the primary endpoint of this trial was not statistically different, the hazard ratio of time to VMI/EHS between the combined therapy group and the monotherapy group was 0.621. This exploratory trial suggests that the combination of sorafenib plus DEB-TACE was feasible in patients with intermediate-stage HCC.

Phase III clinical study (TACE-2) of TACE combined with sorafenib conducted by Meyer et al. in a European population also showed negative results (77). No significant statistical difference between the combined therapy and the monotherapy groups were found in progression-free survival (PFS) (230 vs. 235 days, p=0.94). The failure of TACE-2 may be related to the definition of disease progression. The appearance of new lesions in the liver may not be a sign of stopping TACE or sorafenib treatment and switching to other treatment methods because it is the natural characteristic of HCC. Therefore, it may not be appropriate to use RECIST 1.1 or mRECIST evaluation criteria to define HCC progression after the combined therapy.

Based on these previous studies, a multi-center, randomized controlled, phase II study (TACTICS) confirmed the benefits of combination therapy (79). This study showed that the combined therapy group and monotherapy group had a statistical difference in the primary endpoint of PFS (25.2 months vs. 13.5 months; p=0.006). The secondary endpoints of the two groups, such as TTP (26.7 vs. 16.4 months, p=0.005), time to stage progression time (22.5 months vs. 6.3 months, p=0.001), were significantly different. The most outstanding innovation of this study was that the appearance of new lesions in the liver is not defined as tumor progression. However, the results of the TACTICS study updated in the latest ASCO GI meeting showed that no statistical difference was observed between the combined therapy group and monotherapy group in the median OS (36.2 months vs. 30.8 months; p=0.40). Updated PFS between the two groups is still significantly different (22.8 months vs. 13.5 months, p=0.02) (82).

The analysis found that the follow-up anti-tumor treatment of the trial was more common in the TACE monotherapy group (76.3% vs. 58.5%), and the administration of sorafenib treatment accounted for a higher proportion in the TACE monotherapy group (50% vs. 10.6%). This result might be because patients in the combined therapy group developed resistance to sorafenib treatment after progression. This follow-up positive anti-tumor and systemic therapy (i.e., radiofrequency ablation, TACE, hepatic artery infusion chemotherapy, or other targeted and immune drugs) prolonged survival after progression, and confounded survival analysis and diluted the OS benefit of the combined therapy group. The positive results of PFS in the TACTICS could be due to several reasons. First, new lesions in the liver were not considered tumor progression, which prolonged the combination therapy time. Second, the standard of TTUP is looser than that of the SPACE study. This also prolonged the time to change other treatment methods. The median average dose of

TABLE 2 | Some researches on TACE combined with TKIs.

Trail	Trail design	Type of trail	Inclusion criteria	TACE procedure	Definition of progression	Median OS/ PFS/TTP months	The time of TKIs administration	Median medication time (weeks)	Median medication dose (mg/d)	limitations	Common AEs* (all grade/grade 3,4)	Liver toxicities (all grade/grade 3,4)
Post-TACE (18)	S+TACE vs. P+TACE 229 vs. 229	RCT, III	Child-Pugh A ECOG 0/1 BCLC B:n.a.	cTACE,1-2 times	RECICL 2004	TTP (5.4 vs. 3.7, p = 0.252)	1-3 months after TACE	17.1	386	much lower than planned median daily dose of sorafenib (386 mg).	HFSR (82%35%) Alopecia (41%/-) Rash (40%/4%) Diarrhoea (31%/6%) Hypertension (31%15%)	Elevated AST (25%/12%) Elevated ALT (21%/8%)
BRISK-TA (75)	B+TACE vs. P+TACE 57 vs. 59	RCT, III	Child-Pugh A/B ECOG 0/1 BCLC B:52%	cTACE/D-TACE, on-demand	mRECIST	OS (26.4 vs. 26.1, p =0.5280)	After TACE	24	n.a.	early closure. differences by region.	D-appetite (82%35%) Fatigue (43%/4%) hypertension (47%/14%) A-pain (31%/6%) Diarrhea (36%/7%)	Elevated AST (35%/14%) Elevated ALT (36%/10%)
SPACE (76)	S+TACE vs. P+TACE 154 vs. 153	RCT, II	Child-Pugh A ECOG 0 BCLC B:100%	DEB-TACE, on a fixed interval	mRECIST	TT P (5.6 vs. 5.5, p =0.072)	3-7 days before TACE	21	566	the restrictive definition of TTUP. DEB-TACE on a fixed interval.	A-pain (60.1%/7.8%) Diarrhea (52.9%/3.9%) HFSR (46.4%/9.2%) Fatigue (43.1%/11.1%) Fever (38.6%/0)	Elevated AST (24.8%/24.2%) Elevated ALT (17.0%/15.1%)
TACE-2 (77)	S+TACE vs. P+TACE 139 vs. 138	RCT, III	Child-Pugh A ECOG 0/1 BCLC B:n.a.	DEB-TACE on demand	RECIST1.1	PFS (7.7 vs. 7.8, p =0.94)	2-5 weeks before TACE	17	660	heterogeneity in baseline characteristics. the strict criteria for retreatment.	Fatigue (81%/19%) A-pain (60%/13%) Diarrhoea (56%/11%) Nausea (46%/1%) Rash (38%/2%)	n.a.
ORIENTAL (78)	O+TACE vs. P+TACE 363 vs. 364	RCT, III	Child-Pugh A ECOG 0/1 BCLC B:47%	cTACE, on demand	n.a.	OS (31.1 vs. 32.3, p =0.435)	3-28 days after TACE	43.6	n.a.	early termination. heterogeneity in baseline characteristics.	A-pain (71%/6%) Pyrexia (59%/<1%) D-appetite (47%/4%) Constipation (40%/<1%) Nausea (39%/<1%)	Elevated AST (50%/43%) Elevated ALT (45%/34%)
TACTICS (79)	S+TACEV vs. TACE 80 vs. 76	RCT, II	Child-Pugh A/B7 ECOG 0/1 BCLC B:55%	cTACE, on demand	Inability to TACE/TACE failure/New Lesions are not considered as progress.	PFS (36.2 vs. 30.8; p =0.40) OS (22.8 vs. 13.5, p =0.02)	2-3 weeks before TACE	38.7	355.2	small number of patients included. modified unTACEable progression.	Anaemia (64.9%/1.3%) HFSR (53.2%/5.2%) Hypertension (51.9%/ 10.4%) Malaise (26.0%/0) Fatigue (24.7%/2.6%)	Elevated AST (93.5%/28.6%) Elevated ALT (89.6%/24.7%)
Fu et al. (99)	L+TACE vs. TACE 60 vs. 60	retrospective, nRCT	Child-Pugh A/B BCLC B:55%	D-TACE, on-demand	mRECIST	n.a.	3 days after TACE	n.a.	32.9	retrospective study. patients' willing to choose the lenvatinib treatment. small sample size.	Hypertension (48.3%/ 23.3%) Bleeding** (21.7%/1.7%) Diarrhea (18.3%/0) Diarrhea (16.7%/0) Dysphonia (15.0%/0)	Elevated AST (38.3%/3.3%) Elevated ALT (23.3%/1.7%)
Guo et al. (80)	A+TACE vs. TACE 60 vs. 60	retrospective, nRCT	Child-Pugh A/B ECOG 0/1 BCLC B:44%	cTACE, on demand	mRECIST	n.a.	3-5 days after TACE	n.a.	n.a.	retrospective study. small sample size. the short follow-up time.	HFSR (47.2%/n.a) Hypertension (27.8%/n.a) Erythra (22.2%/n.a) Proteinuria (13.9%/n.a) Hypothyroidism (8.3%/n.a)	n.a

*n.a., not available; OS, overall survival; PFS, progression-free survival; TTP,tome-to-progression; L, Lenvatinib; A, anlotinib; S, sorafenib; P, placebo; O, orantinib; B, brivanib; RCT, randomized controlled trial; D-appet, decreased appetite; A-pain, abdominal pain; AST, aspartate aminotransferase; ALT, alanine aminotransferase; *Top five common AEs; **Bleeding (gingiva).*

sorafenib in this study was only 355.2mg, but the duration of the drug was long enough (38.7 weeks). As in the SPACE study, pre-treatment with 400mg sorafenib day was given before TACE to observe the patient's tolerance to the drug and promote the normalization of tumor blood vessels. However, the pre-treatment time of TACTICS was longer for 2-3 weeks. At the same time, stopping medication is conducive to preserving liver function two days before and after each TACE. Therefore, for combined therapy of intermediate-stage HCC, we should try our best to protect liver function and extend the duration of drug medications, which may be more conducive to the survival of patients than the maximum dose of the drug. Although the OS in this trial was not statistically different between the combined therapy group and monotherapy group, the patients in the combined therapy group extended the time to stage progression, which allowed the patients to stay in the intermediate stage for a longer time and obtain a better quality of life.

For intermediate-stage HCC combination therapy studies, OS may not be a suitable primary endpoint. As a critical endpoint of cancer treatment research, OS has its limitations. First, it may require an extended follow-up to obtain sufficient patient data. Moreover, PFS seems to be a surrogate primary endpoint for OS. A study by Llovet et al. showed that the threshold of PFS ≤ 6 can predict the improvement of OS in advanced HCC (83). However, the benefits of PFS in the TACTICS had not been converted into the benefits of OS. The selection of appropriate endpoints for combination therapy is a question that still needs to be addressed in future clinical trials. Once patients are defined as disease progression during combination therapy, other treatment modalities must be introduced according to the clinical guidelines. However, whether the disease progression is the failure of combination therapy or the natural tumor biology of HCC still remains ambiguous. If the latter was the case, OS data might be confounded by follow-up treatment after disease progression (84). So the definition of progression may require refinement, especially in the combination therapy of the intermediate-stage HCC. The definition of disease progression affects TACE and sorafenib's performance, thereby affecting the endpoints of the trial analysis. At present, more and more interventional physicians are beginning to consider that the appearance of new lesions in the liver cannot be counted as progress.

Combination of TACE and Brivanib

Park et al. confirmed the efficacy of brivanib for advanced HCC (85). The study included 55 patients with unresectable, advanced, or locally metastatic HCC. Studies have confirmed that brivanib and sorafenib are equally effective in treating advanced HCC. The HCC patients is well tolerated with brivanib. Based on this phase II study results, Kudo et al. investigated brivanib as an adjuvant combination therapy for TACE (75). This randomized, double-blind, placebo-controlled phase III clinical study (BRISK-TA) enrolled a total of 870 HCC patients who met TACE criteria. After the first TACE, they were randomly assigned (1:1), and 800mg of brivanib and placebo were taken each day orally. The administration of brivanib in the study varied from 2 to 21 days after TACE according to liver function. There was no statistically significant difference in OS between the combined therapy and monotherapy groups (26.4 months vs. 26.1 months, p=0.5280).

Regarding the negative results of this study, Kudo et al. consider that the trial only recruited 502 patients due to early termination, which is less than the planned 870 patients (81). Although no positive results were observed in mOS, there were statistical differences between time to extrahepatic spread (TTES)/ time to vascular invasion (TTVI) and objective response rate. The number of TACE procedures in the combined therapy group is also less than in the monotherapy group. All these indicated that TACE combined with brivanib has a positive anti-cancer effect.

Combination of TACE and Orantinib

Orantinib is a multi-targeted, orally active, small-molecule tyrosine kinase inhibitor (TKI) that inhibits the VEGF-2 and the PDGF-β receptor (86, 87). Many clinical trials have confirmed the safety and effectiveness of orantinib in treating advanced HCC. In the study by Inaba et al., patients treated with TACE monotherapy were randomly divided into orantinib and no medication groups (88). A total of 103 patients were included in the study. The results showed that the median PFS of the combined therapy group and monotherapy group were 157 and 122 days, respectively. Although there was no statistical difference between the two groups, the mPFS of the combination group had a significant prolongation trend. It is necessary to test the combination of TACE and orantinib further. Kudo et al. explored the efficacy of TACE combined with orantinib in a randomized, double-blind, placebo-controlled, multi-center multi-center, phase III study (ORIENTAL) (78). A total of 889 patients were enrolled in this study. These patients were randomly assigned to the combined therapy and monotherapy groups at a 1:1 ratio. Orantinib administration was given 200mg orally twice a day and 3-28 days after TACE according to whether the patients met the criteria for administration. There was no statistically significant difference in mOS between the combination and control groups (31.1 months vs. 32.3 months, p=0.5280). In the subgroup analysis, it was found that Japanese patients observed a trend toward improved mOS compared with the control group. This could be due to better medication dosages control in Japanese patients. About 50% of Japanese patients had reduced their medication dosages, while only 25% of patients in Korea and Taiwan have reduced their dose. A timely reducing drug dose may decrease drug toxic side effects, affecting patients' treatment and prognosis.

Combination of TACE and Anotinib

A phase III randomized clinical study confirmed that anlotinib has survival benefits for non-small cell lung cancer (89). The mechanism action of anlotinib may be through the Erk and Akt pathways to inhibit HCC proliferation, suppress tumor growth, and induce tumor apoptosis (90–92). A retrospective study compared TACE combined with anlotinib and TACE monotherapy to treat intermediate-stage HCC (80). The study included 82 patients with unresectable HCC. Patients in the combined therapy group (n=36) took orally anlotinib 12 mg daily for 3-5 days after the first TACE (taken for two weeks and

stopped for one week). The results demonstrated a significant difference in PFS (7.35 months vs. 5.54 months, p=0.035). Although no statistical difference was observed in the 3-month survival rate (97.2% vs. 93.5%, p=0.627), the 6-month and 1-year survival rate of the combined therapy group (83.3% vs. 56.5%, p=0.016; 66.7% vs. 19.6%, p = 0.016) are significantly higher than monotherapy group. Meanwhile, no grade 4 adverse events were observed in the two groups of patients, and all the adverse events were alleviated after treatment or dose adjustment. The follow-up durations in this study were relatively short. Whether the benefit of PFS translates into OS benefit is still unclear. Further researches, preferably with large clinical studies, are needed to confirm the clinical effect of TACE combined with anlotinib.

Combination of TACE and Lenvatinib

Lenvatinib is a novel oral multi-kinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, platelet-derived growth factor (PDGF) receptor-alpha, rearranged during transfection (RET), and KIT (93–97). Recently, an open-label, multi-center phase III clinical randomized non-inferiority study (REFLECT) compared the efficacy of lenvatinib and sorafenib in patients with advanced HCC (98). The results demonstrated that most of the lenvatinib group was comparable to that of the sorafenib group. A recent retrospective study compared TACE combined with lenvatinib with TACE monotherapy to treat unresectable HCC (99). This study included 120 patients with unresectable HCC. Patients in the combination group took lenvatinib orally three days after TACE treatment and withdrew the drug three days before repeating on-demand TACE treatment. The dose of lenvatinib is mainly determined according to the weight of patients. Patients (bodyweight≥60kg) take 12mg, and patients (bodyweight<60kg) take 8mg. The final results showed that the combined therapy group's 1-year and 2-year OS (88.4% and 79.8%) were higher than the control group's (79.2% and 49.2%, P =0.047). In terms of PFS, the combination group was also better than the control group (1 year: 78.4% vs. 64.7%; 2 years: 45.5% vs. 38.0%, p<0.001). The combined therapy group also had a better objective response rate (68.3% vs. 31.7%, p<0.001). Meanwhile, the patients in the combined therapy group tolerated lenvatinib well. This study is the first retrospective study of TACE combined with lenvatinib in treating unresectable HCC. Although the results showed that the combined therapy group tends to prolong the OS and PFS, the median follow-up time of the combined therapy group and the control group is only 11.6 months and 17.5 months, respectively. The proportion of treatment in the combined group after disease progression is relatively lower (35.7% vs. 62.2%). The final results of OS and PFS is still unclear. In this study, the TACE treatment interval of the combined group was significantly longer than that of the control group (103.3vs.74.7d, p=0.004), which provided the possibility to protect the liver function of the patients. Therefore, the clinical efficacy of TACE combined with lenvatinib in patients may require further large-scale randomized controlled clinical studies to verify.

WHAT ELSE CAN WE DO?

The treatment of intermediate-stage HCC has always been a hotly debated topic. The emergence of molecule-targeted drugs has provided more treatment options for intermediate-stage HCC with TACE as the main therapeutic modality. With the emergence and update of various new drugs, researcher's attention and the pursuit of treatment effect for intermediate-stage HCC have also increased. The treatment goal of intermediate-stage HCC has gradually expanded from delaying disease progression to achieving tumour downstaging and undergoing curative conversion therapy. In the future, the exploration of treatment strategies for intermediate-stage HCC should focus on the prolongation of OS and the curative conversion therapy after tumour downstaging.

The advent of immune checkpoint inhibitors (ICIs) may provide new directions for the combination treatment of HCC. Previous studies (e.g., KEYNOTE-224 and KEYNOTE-240) have confirmed that pembrolizumab has favorable disease control and side effects for HCC patients previously treated with sorafenib (100, 101). Recently, significant progress has been achieved in a global, open-label, phase 3 trial (IMBRAVE 150). This study compared the clinical efficacy of atezolizumab (anti-PDL1 checkpoint inhibitor) plus bevacizumab(anti-VEGF) and sorafenib for unresectable HCC. Results of the study demonstrated that the mPFS of patients in the atezolizumab–bevacizumab group was significantly longer than that in the sorafenib group (6.8 vs. 4.3 months, <0.001) (102). In the latest ASCO GI 2021 meeting, the result showed that mOS was significantly longer in the atezolizumab–bevacizumab group than in the sorafenib group (19.2 vs. 13.4 months, <0.001). Therefore, in the 2022 updated BCLC strategy, the atezolizumab–bevacizumab therapy is recommended as the first-line treatment for advanced HCC (13). It is not difficult to see that the update of the treatment strategy for advanced HCC will bring more survival benefits to patients and affect the treatment strategy of intermediate-stage HCC. The earlier application of TKIs and their combination with TACE in intermediate-stage HCC could make it possible to reduce the number of TACE treatments, maximize the protection of liver function, and ultimately prolong the overall survival of patients with HCC.

Some studies of TACE combined with ICIs are on the way, and it is unclear whether this combination is beneficial for intermediate-stage HCC. However, a retrospective study by Zheng et al. demonstrated the safety and efficacy of TACE combined with sorafenib plus immune checkpoint inhibitors (TACE+Sor+ICIs) (103). This study included 51 patients with intermediate and advanced TACE-resistant HCC, divided into TACE+Sor+ICIs and TACE combined with sorafenib (TACE+Sor) groups. The results showed that the disease control rate of the TACE+Sor+ICIs group was significantly higher than that of the TACE+Sor group (81.82 vs. 55.17%, P = 0.046). Besides, they observed that the mPFS (16.26 vs. 7.30 months, P < 0.001) and mOS (23.3 vs. 13.8 months, P = 0.012) of the TACE+Sor+ICIs group was significantly longer than that of the TACE+Sor group. Another study also confirmed that for intermediate and

advanced HCC, tumors in the TACE with molecular targeted agents (MTGs) plus immune checkpoint inhibitors (ICIs) group had a higher liquefactive necrosis rate than tumors in the TACE with MTGs group (30% vs. 4.8%, P=0.006) (104). If TACE is combined with TKIs plus ICIs in treating patients with intermediate-stage HCC, is it possible to acquire better clinical efficacy? This needs to be confirmed by further large clinical studies.

Based on the outcomes of REFLECT, lenvatinib is now approved for the first-line treatment of advanced HCC. In the REFLECT study, masked independent imaging review confirmed a significantly higher objective response rate in the lenvatinib arm than in the sorafenib arm by mRECIST (40.6 vs 12.4%, p<0.0001) (98). Previous studies have shown that ORR and sustained response duration are effective predictors of longer OS, and early treatment response remains a reliable predictor of a good prognosis (23, 24). At present, studies have explored how to translate the high objective response rate of lenvatinib into more prolonged survival in patients with intermediate-stage liver cancer. A study conducted by Kudo et al. demonstrated that lenvatinib has higher ORR (73.3% vs. 33.3%, p<0.001) and mOS (37.9 vs. 21.3 months, p<0.01) as first-line versus TACE for intermediate-stage HCC beyond up-to-seven Criteria and child-pugh A liver function (59). Another study investigated lenvatinib-TACE sequential therapy versus lenvatinib alone in patients with intermediate-stage HCC who were not unsuitable for TACE. The results showed that the OS of the combined treatment group was significantly longer than that of the lenvatinib group (not reached vs. 16.9 months, p = 0.007) (105). Two studies suggest that early lenvatinib-TACE sequential therapy may be a good combination therapy for patients with intermediate-stage HCC who are not suitable for TACE. Not just the ongoing TACTICS-Lenvatinib study, more randomized controlled trials are needed to confirm the clinical benefit of this combination in the intermediate-stage HCC. Not only that, but the high objective response rate of lenvatinib will also provide more opportunities for the transformation therapy of intermediate-stage HCC. It can be seen that lenvatinib has shown a trend of replacing other TKI drugs in the combined treatment of intermediate-stage HCC.

The extensive randomized controlled clinical studies of TACE combined with TKIs in the treatment of intermediate-stage HCC have all failed. In the future, the treatment of the intermediate-stage HCC remains challenging. The etiology of HCC gradually changes, and non-viral hepatitis caused by NAFLD and NASH increases. This may also change the holistic treatment concept of HCC in the future. It can be found that the combined treatment has survival benefits in specific subgroups of HCC patients. Therefore, substaging and guidelines for stage B HCC require more refined definitions. The combination treatment regimen for HCC patients should be individualized based on individual patient factors. The selection of the patient population for combination therapy will be very worthy of attention in the future. On the other hand, TKIs combined with more embolization treatments including cTACE, DEB-TACE and TARE need to be explored. At the same time, the efficiency improvement of TACE combined with TKIs might ultimately be implemented by improvement of embolization efficacy and technical limitations of TACE, preservation of liver function and management of adverse events. Several clinical trials are currently underway to explore the efficacy of combination therapy for intermediate-stage HCC. Therefore, better results can be expected in the future.

In conclusion, the road of combined therapy for intermediate-stage HCC is not smooth. However, combined therapy is an inevitable trend for the future development of HCC. It is believed that more optimized combination methods will bring more excellent clinical effects soon.

AUTHOR CONTRIBUTIONS

JD and FW wrote the manuscript. All authors contributed to the article and approved the submitted version.

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