Therapeutic approaches in intermediate-stage hepatocellular carcinoma (HCC): a novel insight of adjuvant transarterial chemoembolization (TACE)

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Prognosis of patients with hepatocellular carcinoma (HCC) is associated to tumor burden, cancer-related characteristics and symptoms, while remains highly dependent on the stage of diagnosis and the therapeutic options available (1). Although great efforts have been made in the last decades, few trials have showed beneficial results, mainly in the clinical setting of intermediate and advanced stages of HCC where management remains intricate (1,2). Most studies have been focused on the assessment of new drugs or their combination for advanced tumor stages, treatments which are primarily represented by immune checkpoint inhibitors and tyrosine kinase inhibitors (TKIs) (3). Conversely, although in intermediate-stage HCC locoregional therapy with transarterial chemoembolization (TACE) represents the standard in common practice, its combination with different drugs has become a promising strategy (2). However, a specific approach is still undefined since some studies have evaluated TACE and drug combination, and others the sequential drug administration after or before TACE intervention (*Table 1*). Moreover, study design is also differentially established, being either TACE or drug alone established as control group (*Table 1*). Therefore, obtaining clear conclusions is a complex task that should be accomplished considering all these variables.

In this regard, some clarity has been shed by results from recent studies, such as those presented by the LAUNCH trial (4). This study showed the superiority of administering oral lenvatinib followed by one TACE intervention in comparison to the treatment only with lenvatinib (4) (*Table 1*). However, as in previous clinical trials, population characteristics and criteria must be always considered for a proper interpretation of the results presented. Similar findings were obtained from a recently published study, although direct benefits from TACE intervention could not be obtained, since patients were assigned to TACE plus lenvatinib or TACE plus sorafenib arms (7). Therefore, despite main conclusions on TACE benefits could not be addressed, similar results in terms of median overall survival (OS) of patients in the TACE plus lenvatinib arm were observed between this prospective study (16.4 months) (7) and the LAUNCH trial (17.8 months) (4). Not only in terms of OS, but also when assessing progression-free survival (PFS), results are also comparable, 8.4 and 10.6 months in patients from the TACE plus lenvatinib arm of the prospective study and LAUNCH trial, respectively (4,7). Regardless of similarities, main conclusions of these

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Table 1 Study design and characteristics of phase III clinical trials and cohort studies assessing benefits from combining TACE and different drugs in patients with HCC

Study (reference) (trial name)	Type of study	Population			Arm A	Arm B	Treatment strategy	Outcomes
		HCC staging	Recruitment	Patients (n)				
Studies assessing benefits of adjuvant TACE compared to drug administration alone								
Peng *et al.* 2023 (4) (LAUNCH trial)	Multicenter, randomized, open-label, parallel group, phase III trial	ECOG PS 0 or 1 Child-Pugh class A	12 hospitals in China	338	Lenvatinib + TACE	Lenvatinib	Lenvatinib before TACE	Primary: OS Secondary: PFS, ORR, SD, DCR, PD
Koch *et al.* 2021 (5)	Retrospective cohort study	ECOG PS ≤2 Child-Pugh class A or B	3 German liver centers	201	Sorafenib + TACE	Arm B: sorafenib Arm C: TACE	TACE before sorafenib	TTP, CR, PR, SD, PD, DCR, ORR, OS
Park *et al.* 2019 (6) (STAH trial)	Randomized, multicenter, phase III trial	ECOG PS ≤2 Child-Pugh score ≤7	13 hospitals in South Korea	339	Sorafenib + TACE	Sorafenib	Sorafenib before TACE	Primary: OS Secondary: TTP, PFS, TRR, CR, PR and SD
Yang *et al.* 2021 (7)	Prospective cohort study	Child-Pugh class A or B ECOG PS ≤2	NR	116	TACE + Lenvatinib	TACE + Sorafenib	Sorafenib or lenvatinib within 7 days before or after TACE	OS, PFS, CR, PR, ORR, DCR and AEs
Wei *et al.* 2018 (8)	Open-labeled, randomized, phase III trial	ECOG PS ≤2 Child-Pugh class A or B	1 center (Sun Yat-sen University Cancer Center, China)	234	Hepatectomy + TACE	Hepatectomy	TACE after hepatectomy	Primary: DFS Secondary: OS and AEs
Wang *et al.* 2018 (9)	Randomized, open-label, controlled, phase III trial	Histopathological confirmed HCC Child-Pugh class A or B	1 center (Hospital in Shanghai, China)	280	TACE	Active surveillance	NR	Primary: RFS Secondary: OS and safety
Doffoël *et al.* 2008 (10)	Multicenter, randomized, controlled, phase III trial	HCC diagnosed based on biopsy Child-Pugh class C	15 French centers	110	Tamoxifen + TACE	Tamoxifen	Tamoxifen before TACE	Primary: OS Secondary: quality of life
Studies assessing benefits of drug administration to TACE compared to TACE alone								
Aramaki *et al.* 2021 (11) (ACE 500 study)	Multicenter, prospective, open-label, phase 2/3 randomized control trial	ECOG PS ≤2 Child-Pugh class A or B	Different centers from Tokyo, Japan	444	TACE + epirubicin	TACE + cisplatin	Cisplatin or epirubicin as part of the TACE	Primary: OS Secondary: TTF, RR and AEs
Kudo *et al.* 2020 (12) (TACTICS trial)	Randomized, open label, multicenter trial	ECOG PS 0 or 1 Child-Pugh score ≤7	33 institutions from Japan	197	TACE + sorafenib	TACE	Sorafenib before TACE	Primary: PFS and OS Secondary: TTUP, TTP, ORR

Table 1 (*continued*)

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Table 1 (*continued*)

Study (reference) (trial name)	Type of study	Population			Arm A	Arm B	Treatment strategy	Outcomes
		HCC staging	Recruitment	Patients (n)				
Kudo *et al.* 2018 (13) (ORIENTAL study)	Randomized, double-blind, placebo-controlled, multicenter, phase 3 study	ECOG PS 0 or 1 Child-Pugh score ≤6	75 sites from Japan, South Korea, and Taiwan	888	TACE + orantinib	TACE	Combination	Primary: OS Secondary: TTF, TTP
Ikeda *et al.* 2018 (14)	Prospective, multicenter, open-label, randomized, phase III trial	ECOG PS 0–2 Child-Pugh class A or B	29 hospitals from Japan	257	TACE + miriplatin	TACE + epirubicin	Combination, miriplatin or epirubicin as part of the TACE	Primary: OS Secondary: TE, TTF, and AEs
Meyer *et al.* 2017 (15) (TACE 2 trial)	Multicenter, randomized, placebo-controlled, phase 3 trial	ECOG PS ≤1 Child-Pugh class A	20 hospitals from United Kingdom	399	TACE + sorafenib	TACE	Sorafenib before TACE	Primary: PFS Secondary: OS, TTP, OR, DC, QOL, number of TACE procedures
Lu *et al.* 2017 (16)	Single-center, randomized, controlled trial	ECOG PS ≤2 Child-Pugh class A or B	1 center (Navy General Hospital, China)	44	TACE	TACE + apatinib	TACE before apatinib	PFS CR, PR, SD, PD
Hoffmann *et al.* 2015 (17)	Multicenter, randomized, placebo-controlled, double-blind, phase III trial	NR	4 centers from Germany	50	TACE + sorafenib	TACE	Sorafenib before TACE	Primary: TTP Secondary: ORR, PFS, time to liver transplantation
Kudo *et al.* 2014 (18) (BRISK-TA study)	Randomized, double-blind, placebo-controlled, phase III study	ECOG PS 0 or 1 Child-Pugh class A or B	83 academic hospitals from 12 different countries	502	TACE + brivanib	TACE	TACE before brivanib	Primary: OS Secondary: TTDP, TTES/VI, TTP, number of TACE procedures, and safety
Kudo *et al.* 2011 (19)	Double-blind, placebo-controlled, phase III trial	ECOG PS 0 or 1 Child-Pugh score A	Patients from Japan and South Korea	552	TACE + sorafenib	TACE	TACE before sorafenib	Primary: TTP Secondary: OS

TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology group; PS, performance status; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; SD, stable disease; DCR, disease control rate; PD, progressive disease; TTP, time to progression; CR, complete response; PR, partial response; TRR, tumor response rate; NR, not reported; AEs, adverse events; DFS, disease-free survival; TTF, time to treatment failure; RR, response rate; TTUP, time to untreatable progression; TE, treatment effect; OR, overall response; DC, disease control; QOL, quality of life; TTDP, time to disease progression; TTES/VI, time from the date of the first TACE to the date when extrahepatic spread or vascular invasion.

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studies remain distant, only settling the safety of TACE combination with molecular targeted drugs in HCC patients.

Sorafenib represents the first multikinase inhibitor available as first-line treatment against advanced HCC, being lenvatinib approved 10 years later (3). This delay seems to be transferred to the clinical trials performed to evaluate benefits from combining these TKIs with TACE, since TACE plus sorafenib combination was previously evaluated in the STAH trial in comparison to sorafenib treatment alone (6). Contrary to those results from LAUNCH trial, the STAH study did not show improved survival or patients' outcomes from combining sorafenib with TACE compared with sorafenib alone (6) (*Table 1*). Nevertheless, a retrospective cohort study recently published found that patients included in the TACE plus sorafenib arm had significant benefits in terms of OS and time to progression (TTP) in comparison to sorafenib alone and TACE alone (5) (*Table 1*). These apparent discrepancies could be mostly due to study design, clinical trial (6) versus retrospective cohort study (5), but also to patients' characteristics. The initial purpose of the LAUNCH trial was to assess the benefits on intermediate-stage HCC patients from combining TACE and lenvatinib. Therefore, including patients with Eastern Cooperative Oncology group (ECOG) performance status (PS) 0 or 1 and liver function set by Child-Pugh class A (4). Similar criteria were used by both STAH trial (6) and the retrospective cohort study (5), whereas patient recruitment was performed in hospitals from South Korea or liver centers in Germany, respectively (*Table 1*). Both study design and patients' origin could partially explain differences between the main results exhibited, reinforcing the importance of the criteria defined and recruitment center.

Beneficial effects from TACE intervention in the clinical setting of HCC patients in intermediate stage have been extensively evaluated by previous studies (8-10). In addition to the high mortality rate, HCC is also associated to a still elevated recurrence rate even after curative hepatectomy (20), where adjuvant TACE has shown to significantly improve patient survival in two different phase III trials (8,9) (*Table 1*). Moreover, as observed with the multikinase inhibitors lenvatinib and sorafenib, TACE also demonstrated to improve patients' outcomes when combined with tamoxifen in comparison to tamoxifen alone in a multicenter, randomized, controlled phase III trial (10). Despite relevant differences in the study design, treatment arms and patients' origin of these trials and retrospective studies, what seems to remain constant throughout is the increased benefits observed in the TACE combination arm on patients with specific features of intermediate-stage HCC. However, results are highly sensitive to study and patients' characteristics, which should be considered in the clinical management of HCC patients to provide a suitable treatment strategy.

During the last years, an increased number of clinical trials have been proposed and performed including TACE as an adjuvant approach with different chemotherapeutic agents in HCC patients. However, most studies have focused on the derived effects of drug administration to increase TACE-derived benefits, establishing as control arm patients subjected to TACE (11-19) (*Table 1*). Most clinical trials have been designed in order to recruit patients in intermediate stages, specifically defined with a liver function ECOG PS 0–1 (12,13,15,18,19) or 0–2 (11,14,16) and Child-Pugh score A (12,13,15,19) or A–B (11,14,16,18) (*Table 1*), similarly to the study criteria established by the LAUNCH trial (4). Furthermore, some of these trials obtained a comparable survival in the TACE-combination group to the LAUNCH trial in terms of median OS (17.8 months) and median PFS (10.6 months). Specifically, comparable or better results in OS were found from combining TACE with orantinib (31.1 months) (13), epirubicin (36.3 months) (14), sorafenib (23.3 and 29.7 months) (15,19), and brivanib (26.4 months) (18), as well as in PFS when TACE was combined with sorafenib (25.2 and 10.5 months) (12,15), and apatinib (12.5 months) (16). Nevertheless, superiority was only observed with sorafenib in the TACTICS trial (12) and apatinib (16) in combination with TACE when compared with TACE alone. For this reason, doubts arise in the more likely benefits that TACE could provide to drug treatment instead of proposing drug administration to increase TACE effects, which has not exhibited positive results in a great number of trials (11,13-15,17-19). Therefore, further studies should be conducted to confirm the potential use of adjuvant TACE with different drugs or to discard this therapeutic strategy, considering the establishment of a drug-only arm to obtain TACE-derived benefits.

Overall, most studies have been focused on evaluating the advantages from including chemotherapy to a TACE regimen instead of increase survival outcomes derived from drug treatment with adjuvant TACE. In this regard, the LAUNCH trial represents the first phase III study reporting benefits from including TACE intervention to the oral administration with lenvatinib in intermediate-stage HCC patients (4), with only two previous studies performed

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with sorafenib (5,6). However, increased evidence highlights the potential of drugs approved against advanced HCC in intermediate stages, that could be beneficed through their combination with TACE (2), as shown by the LAUNCH trial with the administration of lenvatinib plus sequential TACE (4). This therapeutic strategy is proposed for patients with intermediate HCC with the aim to achieve a strong tumor reduction and a better prognosis, since the addition of drugs to TACE intervention has not shown increased benefits in patients' outcomes compared to TACE alone, while TACE could benefit drug-derived effects on patients' prognosis. Great efforts are being made to provide more suitable and effective therapeutic options to patients with intermediate-stage HCC. Recent studies, such as the LAUNCH trial, offer novel and interesting results to translate to the clinical setting, but also increase the necessity of thoughtful and careful decisions on the HCC patient's treatment.

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