COMBINATION OF TACE AND TKIs IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA: FROM THEORY TO CLINICAL PRACTICE

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ABSTRACT

Background: Over recent decades, hepatocellular carcinoma (HCC) has remained one of the Major challenges in oncology, particularly in countries with a high prevalence of viral hepatitis, such as Vietnam. Intermediate-stage HCC according to the Barcelona Clinic Liver Cancer (BCLC-B) classification represents a heterogeneous population in terms of tumor burden and baseline liver function. Transarterial chemoembolization (TACE) is currently considered the standard treatment for this stage. However, not all patients are suitable candidates for TACE, and repeated TACE alone may lead to deterioration of liver function. The advent of tyrosine kinase inhibitors (TKIs) has ushered in a new era of systemic therapy for HCC, initially in advanced-stage disease, and subsequently explored in combination with TACE in earlier-stage settings to exploit the potential synergy between locoregional tumor control and inhibition of angiogenesis.

Objective: To review and analyze the available evidence regarding the efficacy and emerging trends of combining TACE with tyrosine kinase inhibitors in the treatment of HCC.

Methods: A narrative review of expert consensus statements, clinical studies, and treatment guidelines from the AASLD, EASL, and BCLC was conducted. Relevant literature was retrieved from PubMed, Google Scholar, ScienceDirect, and domestic Vietnamese medical journals.

Results: Recent evidence suggests that the combination of TACE and TKIs may improve tumor control and prolong progression-free survival in patients who are no longer suitable for TACE monotherapy, particularly when patient selection and treatment timing are optimized.

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Conclusion: The combination of TACE and TKIs is increasingly regarded as a critical transitional strategy between locoregional and systemic therapies in the management of HCC. This approach highlights the need for further research to identify patients most likely to benefit, optimize treatment sequencing, and assess long-term efficacy and safety. In Vietnam, this combined modality is being progressively adopted in clinical practice.

Keywords: Hepatocellular carcinoma, transarterial chemoembolization (TACE), tyrosine kinase inhibitors (TKIs), combination therapy.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) has remained a major global cancer burden for decades. According to GLOBOCAN 2022, HCC ranks sixth in incidence and third in cancer-related mortality worldwide. The disease burden is particularly high in the Asia–Pacific region, with Vietnam being one of the most affected countries, ranking second in incidence and first in mortality in both sexes [1].

In Vietnam, HCC is strongly associated with the high prevalence of chronic hepatitis B and C infections, as well as alcohol-related liver disease and other causes of cirrhosis. Most patients are diagnosed with HCC on a background of cirrhosis, which significantly limits the feasibility of curative treatment options such as surgical resection or liver transplantation. In addition, the majority of cases are detected at intermediate or advanced stages, making treatment strategies more complex and resulting in poor overall prognosis.

Patients with intermediate-stage HCC (BCLC stage B) are primarily treated with transarterial chemoembolization (TACE). However, TACE monotherapy has several limitations, particularly in large tumors, multifocal disease, or cases requiring repeated procedures. Moreover, repeated TACE may induce tumor recurrence and progression through upregulation of angiogenic factors. Although systemic therapy has become the standard of care for advanced-stage disease (BCLC stage C), outcomes remain unsatisfactory due to poor prognosis and limited treatment response in this stage [2].

Given the limitations of single-modality therapy, combination strategies involving TACE and systemic treatment have been increasingly investigated worldwide, particularly combinations with tyrosine kinase inhibitors (TKIs). This approach is based on a synergistic mechanism, whereby TACE provides local tumor control while TKIs inhibit angiogenesis and suppress microscopic tumor progression.

Objective of the review: This narrative review aims to summarize and critically analyze the existing evidence on the therapeutic efficacy and current trends in the application of combined TACE and TKI-based therapy in the treatment of hepatocellular carcinoma (HCC).

2. LITERATURE REVIEW

This narrative review was synthesized from expert consensus documents, clinical trials, and treatment guidelines issued by major international societies such as AASLD, EASL, JSH, and the Barcelona Clinic Liver Cancer (BCLC) staging system. Relevant literature was searched in PubMed, Google Scholar, ScienceDirect, and peer-reviewed medical journals covering the period from 2008 to 2025.

The search strategy used key terms and their synonyms combined with Boolean operators (AND/OR), including: “Hepatocellular carcinoma,” “HCC,” “transarterial chemoembolization,” “TACE,” “tyrosine kinase

inhibitor," "TKIs," "sorafenib," "lenvatinib," "combination," "concurrent," and "sequential."

Eligible studies included phase II–III clinical trials, meta-analyses, systematic reviews, and clinical practice guidelines. Studies with small sample sizes, single case reports, or those not directly related to the topic were excluded. After the screening process, a total of 19 articles were included in the final analysis and synthesis of this review.

3. HISTORICAL ROLE OF TACE IN THE TREATMENT OF HCC

3.1. Biological basis and principles of TACE

The vascular supply of tumors varies depending on their degree of malignancy. During hepatocarcinogenesis, the arterial blood supply initially decreases and then abnormally increases [3]. In contrast, the portal venous blood supply progressively decreases and eventually disappears in moderately or poorly differentiated HCC [4]. Based on this vascular shift, intra-arterial delivery of embolic agents into the main tumor-feeding artery can induce ischemia, leading to tumor necrosis.

3.2. Position of TACE within staging systems

Within current staging systems, TACE plays a central role as the standard treatment for patients with intermediate-stage HCC. In addition, TACE is also flexibly applied across different stages depending on therapeutic intent. In early-stage disease (BCLC A), TACE may be used as a bridging therapy or for downstaging in patients who are not initially eligible for curative treatments such as resection or liver transplantation. TACE may also be considered in carefully selected patients with advanced-stage disease who have limited macrovascular invasion, no extrahepatic spread, and preserved liver function, particularly when combined with systemic therapy [5–8].

3.3. Limitations of TACE monotherapy

The efficacy of TACE as a standalone treatment remains limited. Tumor recurrence rates after TACE are high, often necessitating repeated procedures. Repeated TACE sessions may lead to progressive deterioration of liver function and reduced tumor response, thereby negatively affecting long-term patient prognosis [9].

In addition, TACE induces significant changes in the tumor microenvironment. The ischemic conditions triggered by embolization activate hypoxia-inducible factors such as HIF-1α, which in turn upregulate angiogenic mediators including VEGF and PDGF. This neovascularization contributes to tumor recurrence, progression, and metastatic potential, highlighting the biological limitations of TACE when used as monotherapy [10].

4. EMERGENCE OF TKIS AND EXPANSION OF SYSTEMIC THERAPY IN HCC

4.1. Mechanisms of TKIs in HCC

Tyrosine kinase inhibitors (TKIs) exert their anti-tumor effects by inhibiting tumor cell proliferation, suppressing angiogenesis, and promoting widespread apoptosis of cancer cells. These effects are mediated through the blockade of multiple signaling pathways, including VEGF, PDGF, and FGF receptors, as well as intracellular cascades such as Raf-1 and B-Raf [11]. In addition, TKIs modulate the tumor immune microenvironment by reducing immunosuppressive cell populations, including myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), while enhancing the activity of cytotoxic CD8+ T cells [1]. Based on these mechanisms, the combination of TACE and TKIs is expected to produce a synergistic effect, improving tumor control and overall therapeutic outcomes in HCC.

4.2. TKIs in advanced HCC treatment

The introduction of tyrosine kinase inhibitors (TKIs) represented a breakthrough in the management of advanced-stage hepatocellular carcinoma (HCC). Sorafenib was the first agent to demonstrate a survival benefit, extending median overall survival (OS) from 7.9 months to 10.7 months [2]. Subsequently, lenvatinib showed superiority in improving progression-free survival and overall response rate compared with sorafenib in clinical trials [1,3]. However, TKI monotherapy remains limited in clinical efficacy. Although it improves overall survival, response rates are relatively low, and treatment-related toxicities may affect adherence and long-term treatment continuity [5,6].

5. SCIENTIFIC RATIONALE FOR TACE + TKI COMBINATION STRATEGY

5.1. Biological synergy

The rationale for combining TACE and TKIs is based on two complementary mechanisms: (i) TACE induces rapid tumor shrinkage but subsequently leads to increased expression of pro-angiogenic factors, and (ii) TKIs counteract this effect by inhibiting VEGF, PDGF, and FGF receptor signaling pathways, thereby suppressing tumor angiogenesis and growth [4]. These two modalities therefore exhibit both independent antitumor effects and a synergistic biological interaction when used in combination.

5.2. Combination strategies

5.2.1. Sequential strategy (TACE → TKIs)

In this approach, TACE is performed first to achieve local tumor control, followed by the initiation of TKI therapy when residual disease persists or when tumor progression is observed. This strategy is consistent with conventional clinical practice, allowing clinicians to evaluate the response to TACE before transitioning to systemic therapy. However, delayed initiation of TKIs may result in missing the post-TACE angiogenic surge window. In addition, liver function may deteriorate after repeated TACE sessions, potentially limiting the eligibility for subsequent TKI therapy [5].

5.2.2. Concurrent strategy (TACE combined with TKIs)

This approach involves administering TKIs during the peri-TACE period to suppress early angiogenic activation induced by TACE. TKIs are typically initiated before TACE and continued for a short duration around the procedure. This strategy provides enhanced tumor control based on the biological synergy between the two modalities.

5.2.3. "On-demand" TACE on a TKI backbone

In this strategy, TKIs are maintained continuously throughout treatment, while TACE is performed only when intrahepatic lesions show progression. This approach reduces unnecessary repeated TACE sessions and helps preserve liver function. It has gained increasing attention in the context of personalized treatment strategies for HCC.

6. CLINICAL EVIDENCE OF TACE + TKIS WORLDWIDE

6.1. Early-phase trials and inconsistent results

Initial clinical trials did not demonstrate a clear survival benefit of the combined TACE and TKI strategy. In the SPACE study, TACE was performed on a fixed schedule rather than based on tumor response, which may have limited treatment optimization. Similarly, the TACE-2 trial did not optimize the timing of TKI administration; delayed initiation and treatment interruption around the TACE procedure

potentially reduced anti-angiogenic efficacy and overall tumor control. In addition, these studies mainly used conventional response assessment criteria (RECIST), which do not adequately capture the therapeutic effects of TACE, thereby potentially underestimating the true benefit of combination therapy.

6.2. Recent studies and analyses

Table 1: Studies evaluating TACE combined with TKIs

TACE-2 Phase 2, randomized August 2017	N= 313	PFS DEB-TACE + Sorafenib vs DEB-TACE + placebo	Sorafenib + DEB-TACE did not improve progression-free survival (PFS) compared with TACE alone in European patients with intermediate-stage hepatocellular carcinoma (HCC)
SPACE Phase 3, randomized May 2016	N= 307	TTP DEB-TACE + Sorafenib vs DEB-TACE + placebo	DEB-TACE + sorafenib did not show a clinically meaningful improvement in time to progression (TTP) compared with DEB-TACE monotherapy
TACTICS Phase 2, RCT, randomized December 2019	N= 156	PFS, OS Sorafenib + TACE vs TACE unresectable HCC	PFS was significantly improved in the sorafenib + TACE group (25.2 vs. 13.5 months; p = 0.006). Overall survival (OS) did not show a statistically significant improvement (36.2 vs. 30.8 months), although an absolute gain of 5.4 months was observed.
TACTICS-L (Lenvatinib) Phase 2, Single-arm study 2023	N= 62	PFS, OS, ORR LEN-TACE	Significant improvements in both PFS and OS were reported in patients with unresectable disease. Median TACE-specific PFS was 25.9 months (RECICL), and median OS was 40.1 months. Best overall response rate (ORR) reached 88.7% (90% CI: 79.8-95.6).

Recent evidence suggests that optimizing treatment strategies by using a TKI backbone combined with on-demand or early sequential TACE may improve progression-free survival (PFS), time to progression (TTP), and objective response rate (ORR). In the TACTICS trial evaluating the combination of TACE and sorafenib, a marked improvement in PFS was observed (25.2 months vs. 13.5 months), along with a significant prolongation of TTP (26.7 months vs. 16.4 months). However, overall survival (OS) was not fully analyzed due to only 73.6% OS events being reached, and ORR data were also reported [15]. In the single-arm TACTICS-L study by the same group, which replaced sorafenib with lenvatinib due to its stronger anti-VEGFR activity, encouraging results were also reported. Median OS reached 40.1 months (data cut-off April 2024), while median PFS was 28 months. The ORR at 4 weeks was 79%, with a best ORR of 88.7%.

The selection of appropriate patients, the timing of selective or on-demand TACE based on tumor response, and the optimal timing of

TKI administration are key determinants for maximizing the biological synergism between the two treatment modalities. Careful patient selection with preserved liver function, including Child–Pugh A status, absence of macrovascular invasion or extrahepatic metastasis, and ECOG performance status 0–1, is essential to minimize the risk of post-TACE hepatic decompensation and to maintain effective dosing of TKIs. Selective or on-demand TACE, rather than a fixed-schedule approach, may reduce irreversible liver injury and allow prolonged continuation of TKI therapy. TKIs initiated 2–3 weeks prior to the first TACE procedure may help normalize tumor vasculature and enhance TACE efficacy. Continued TKI administration after TACE is important to counteract hypoxia-induced angiogenesis, thereby contributing to prolonged progression-free survival (PFS) [15]. In addition, PFS assessment using RECICL criteria, rather than mRECIST, is considered more appropriate in intermediate-stage disease, as mRECIST may underestimate treatment benefit and lead to premature stage migration.

6.3. Position of TACE + TKIs in current guidelines

Despite encouraging results from several studies, the combination of TACE and TKIs has not yet been formally incorporated into major international guidelines such as BCLC or EASL, primarily due to the lack of consistent evidence demonstrating an overall survival (OS) benefit [5,7]. The AASLD guidelines also emphasize that although progression-free survival (PFS) improvement has been observed in some trials, the OS benefit remains unclear. In addition, the heterogeneity of patients with intermediate-stage HCC makes it challenging to standardize indications for this combination strategy [6].

7. CLINICAL PRACTICE OF TACE + TKIS IN VIETNAM

7.1. Characteristics of HCC patients in Vietnam

In Vietnam, hepatocellular carcinoma (HCC) remains a major challenge in oncology, ranking second in incidence and first in mortality in both sexes according to GLOBOCAN 2022. The epidemiological profile of HCC patients in Vietnam is characterized by a high prevalence of viral hepatitis-related liver disease and late-stage diagnosis. According to a study by Trần Ngọc Ánh at Hanoi Medical University Hospital, hepatitis B virus infection is the most common risk factor for HCC, accounting for 73% of cases, followed by hepatitis C at 19%. Most patients are diagnosed at intermediate and advanced stages, accounting for 34% and 37%, respectively [6].

7.2. Real-world application of TACE + TKIs in Vietnam

In clinical practice in Vietnam, the combination of TACE and TKIs is applied in a flexible and individualized manner. As most patients are diagnosed at non-curative stages, TACE remains the most used locoregional treatment modality. When there is evidence of poor response to TACE or a high risk of tumor recurrence, early initiation of TKIs instead of repeated TACE sessions is often considered to reduce the risk of liver function deterioration, and this strategy is increasingly adopted in many treatment centers.

Given the current limitations of immunotherapy in Vietnam, including high costs and limited insurance coverage, the implementation of combination strategies has not yet been standardized. Therefore, treatment decisions are largely individualized, depending on clinical experience, hepatic functional reserve, tumor burden, and the patient's financial capacity.

7.3. Factors influencing treatment decisions

Treatment cost remains a major barrier, particularly as TKIs are not yet fully covered by health insurance. According to Circular No. 20/2022/TT-BYT, sorafenib is reimbursed at 50% for the treatment of hepatocellular carcinoma (HCC) in national special-grade, grade I, and grade II hospitals. However, when compared with newer systemic agents or immunotherapy, which are not covered by insurance, TKIs remain more accessible and are therefore more commonly selected in combination with TACE in many clinical settings.

The experience of the treatment center plays a crucial role in determining therapeutic outcomes. Variations in resources and clinical expertise across institutions may lead to differences in implementation and results of combination therapy. In centers with limited manpower and monitoring facilities, treatment decisions may be more conservative or primarily based on individual clinical judgment.

The decision to initiate combination therapy also depends on the ability to monitor and manage treatment-related toxicities. TKIs are associated with adverse effects such as hypertension, hand–foot skin reaction, and other toxicities that require close monitoring and timely dose adjustment. In centers with adequate follow-up systems and multidisciplinary collaboration, this strategy can be implemented more safely and effectively.

8. PATIENT SELECTION AND TREATMENT MANAGEMENT

Patient selection is based on multidisciplinary tumor board decisions and is typically indicated for intermediate-stage HCC patients who are likely to be TACE-refractory or unsuitable for TACE, as well as for selected advanced-stage patients with disease confined to both liver lobes and preserved liver function (Child–Pugh A) [7]. The definition of "unsuitable for TACE" follows the criteria proposed by the Japanese Society of Hepatology [8], including:

- High likelihood of TACE refractoriness: tumors beyond the "up-to-7" criteria.

- High risk of post-TACE hepatic decompensation, particularly in bilobar disease and patients with mALBI grade 2b.

- Poor or absent response to TACE, including multinodular diffuse disease, infiltrative type, nodular lesions with extranodular growth, disseminated lesions, or sarcomatoid transformation following TACE.

Transition from TACE monotherapy to TACE + TKIs and treatment management considerations

The combination strategy may increase toxicity due to overlapping effects between TACE-induced hepatic ischemia and the systemic adverse events of TKIs. Management of adverse events is therefore based on dose reduction or temporary interruption of TKI therapy when necessary. In the TACTICS-L study, 79% of patients required temporary interruption of TKIs and 80.2% required dose reduction, indicating a high incidence of treatment-related adverse events; however, toxicity management did not compromise overall treatment efficacy [9]. Liver function should be closely monitored using Child–Pugh classification and ALBI score. Treatment should be discontinued in cases of unacceptable toxicity or radiological disease progression.

9. CONCLUSION

Currently, in real-world clinical practice in Vietnam, there remains a lack of robust local data regarding the efficacy and safety of the TACE plus TKIs combination strategy. Differences in epidemiology, tumor burden, healthcare

infrastructure, follow-up capacity, and financial accessibility may significantly influence treatment outcomes compared with international study populations. Therefore, real-world evidence studies are essential to identify which subgroups of Vietnamese patients derive the greatest benefit and to help standardize treatment protocols.

The combination of TACE and TKIs represents an important transitional strategy between locoregional and systemic therapy in the management of intermediate-stage HCC or advanced-stage disease confined to the liver. In Vietnam, where most patients are diagnosed at non-curative stages and access to immunotherapy remains limited, TACE combined with TKIs is a feasible and appropriate treatment option. However, further real-world data are needed to determine the optimal patient population and to refine treatment strategies tailored to the specific resource constraints in Vietnam.

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