Hepatic Oncology

The status of transarterial chemoembolization treatment in the era of precision oncology

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Practice points

- Improved selection of patients who will benefit from transarterial chemoembolization (TACE) treatment is a current unmet clinical need.
- Optimization of the TACE procedure, including the use of targeted therapies and gene-based therapy, is the focus of current clinical trials.
- Advancements in both the collection of patient 'omics' data and in imaging procedures have allowed for the discovery of potential prognostic biomarkers and gene signatures for predicting response to TACE, both pre- and posttreatment.
- Priority should be placed on investigating biomarkers and gene signatures that are biologically relevant and are linked to drivers of TACE resistance.
- Modification of current staging systems and treatment guidelines, by integrating prognostic biomarkers or gene signatures with information technology, is an important future approach to improving patient outcomes with TACE.

Transarterial chemoembolization (TACE) is the gold standard of therapy for patients with unresectable intermediate stage hepatocellular carcinoma (HCC), and is also commonly used as postresection adjuvant therapy in Asia. The delivery of TACE is highly variable from center to center, and clinical decision making for patients is based primarily on tumor staging guidelines, with very little focus on individualized tumor features. This review will discuss recent efforts for improving patient outcomes with TACE treatment through personalized medicine advances, including ongoing clinical trials investigating the combination of targeted therapy with TACE and the discovery of prognostic biomarkers for predicting TACE response.

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Hepatocellular carcinoma (HCC) is a highly heterogeneous disease for which there are multiple causes, including hepatitis B and C infection, cirrhosis, nonalcoholic steatohepatitis and nonalcoholic fatty liver disease, alcohol use and chemical exposure. In addition to the multiple etiological factors leading to HCC, patients with HCC also have varying liver function, which affects treatment planning [1]. Currently, various sets of guidelines drive clinical decision making and treatment recommendations for HCC management. Clinicians in North America and Europe commonly use the Barcelona Clinic Liver Cancer (BCLC) staging guidelines [2], whereas in Asia, the Chinese University Prognostic Index (CUPI score) [3] and Japan Integrated Staging [4] are two examples of guidelines, among others, that are in place. Although each guideline system is slightly different, all drive treatment recommendations based on tumor stage and liver function. There is very little focus placed on the tumor biology of individual patients, with the exception of Japan Integrated Staging, which now includes three tumor biomarkers in its classification system [5]. Further improvements that refine staging systems by incorporating biomarkers or prognostic scores based on individualized molecular tumor features remains a key goal of HCC precision oncology moving forward.

KEYWORDS

• hepatocellular carcinoma
• precision cancer medicine • transarterial chemoembolization

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For patients with intermediate disease (e.g., BCLC B) and good liver function, which comprises nearly 50% of patients with HCC, transarterial chemoembolization (TACE) is the first-line palliative treatment of choice and is recommended for patients with large or multinodular tumors with no vascular invasion or metastasis outside the liver [6]. TACE, which was initially developed in the 1980s in Japan [7,8], is an interventional radiology procedure in which a highly concentrated dose of chemotherapy is injected directly into the tumor via the hepatic artery, which serves as the main blood supply to the tumor, via a minimally invasive, image-guided procedure. Then, the TACE procedure blocks the hepatic artery with an embolizing agent, thus cutting off the blood supply to the tumor. This procedure directly targets the tumor with the chemotherapeutic agent while minimizing systemic exposure, and sparing healthy liver tissue, which is mainly supplied by the portal vein [9]. When selecting patients for TACE therapy, guidelines only consider tumor characteristics, performance status and liver function. Other factors such as histological features of the tumor, etiology of HCC or other comorbidities are not considered.

Following a number of previous clinical trials demonstrating discordant results, two clinical trials, one performed in a European patient population [10] and the other in an Asian patient population [11], showed an improvement in overall survival in patients with unresectable HCC when treated with TACE, compared with symptomatic treatment. However, the benefit demonstrated in these patients was likely due to very strict selection criteria, in which only ~12–20% of trial entrants passed the exclusion criteria. In Asian countries, the use of adjuvant TACE following surgical resection remains the first-line palliative treatment for HCC, despite mixed success in randomized control trials, with some trials demonstrating a benefit and others demonstrating no effect or even a harmful effect [12]. Optimization of the TACE procedure, including better selection and stratification of patients who are most likely to benefit from TACE, represents an important clinical need in the management of HCC, especially as efforts expand to incorporate precision oncology approaches into therapeutic modalities.

Clinical trials for improving TACE

The TACE procedure varies greatly among different physicians and clinical centers, and the

technique and number of administrations for achieving maximum tumor regression and optimal outcome remains unclear. As such, many of the current clinical trials evaluating TACE aim to examine the use of various chemotherapeutic and embolizing agents to optimize the procedure, and there has also been considerable interest in combining targeted therapies with the TACE procedure [13]. For example, sorafenib, a multikinase inhibitor that is currently the sole systemic chemotherapeutic that is US FDA approved for HCC treatment, has also been of interest for use in combination with TACE. Sorafenib is known to inhibit VEGFR, which promotes angiogenesis and tumor cell survival and growth, and is activated by hypoxia. Since the TACE procedure itself relies on a combination of chemotherapy with the induction of a hypoxic tumor microenvironment to initiate tumor necrosis, there has been great interest in using sorafenib in combination with the TACE procedure to inhibit the activation of angiogenesis by TACE-induced hypoxia. However, a Phase II clinical trial, the SPACE study, examined the use of sorafenib plus TACE with doxorubicin drug-eluting beads and found no significant difference in time to progression in HCC patients compared with TACE alone [14]. A Phase III study investigating the use of sorafenib in combination with TACE found similar results [15].

A number of clinical trials have evaluated the use of TACE in combination with other targeted antiangiogenic agents, but most have been met with negative outcomes. For example, Phase III trials evaluating brivanib, a dual inhibitor of VEGFR and FGFR [16], and orantinib, an inhibitor of VEGFR and PDGFR [17], both failed to demonstrate improved overall survival with combination therapy. Two Phase II trials evaluated bevacizumab, an anti-VEGF monoclonal antibody, in combination with TACE, which demonstrated the use of bevacizumab to exhibit antitumor activity, thus warranting further studies [18,19], although no Phase III trials are currently underway.

There is also interest in evaluating the feasibility of gene-based therapy in combination with TACE, which has the advantage of localized delivery while reducing systemic toxicities, and has the potential to advance personalized medicine initiatives, by targeting individual tumor characteristics. Several previous clinical trials evaluating combined gene therapy and

TACE approaches have shown mixed results, but a Phase II clinical trial evaluating recombinant adenovirus expressing human *p53* tumor suppressor gene in combination with TACE (NCT02418988) and a Phase III clinical trial evaluating the antitumor recombinant human adenovirus type 5 in combination with TACE (NCT01869088) are currently ongoing [20]. Clinical trials evaluating pharmacological agents or gene therapy in combination with TACE are summarized in **Table 1**.

Biomarkers to predict TACE response

The failures of various clinical trials indicate that there is a great need to stratify patients based on prognostic biomarkers or other companion diagnostics, to enrich the subset of patients who are most likely to benefit from TACE or a certain TACE combination therapy. The discovery and validation of biomarkers for diagnosis, prognosis and treatment of HCC has advanced greatly in recent years due to the development of new technologies to capture various types of ‘omics’ data. A number of studies have focused on the predictive value of single pretherapeutic biomarkers for determining TACE response, many of which are circulating biomarkers in the serum, representing a class of prognostic candidates that are commonly used clinically [21]. For example, levels of serum AFP, a diagnostic biomarker commonly measured in HCC patients, also has prognostic value for patients receiving TACE, in that patients who test negative for AFP have

better treatment response and prognosis following TACE, compared with patients who are positive for AFP [22]. Studies have shown that other biomarkers in the serum also have predictive value for TACE clinical outcome, including LDH [23], VEGF [24] and IGF1 [25].

Several microRNAs (miRNA) have also been implicated in TACE response, both circulating in serum and expression in tumor tissue. A study investigating serum miR-199a/b-3p observed that patients who were refractory to TACE had a lower serum level of miR-199a/b-3p at baseline compared with patients who responded to treatment, indicating that miR-199a/b-3p could predict the efficacy of TACE, thus acting as a novel biomarker for HCC patients prior to treatment [26]. Tumor miRNA expression has also been shown to predict survival in patients with low miR-1268a expression, who had improved prognosis following TACE treatment. Inhibition of miR-1268a was associated with enhanced cell killing by doxorubicin, suggesting that miR-1268a may serve both as an independent prognostic indicator for HCC patients receiving TACE and as a novel therapeutic target for improving tumor cell killing with TACE treatment following surgical resection [27].

Multiple studies have provided evidence that genetic polymorphisms may also have predictive value of survival following TACE. For example, a guanosine insertion/deletion polymorphism in the *SERPINE1* gene promoter region is associated with elevated plasma levels of PAI-1 and

Table 1. Summary of clinical trials evaluating therapeutic combinations with transarterial chemoembolization.

Clinical trial	Target	Phase	Result	Ref.
<i>Pharmacological agents</i>				
TACE + sorafenib (SPACE trial)	VEGFR	Phase II	No significant difference in time to progression compared with TACE alone	[14]
TACE + sorafenib	VEGFR	Phase III	The addition of sorafenib did not prolong time to progression in patients who responded to TACE	[15]
Brivanib	VEGFR + FGR	Phase III	No improvement in overall survival compared with placebo in combination with TACE	[16]
Orantinib	VEGFR + PDGFR	Phase III	No improvement in overall survival compared with placebo in combination with TACE	[17]
Bevacizumab	Anti-VEGF	Phase II	Concurrent treatment of bevacizumab with TACE is safe and well tolerated. The combination may have antitumor activity	[18,19]
<i>Gene therapy</i>				
Recombinant adenovirus expressing human <i>p53</i>		Phase II	Ongoing (NCT02418988)	Reviewed in [20]
Recombinant human adenovirus type 5		Phase III	Ongoing (NCT01869088)	Reviewed in [20]

TACE: Transarterial chemoembolization.

poor prognosis in patients who have undergone TACE [28]. Additionally, the rs157077 polymorphism of *GSTO2* was significantly associated with higher risk of death in HCC patients who had received TACE, and that carriers of the polymorphism had a higher tissue expression of *GSTO2*, indicating potential use as a prognostic marker [29]. Another study found that patients with the *ADAMTS5* rs2830581 polymorphism experienced decreased risk of tumor recurrence and death following TACE treatment [30].

While predicting which patients are most likely to benefit from TACE using biomarkers as a pretreatment strategy remains a key goal of precision oncology efforts moving forward, improvements in the early assessment of HCC response to TACE posttreatment is also critical for guiding future treatment plans. Several biomarkers measured post-TACE are correlated with TACE response. For example, the concentration of circulating nucleosomes, along with other liver markers such as ALP, measured post-treatment, have been shown to serve as an early estimator of TACE response in patients [31]. An increase in circulating CD4⁽⁺⁾ T-cell Th17 measured 30 days after TACE was found to be an independent prognostic factor for improved overall survival [32], and an decrease in blood neutrophil-to-lymphocyte ratio following TACE treatment independently predicted poor survival in HCC patients [33]. Post-treatment changes, compared with baseline measured pre-treatment, in AFP [34], VEGFR2 [35], and DCP, which is correlated to angiogenesis [36], are also predictive of overall survival.

As researchers and clinicians are working toward enhanced selection and treatment of HCC patients with TACE, it should be noted that interventional radiological advances in early imaging biomarkers to predict TACE response are also improving, which can determine the potential effect of TACE during, or soon after, the procedure. For example, intraprocedural transcatheter intra-arterial perfusion magnetic resonance imaging (TRIP-MRI) can measure semiquantitative changes in HCC perfusion during the TACE procedure. A reduction in tumor perfusion during TACE was associated with tumor response [37]. Early changes in vascular and cellular findings in MRI after TACE indicated that changes in tumor vascularization followed by changes in apparent diffusion coefficient (ADC), a functional imaging parameter, may serve as indicators of a successful

procedure [38]. Follow-up imaging has also been shown to be beneficial to patients, as the ADC ratio measured 1 month following TACE compared with baseline is an independent predictor of progression-free survival [39]. Advances in imaging software may also lead to a better determination of TACE response after treatment, and one study used MRI imaging data and investigational semiautomated software to determine functional imaging parameters that are associated with tumor response to TACE [40]. Biomarkers associated with TACE response are summarized in **Table 2**.

Despite the number of research studies focusing on biomarker development to predict TACE response, few are measured clinically. Personalized medicine strategies for patients with HCC have also included utilizing gene signatures based on mRNA, miRNA, genomic DNA structural alteration and DNA methylation signatures from analyzed in tumor tissue, nontumor tissue or in the plasma/serum. However, these studies have focused on determining gene signatures that predict the presence of HCC, poor survival, or recurrence in patients with various etiological backgrounds [41], and few studies have examined the potential of gene signatures to stratify patients who are most likely to respond to TACE. One pilot study aimed to identify signature genes associated with better TACE treatment response and determined that patients whose tumors experienced complete radiologic response exhibited higher pretreatment expression of genes associated with chemotherapy sensitivity and mitosis [42]. Another recently published study examined gene mutations in tumors treated with transarterial embolization (a procedure similar to TACE but with no chemotherapy included), and determined that mutations in the Wnt/ β -catenin signaling pathway may be associated with tumor response to transarterial embolization [43]. Both studies indicate that stratification of patients based on gene signatures represents a realistic goal for treatment of HCC patients with TACE.

Clinical implications & recommendations

Intermediate stage HCC represents a highly heterogeneous group of patients with varying disease etiology, liver function and histological features, and current treatment guidelines are inadequate for determining the appropriate treatment for individual patients. A number of clinically evaluated patient and disease

characteristics, such as histological features or etiology of HCC, have been associated with positive or negative survival outcomes with TACE (reviewed in [44]). For example, low (≤ 200 ng/ml) or high (≥ 400 ng/ml) AFP has been associated with positive or negative survival outcome, respectively, following TACE, yet like many of the novel biomarkers that have been discovered, these factors have not been evaluated in randomized control trials and have not been added to current staging guidelines. Therefore, until various clinical features, biomarkers and prognostic signatures can be evaluated through prospective randomized control trials, clinicians should continue to use guidelines for HCC treatment that are currently in place, while searching for ways to improve and expand guidelines. One group has demonstrated the ability to more accurately predict HCC risk through the incorporation of clinical biomarkers into prediction models that could be translated into clinical use [45], which is a strategy that could be applied to TACE response prediction. Another recent study found that patients treated with TACE outside

of recommended American Association for the Study of Liver Diseases guidelines experienced a survival benefit with TACE treatment, providing clinical evidence that other patients stand to benefit from TACE treatment and demonstrating the suboptimal design of the guidelines [46]. Thus, updating guidelines to both predict and enhance patient outcomes is an important, and potentially achievable, goal. Researchers and physician scientists should focus on the discovery of biologically relevant biomarkers and gene signatures that have mechanistic links to TACE response, with high levels of evidence [47], which are more likely to be successfully developed into a clinical prognostic test. The very recent Phase III clinical trial failure of MET inhibitor tivantinib (NCT01755767), which did not improve overall survival, stratified patients by MET expression and those with MET-overexpressing HCC tumors were included in the trial [48]. However, another recent study demonstrated that tivantinib acts as an antimitotic compound targeting cellular proliferation, and did not suppress MET signaling, *in vitro* [49]. Thus, it is possible that

Figure 1. Opportunities for personalized medicine advancements in transarterial chemoembolization use and methodology. TACE: Transarterial chemoembolization.

Table 2. Summary of biomarkers associated with transarterial chemoembolization treatment outcome.

Biomarker	Association with TACE	Ref.
Pre-TACE biomarkers		
Serum biomarkers		
AFP	AFP negative patients experience better treatment response and prognosis	[22]
LDH	Lower levels of LDH are associated with an increase in overall survival	[23]
VEGF	High VEGF levels predict poor response to TACE	[24]
IGF1	Low IGF1 is associated with poor overall survival	[25]
microRNAs		
miR-199a/b-3p (serum)	Lower miR-199a/b-3p level at baseline is associated with TACE resistance	[26]
miR-1268a (tumor)	Low miR-1268a expression is associated with improved prognosis after TACE	[27]
Genetic polymorphisms		
Insertion/deletion in <i>SERPINE1</i>	Associated with poor prognosis following TACE	[28]
rs157077 of <i>GSTO2</i>	Associated with higher risk of death in patients receiving TACE	[29]
rs2830581 of <i>ADAMTS5</i>	Associated with decreased risk of tumor recurrence and death following TACE	[30]
Post-TACE biomarkers		
Physiological markers		
Circulating nucleosomes	An increase 24 h following TACE is associated with nonresponse to TACE	[31]
Circulating CD4 ⁽⁺⁾ T cell Th17	Increase is independently associated with improved overall survival	[32]
Blood neutrophil-to-lymphocyte ratio (NLR)	Decrease in NLR is associated with poor outcome following TACE	[33]
AFP	A decrease in post-treatment AFP is associated with tumor response and overall survival	[34]
VEGFR2	A decrease in post-treatment VEGFR2 is associated with favorable overall survival	[35]
DCP	A decrease in post-treatment DCP is associated with better overall survival	[36]
Imaging biomarkers		
TRIP-MRI	Reduction in tumor perfusion during TACE is associated with tumor response	[37]
ADC	The ADC ratio 1 month after TACE independently predicts progression-free survival	[38,39]
Functional imaging parameters	Increase in ADC and decrease in venous enhancement 1 month after TACE provides early indication of tumor response to treatment	[40]

ADC: Apparent diffusion coefficient; NLR: Neutrophil-to-lymphocyte ratio; TACE: Transarterial chemoembolization; TRIP-MRI: Transcatheter intra-arterial perfusion magnetic resonance imaging.

tivantinib was not targeting the functional effect of MET and was instead targeting an off-target passenger effect of proliferation, leading to the clinical trial failure due to incorrect patient stratification. The importance of determining which biomarkers and gene signatures are associated with oncogenic drivers of tumorigenesis, rather than bystander or passenger effects, cannot be overstated, as evidenced by a number of other Phase III clinical trial failures of targeted HCC therapies that did not lead to improvements in overall survival [50].

Conclusion & future perspective

With the monumental advancements that have already been made since the development of TACE in the 1980s, and continued evolution of the use of TACE in clinical practice, TACE has shown great promise to be an

effective, personalized treatment modality for patients with HCC both now and in the future. However, a number improvements could be made to progress the use of TACE in precision oncology efforts, such as changes in current staging systems based on biomarkers and information technology; collection of patient 'omics' data for the development of prognostic gene signatures and the development of individualized combination therapies based on tumor features; optimization of the TACE procedure itself including continued clinical trials for promising therapeutic combinations; and advances in imaging and software during and after the procedure (Figure 1). New combination therapies that pair TACE with molecularly targeted therapies based on individualized tumor features, as well as studies to determine biomarkers or gene signatures that can be translated into clinically

relevant prognostic devices for predicting TACE response, are two important avenues of study for improvement of patient outcomes with TACE that could be initiated within the next several years. Additionally, focus is likely to be placed on the enhancement and expansion of current staging systems, such as updating guidelines to include new prognostic biomarkers.

As technological advances lead to increased ease and feasibility of collecting ‘omics’ data from individual patients, the search for prognostic biomarkers and gene signatures to predict treatment response is likely to remain a cornerstone of precision oncology. However, while these advances in technology have continued to push the breadth of scientific knowledge forward, finding practical ways to implement seemingly unlimited patient data into clinical practice has lagged behind. Therefore, as technology continues to progress, we speculate that implementation of informational technology systems for predictive, preventive and personalized medicine, which integrates diagnosis and therapy management with IT, is a likely model to bridge the gap between patient data generation and personalized disease treatment, and represents how medicine will be practiced in

the future. Informational technology systems for predictive, preventive and personalized medicine focuses on using enhanced IT and modeling techniques to identify optimal treatment modalities for each patient based on their clinical status and pathophysiology [51]. TACE in the era of precision oncology will depend on a collaborative effort from both the scientific and clinical communities, and as accumulation of vast amounts of patient data continues with the use of advanced sequencing techniques, new methodologies that integrate model-based and evidenced-based medicine is a likely direction for the future use of TACE in the management of HCC.

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