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Transarterial Therapies for Hepatocellular Carcinoma

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Key Words

Predictors of response after TAE and TACE for HCC · TAE and TACE for HCC

Abstract

Background: The treatment of hepatocellular carcinoma (HCC) is still a major health issue because of its increasing incidence and because of the complexity of its management. Transarterial embolization (TAE) and transarterial chemoembolization (TACE) are two widely used locoregional therapies in the treatment of HCC, especially for unresectable intermediate and advanced HCCs. **Summary:** The modern use of TAE and TACE opens new scenarios for the treatment of unresectable HCC and has yielded interesting results. The present work describes the role of transarterial therapies for HCC and focuses on the different Western and Eastern approaches to the study of response predictors. **Key Messages:** Recent refinements in interventional radiology techniques and in HCC patient selection have facilitated better local control of the disease. The molecular profiling of HCC to predict the response to TACE and TAE will greatly help clinicians identify the optimum therapy.

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Introduction

Transarterial embolization (TAE) and transarterial chemoembolization (TACE) are two widely used locoregional therapies in the treatment of hepatocellular carcinoma (HCC), especially for unresectable intermediate and advanced HCCs [1]. Although TAE and TACE are considered to be noncurative therapies, for patients with advanced HCC, no other therapy is usually recommended when surgery, percutaneous ablation, and sorafenib are unfeasible. Transarterial radioembolization (TARE) is an emerging modality that has achieved promising results for intermediate and advanced HCC [2]. The present work describes the role of transarterial therapies for HCC, starting with the techniques themselves and then focusing on the predictors of response.

TACE for HCC

The HCC vasculature is supplied by the hepatic artery rather than by the portal vein. Consequently, the segmental hepatic arteries may be selectively catheterized via retrograde femoral access, and the tumor can be visualized by means of superselective angiography. Then, different embolic agents can be injected with the aim of obliterating the vascular supply to the tumor and/or delivering drugs/radioisotopes, thereby halting or slowing tumor progression.

Liver embolization for HCC is commonly used in two main settings: (1) large unresectable HCCs unsuitable for surgery or ablation, and (2) prior to resection or to liver transplantation as a bridge therapy. In general, the best candidates are those patients with unresectable lesions without vascular invasion or extrahepatic spread and with well-preserved liver function.

Although there is no standard technique for HCC embolization, two main approaches are traditionally recognized: TACE and TAE [3]. A third, more recent and promising technique is TARE, which delivers to the tumor radioactive isotopes (eg, iodine-131-labeled lipiodol or yttrium-90 [90-Y]-tagged glass or resin microspheres).

The goal of TACE is to fill the tumor with a chemotherapeutic drug (eg, doxorubicin, epirubicin, cisplatin, or mitomycin C) using a carrier agent. Historically, the carrier agent was Lipiodol, but this has been largely replaced by drug-eluting beads TACE, which are available in different sizes [3–9]. The use of a chemotherapeutic agent requires preventive medication to avoid drug-related side effects [10]. In contrast, TAE aims to achieve superselective vascular embolization using gelatin sponge, Lipiodol, or microparticles as small as 40 μm in diameter [11]. No drugs are injected during TAE, and recent evidence has suggested that no survival benefit is derived by the use of chemotherapy in TACE versus TAE [12]. In contrast to TAE and TACE, TARE achieves cell death by local radiation damage; TARE is thus considered to be a form of brachytherapy with no significant embolic effect. TARE using 90-Y-tagged glass beads has been shown to be safe and probably effective in patients with unresectable HCC [13–15]. A recent meta-analysis suggested that TARE is significantly better than TACE in terms of survival, time to progression, hospitalization time, and complication rates for patients with HCC [16]. A further role of TARE in advanced HCC patients is as a conversion treatment for patients considered otherwise unresectable or even as a bridge to transplantation [17]. Moreover, in HCC patients with a future remnant liver (FRL) inadequate for up-front surgery, TARE may represent a surrogate for portal vein embolization, combining FRL hypertrophy and tumor treatment [18].

In the HCC setting, the degree of survival advantage offered by TAE/TACE versus medical therapy is still a matter of debate. Two controlled trials have shown a survival advantage

Table 1. Essential literature review on transarterial embolization for HCC

Author, Year	Treatment	Summary	Main findings
Salem et al., 2010 [13]	TARE	291 patients with HCC treated with ⁹⁰ Y radioembolization	Response rates 42% (WHO criteria) and 57% (EASL criteria) Time to progression and overall survival varied by tumor stage and liver function
Mazzaferro et al., 2013 [14]	TARE	52 patients with intermediate to advanced HCC Prospective, phase II study	Median time to progression 11 months (no difference between portal vein thrombosis vs. no portal vein thrombosis) Median overall survival 15 months Various grades of reduced liver function in 36.5% within 6 months
Llovet et al., 2002 [18]	TACE	112 patients with unresectable HCC Randomized controlled trial 3 treatment arms: TAE, TACE, and symptomatic treatment	TACE improved survival of stringently selected patients
Lo et al., 2002 [19]	TACE	80 patients with unresectable HCC Randomized controlled trial TACE vs. symptomatic treatment	TACE significantly improved survival in select patients

WHO=World Health Organization; EASL=European Association for the Study of the Liver.

for TACE compared with symptomatic treatment alone in selected patients with unresectable HCC and preserved liver function [19, 20]; however, a more recent Cochrane meta-analysis failed to find evidence of a survival benefit [20]. Table 1 details the results of a literature review on TAE for HCC.

An unresolved issue in the treatment of HCC with TACE/TAE is the timing of repeat treatment. In clinical practice, it remains difficult to predict the failure of such retreatments. Moreover, even the definition of refractory TACE/TAE is still unclear. To address this problem, scoring systems have been proposed to help physicians to identify patients who will not profit from retreatment with TACE. Among these scores, the assessment for retreatment with TACE score seems to be one of the most promising [21]. The accurate review of the imaging findings after TAE/TACE still remains one of the most important steps in interpreting the results of the procedures [22].

Another important open issue in the treatment of HCC with TACE/TAE is the association between these therapies and sorafenib. Recently, Lencioni et al. [23] reported that the use of TACE with doxorubicin-eluting beads plus sorafenib did not improve patient survival over TACE alone. Despite these negative results, further studies on the benefit of combined therapy should be undertaken.

Complications from liver embolization may include upper quadrant pain, nausea, moderate ileus, fatigue, fever, and transient elevations of aspartate aminotransferase, alanine aminotransferase, and bilirubin levels. Symptoms are usually self-limiting and may be worsened by the use of chemotherapy in TACE [20, 24]. Serious complications such as hepatic failure, gastroduodenal ulceration, kidney failure, and death (2–3%) have been reported at very low percentages [3].

Predictors of Response to TACE/TAE Treatments: The Western Perspective

TACE and TAE promote local disease control through tumor necrosis and apoptosis induced by hypoxic and cytotoxic agents. Although potentially very useful in optimizing patient selection and follow-up, the individual response to TACE is generally unpredictable [19]. Investigators from both Eastern and Western countries have proposed several prognostic indices, based on combinations of clinical and laboratory parameters, to help clinicians select appropriate candidates for initial or repeat TACE or TAE. Unfortunately, no prognostic index is today universally accepted because they are difficult to implement, insufficiently discriminatory, or present methodological problems [25]. Such studies essentially identify a set of parameters that appear to maximize predictive performance, but this predictive performance cannot be repeated elsewhere because of random fluctuations of patient characteristics and differences in clinical management and the technical execution of TACE and TAE. This fact suggests that studies with larger target populations are needed [25]. Moreover, the sensitivity of HCC to transarterial therapy may also vary according to the tumor biology, but very few studies have focused on the predictive value of tumor morphological or molecular markers of response to TACE or TAE.

A study conducted in Italy and France investigated the association of post-TACE tumor necrosis, as assessed in surgical specimens, with the immunohistochemical expression of biomarkers involved in adaptive mechanisms to hypoxia that are hypothetically able to influence the response to TACE [26]. The markers selected in this study were hypoxia-inducible factor 1- α (HIF1 α) and vascular endothelial growth factor (VEGF) for neoangiogenesis, CD34 for microvessel density, CA9 for antiapoptotic activity, CD133 and nestin for stem cell features, and vimentin and E-cadherin for the epithelial-mesenchymal transition (EMT); all these markers have previously been identified as being related to treatment resistance in several types of malignancies [27–30]. In the above study, multivariate analysis found that only CD34 and VEGF retained a significant association with TACE response [26]. A typical pattern of expression (VEGF-, CD34+) was associated with resistance to TACE, suggesting that HCCs with this expression pattern are more resistant to hypoxia because they have already developed a complete vascular network (increased CD34) without requiring further neoangiogenesis (decreased VEGF). This finding was also confirmed based on the results of pretreatment liver biopsies and their correlation with the radiological evaluation of responses to TACE.

These data suggest that further investigations are needed on the role of HCC biology in influencing responses to TACE, in particular because easily applicable and validated predictors of response to treatment are currently lacking. Prototypical characteristics of these markers have recently been proposed: ideally, they should be cost-effective, reproducible, and easy to evaluate also on pretreatment specimens, such as liver biopsy or liquid biopsy specimens [31].

Predictors of Response to Intra-Arterial Treatment: The Eastern Perspective

TACE induces marked ischemic tumor necrosis by obstructing tumor-feeding arteries with a chemotherapeutic agent emulsified with Lipiodol and embolic agents. However, a significant number (50–86%) of HCCs show residual viable tumor [32]. To adapt and survive in a hypoxic tumor microenvironment, cancer cells express hypoxia-inducible factors, including HIF1 α , to activate target genes involved in proliferation, angiogenesis, and EMT, resulting in a more aggressive tumor phenotype [33]. Hypoxia is reportedly important in reprogramming cancer cells to a cancer stem cell phenotype, which plays an important role in tumor

maintenance and recurrence [34]. HCCs that express stemness-related markers, such as K19, EpCAM, or CD133, are known to have aggressive biological behavior with poorer prognosis compared to HCCs not expressing these markers [35]. Hepatitis B virus (HBV) is the main etiology of HCC in Eastern countries, and, recently, Hepatitis B protein x (HBx) antigen was reported to enhance hypoxia signaling through HIF1 α activation and to enhance EpCAM expression by activating β -catenin and regulating EpCAM promoter methylation [35]. Thus, HBx is suggested to be an additional player in the promotion of the switch in gene expression to stemness in hepatocarcinogenesis, especially in hypoxic tumor microenvironments.

To study the effect of stemness on the TACE response, the authors (HR and YNP) evaluated the transcript levels of hypoxia- (*HIF1A*), stemness- (*EPCAM*, *KRT19*, *POU5F1*, *NANOG*), and EMT-related (*SNAI1*, *TWIST1*) markers by real-time reverse-transcription polymerase chain reaction in HBV-related progressed HCCs that had and had not undergone preoperative TACE; totally necrotic HCCs after TACE were excluded [*unpublished data*]. Residual HCCs that had undergone preoperative TACE exhibited upregulation of *HIF1A* and *SNAI1* mRNA compared to those that had not undergone preoperative TACE. HCCs with high *HIF1A* mRNA levels showed greater transcription levels of stemness- and EMT-related markers, more invasive pathological features, and poorer outcomes than those with low *HIF1A* mRNA levels. Therefore, stemness is considered to be involved with TACE resistance via upregulation of *HIF1A*. Consequently, controlling stemness is suggested to be important to increase the TACE response of HBV-related HCC. Further studies are needed to validate and confirm our findings.

Conclusions

TACE and TAE are two widely used therapies for HCC. Recent refinements in interventional radiology techniques have facilitated better local control, and TARE is rapidly emerging as an alternative therapy, thereby further expanding the indications for intra-arterial therapies. Further refinement of the patient selection criteria will optimize the use and role of such treatments. In the future, the molecular profiling of HCC to predict the response to TACE and TAE will help clinicians select the optimum treatment.

Conflicts of Interest

The authors declare that no conflicts of interest exist.

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