Transcatheter Arterial Chemoembolisation (TACE) for HCC – Classic Concepts and Future Evolution

a report by
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Hepatocellular carcinoma (HCC) is among of the common malignant tumours in the world, with a global increasing annual incidence, as reported recently. Almost half of this increase has been attributed to hepatitis C virus (HCV), while a minimal or no increase has been related to hepatitis B virus (HBV) or alcoholic liver disease. Untreated HCC has an notoriously poor prognosis, with a median survival of one to eight months and a five-year survival of around 3%. Potentially curative surgical therapeutic options include partial hepatic resection with adequate margins and liver transplantation. However, only 30–40% of patients with HCC qualify for surgery, mostly due to advanced disease at presentation and poor hepatic function, rendering the majority of patients eligible only for palliation. Non-surgical palliative management of unresectable HCC has undergone major changes over the past two decades. Improved outcomes may partly be attributed to earlier detection, advances in imaging, more accurate patient assessment and constant development of locoregional therapies. Among locoregional therapies, transcatheter arterial chemoembolisation (TACE) is a minimally invasive approach for palliative treatment of unresectable HCC that, despite its heterogeneity and variations, has been proven to control symptoms and prolong survival. This article will present some classic concepts that define this popular procedure and some future models of advancement for this technique.

Classic Concepts of TACE

TACE, initially launched by Yamada, exploits HCC's preferential blood supply by the hepatic artery to precisely deliver chemotherapeutic and embolic agents to the tumour, while sparing the surrounding liver parenchyma and avoiding concomitant systemic toxicity. Since TACE was first introduced as a palliative treatment in patients with unresectable HCC, it has become one of the most commonly performed procedures in interventional radiology. Nowadays, chemo-embolisation is the preferred treatment for unresectable HCC. Moreover, for unresectable HCC larger than 10cm in diameter, TACE is the only treatment option. TACE is also employed as an adjunctive therapy to liver resection or as a bridge to liver transplantation, as well as prior to radiofrequency ablation.

TACE typically involves the injection of chemotherapeutic agents, with or without lipiodol and embolic agents, into the branch of the hepatic artery that feeds the tumour. The most commonly used chemotherapeutic drug combination includes doxorubicin, cisplatin and mitomycin C, whereas doxorubicin is the most common single agent used. The absolute and relative contraindications to this technique are listed in *Table 1*. Patient selection is important, as not every patient with HCC may benefit from chemoembolisation. One important aspect in the selection of patients is the presence of adequate liver function. In patients with advanced liver disease, treatment-induced liver failure may offset the anti-tumoural effect or survival benefit of the intervention. Predictors of outcome are related to tumour burden (tumour size, vascular invasion, and alpha-fetoprotein (AFP) levels), liver functional impairment (Child-Pugh, bilirubin, ascites), performance status (Karnofsky index, Eastern Cooperative Oncology Group (ECOG)) and response to treatment. Thus, the best candidates are patients with preserved liver function and asymptomatic lesions without vascular invasion or extrahepatic spread.

In the authors' institution, before each TACE procedure, all patients undergo a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the liver, preferably with perfusion/diffusion sequences. This will define the extent and viability of tumour and serve as a baseline study to plan future treatment. A dual-phase MRI or computed tomography (CT) are also acceptable but the addition of the diffusion sequences may demonstrate and quantify tumour necrosis. In addition to information regarding tumour viability, cross-sectional imaging may add important details about its vascular supply and invasion. For example, the presence of portal vein thrombosis and/or variant vascular anatomy may alter

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Table 1: Contraindications for TACE

Absolute
1. Tumour respectability
2. Extensive intractable infection
3. Extensive liver disease
Relative
1. Borderline liver function
2. Total bilirubin >4mg/dl
3. Inadequate renal function (creatinine >2.0mg/dl)
4. Portal vein thrombosis
5. Uncorrectable coagulopathy
6. Poor general health – Eastern Cooperative Oncology Group score of >2
7. Significant arterio-venous shunting through the tumour
8. Encephalopathy

Table 2: Most commonly encountered complications of TACE

Complication
Post-embolisation syndrome (pain, fever, nausea, fatigue and leucocytosis)
Liver abscess
Gallbladder infarction
Septicaemia
Irreversible liver failure
Hepatorenal syndrome
Pulmonary oil embolisation
Cerebral embolisation

the embolisation part of the procedure or reduce the procedure time and contrast load. TACE is typically well tolerated, with most patients requiring only one overnight admission for observation. Transient adverse effects are commonly related to the post-embolisation syndrome. Most commonly encountered complications of TACE are listed in *Table 2*. The most common serious adverse events are liver abscess or liver infarction, which occur in approximately 2% of cases each.

Overall results with TACE in Western and Eastern studies have been difficult to interpret, partly due to variable criteria for patient selection and the intent to treat for cure versus palliation. The only recent prospective randomised trials evaluating patient survival after TACE for HCC were published in 2002. Both trials demonstrated significantly longer survival with chemoembolisation. The first, by Lo et al., compared survival outcomes with chemo-embolisation versus symptomatic management, with 40 patients in each group. One-, two-, and three-year survival rates in the study group were 57%, 31%, and 26%, respectively, compared with 32%, 11%, and 3% in the control group (p=0.02). In the included univariate analysis, chemoembolisation was found to be a significant predictor of survival (OR=0.49; p=0.006).

The second study, by Llovet et al., included 112 patients in three arms and compared outcomes with chemoembolisation versus embolisation alone versus symptomatic treatment. The trial was prematurely terminated when a significant survival benefit was demonstrated with chemoembolisation (survival rates, 82% at one year and 63% at two years) over symptomatic treatment (63% at one year and 27% at two years; p=0.009). At the time the trial was halted, there was not a survival benefit identified with embolisation alone (75% at one year and 50% at two years) versus symptomatic treatment. The only variable associated with prolonged survival was assignment to the chemoembolisation group (OR= 0.45; p=0.02). A meta-analysis that included seven randomised trials of arterial embolisation for unresectable HCC provided further support of the efficacy of TACE. TACE showed a median survival of more than two years and in a few cases converted some patients into operable candidates.

Several challenges regarding the interpretation of the efficacy of TACE, as well as such as obstacles regarding the development of multi-drug resistance mechanisms and tumour revascularisation, are yet to be solved. Variations on the technique, as well as different drug regimens, hinder a more systematic approach and implementation of meta-analyses. Moreover, it is highly unlikely that there will be any prospective randomised controlled trials of chemoembolisation for HCC in the future. The lack of randomised controlled trials for HCC in the US reflects the reality that patients are not willing to be randomised to receive no therapy, mainly because TACE is a widely accessible treatment with a 20-year track record for this disease. Decisions regarding the merits of this therapy must be made based on the best available data and should not be withheld based on the absence of randomised controlled trial data that is highly unlikely to be published.

Future Evolution of TACE

Anti-VEGF Antibodies in Combination with TACE

HCCs are vascular tumours, and increased levels of vascular endothelial growth factor (VEGF) and microvessel density have been observed. High VEGF expression has been associated with inferior survival. Therefore, inhibition of angiogenesis represents a potential therapeutic target in HCC. Interestingly, and in contrast to the traditional belief that tumour ischaemia is favourable, several recent studies have shown that tumour ischaemia and hypoxia upregulate several molecular factors, including VEGF, provide resistance to cell apoptosis and stimulate the growth of HCC. Moreover, the degree of VEGF expression is reported to be associated with HCC tumour size and histologic grade.

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> Dr M. Varela, Barcelona Liver Cancer Clinic, Spain

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	Response Rate	Complications
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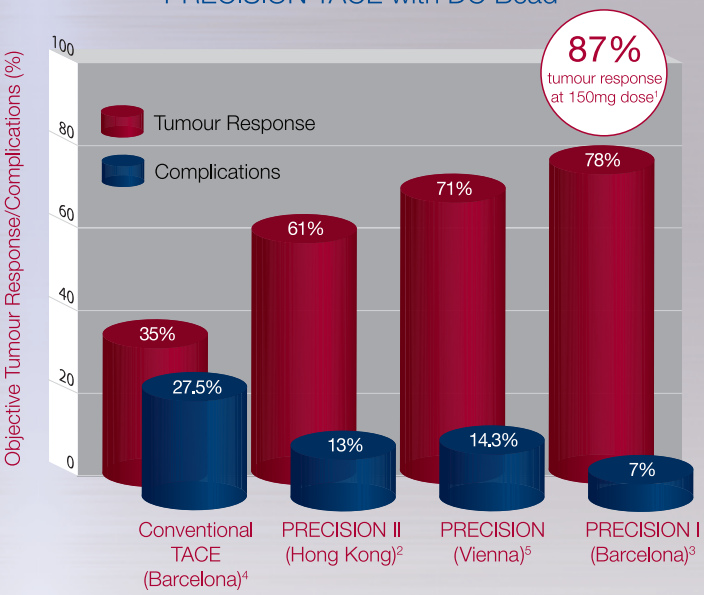
Conventional TACE	35%	27.5%

Improved Response and Reduced Complications with PRECISION TACE with DC Bead



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Bevacizumab (Avastin™, Genentech Inc., San Francisco, CA), a humanised monoclonal antibody that binds VEGF and prevents its interaction to receptors on the surface of endothelial cells, has recently emerged as an important therapeutic agent in colorectal cancer and has been added to the triple chemoembolisation cocktail for patients with primary and metastatic liver cancer. In addition to its direct anti-angiogenic effects, bevacizumab may enhance chemotherapy administration by normalising tumour vasculature and decreasing the elevated interstitial pressure in tumours. A recent pilot study suggested that bevacizumab can be given safely at both 5mg/kg and 10mg/kg in HCC patients with localised unresectable HCC, preserved liver function and no significant oesophageal varices. In another pilot study, selected HCC patients undergoing TACE additionally received intravenous bevacizumab, which was well tolerated and prolonged disease control. Currently, there are two US National Cancer Institute (NCI) phase II trials evaluating the safety and efficacy of bevacizumab in patients with primary unresectable liver cancer. In the authors' institution, a phase II trial of bevacizumab with TACE for HCC has just started enrolling patients. TACE is designed to be performed on day one of a 42-day therapy cycle and intravenous (IV) administration of bevacizumab (10mg/kg) will be administered on days seven, eight and 22. Data from these trials may guide to the development of novel anti-angiogenic liver cancer regimens. It is important to note that successful execution of these trials depends not only on the transfer of expertise from the bench to the bedside, but also on the productive collaboration of clinicians in a multidisciplinary oncologic setting.

Inhibition of angiogenesis represents a potential therapeutic target in HCC.

Drug-eluting Beads for TACE

Currently, there is intense research activity in the area of nanotechnology and drug-delivery systems. The ideal drug-loaded carriers should deliver the agent precisely, release it in a controlled and sustained manner and achieve high intra-tumour drug concentration for a sufficient period, without damaging the surrounding hepatic parenchyma. Several drug-delivery systems for intra-arterial treatment of hepatic lesions, such as polyvinyl alcohol microspheres and poly(lactide-co-glycolide) (PLCG) microspheres, have been recently tested. Polyvinyl alcohol (PVA) hydrogel microspheres can be loaded with a single chemotherapeutic agent, such as doxorubicin or irinotecan, and infused intra-arterially for selective tumour targeting. Doxorubicin-eluting beads (DC Bead™ for loading by the physician and Precision Bead™ preloaded with doxorubicin (Biocompatibles UK Ltd, Surrey, UK)) were initially tested on the rabbit Vx-2 tumour model and demonstrated consistent drug release over time with excellent tumour control. These recently published animal data have shown that the concentration of doxorubicin within the tumour remains high up to seven days post-transcatheter infusion, suggesting continuous release of doxorubicin from the microspheres, whereas systemic drug concentration is kept at minimal level. However, further clinical studies need to support this initial report of efficacy for this drug-delivery system.

3-Bromopyruvate Intra-arterial Injection for Liver Cancer-preclinical Studies

3-Bromopyruvate (3-BrPa) is an example of a drug disrupting a metabolic pathway, which has been recently tested via transcatheter infusion. 3-BrPa is a potent ATP inhibitor of glycolysis. In a recent study, conducted on human hepatoma cell lines, 3-BrPa induced HCC cell apoptosis, besides inhibiting ATP production. This apoptotic cell type of death was likely responsible for the full effect of 3-BrPa on growth suppression, as induced apoptosis reached over 90% within six hours of treatment. It should be noted that previous studies have suggested that apoptosis is an ATP-dependent process.

In another study, cell death induced by 3-BrPA was shown to contain both apoptotic and necrotic components, in a ratio depending on the 3-BrPA concentration. This study also demonstrated that 3-BrPA preferentially kills cancer cells with mitochondrial defects and tumour cells in a

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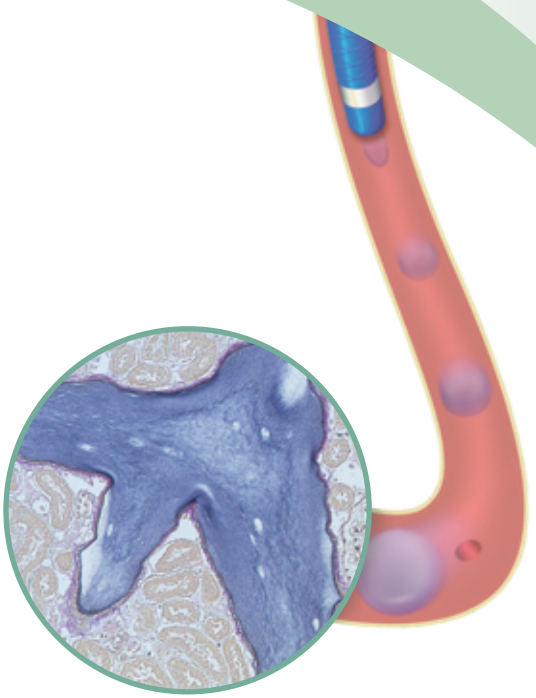

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hypoxic environment. Preliminary studies on the rabbit Vx-2 liver tumour model with direct intra-arterial infusion of 3-BrPa showed complete tumour destruction, without affecting the surrounding normal liver parenchyma. In a more recent VX2 animal study, one-hour intra-arterial injection of 1.75mM of 3-BrPa resulted in tumour cell death in all treated animals. Moreover, the one-hour intra-arterial infusion of 3-BrPA resulted in complete tumour destruction and was significantly greater than that of serial bolus injection. In addition, animals treated in this manner had no liver toxicity. Nevertheless, the exact mechanisms of resistance of normal cells against 3-BrPa, as well as the exact pathway of 3-BrPa action, are still under investigation.

Advanced Imaging Techniques for Monitoring the Efficacy of TACE

Despite the fact that evaluating the effectiveness of TACE is critical in determining the success of treatment and would help to guide subsequent therapeutic planning, there is no single reliable imaging method for monitoring the early response to this treatment method. Good iodised oil retention at CT is associated with substantial prolongation of median survival of the patient, but does not indicate complete tumour necrosis, nor is it correlated with the size or extent of the necrotic area. On dynamic CT studies, hyper-attenuating iodised oil impairs assessment of residual tumour enhancement. Enhancing areas in the embolisation site on gadolinium-enhanced MR images presumably represent viable tumour but could also result from post-treatment granulation tissue.

Perfusion-diffusion MRI can successfully overcome this obstacle, as lipiodol does not obscure gadolinium enhancement and measurement of increased free water content within the tumour translates into cancerous cell death. Furthermore, diffusion MRI may prove more useful in the early post-treatment period after TACE, when tumours are not expected to change in size, despite the fact that they may be nonviable. A recent study by the authors' group showed that diffusion-weighted images and the generated apparent diffusion coefficient (ADC) maps provide functional information on a molecular level regarding the viability of tumour cells after TACE, allowing, therefore, an cellular-based assessment of treatment response after TACE. Viable tumour cells have intact cellular membrane, which restrict the movement of water molecules, resulting in low ADC values. With cellular death, cellular membranes eventually are disrupted, and diffusion of water molecules is no longer restricted, leading to an increase of the ADC values within the necrotic tumour tissue, confirming, therefore, the presence and invasion of extracellular water inside the cancerous cells. In this study, there was a statistically significant decrease in the ADC value of treated HCC after TACE, compared to values before treatment ($p=0.026$). In this way, the ADC value measurements allow for the accurate quantification of the degree of cellular damage, and this may prove especially valuable after TACE because of the wide spectrum of histopathologic findings, ranging between complete necrosis and the absence of necrosis.

Diffusion MRI may prove more useful in the early post-treatment period after TACE, when tumours are not expected to change in size.

Conclusion

Knowledge of the molecular basis of hepatic tumourigenesis is evolving continuously. Main areas of interest include the development of new cytostatic agents that interact upon some disrupted pathways, inhibit angiogenesis and limit chemotherapeutic dose-related toxicity. Phase I/II/III studies are currently testing whether anti-angiogenesis agents, inhibitors of growth-factor-signalling and cell cycle enzymes, non-specific growth inhibitory agents, specific antagonists of HCC tumour markers and anti-inflammatory agents may have a potential impact on the treatment of liver cancer. The combination of these emerging agents with TACE seems challenging and promising. Moreover, monitoring the efficacy of TACE by imaging is also crucial for effective patient care and prolongation of patient survival. ■

A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchoncologicaldisease.com).