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Current concepts in transarterial chemoembolization of hepatocellular carcinoma

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Abstract

Transarterial chemoembolization (TACE) has the potential to improve survival in patients with intermediate stage hepatocellular carcinoma (HCC). Careful selection of patients is mandatory to gain survival benefit and safe quality of life. Basic principles of TACE in HCC include selective treatment via intrahepatic and extrahepatic arteries, proper management of side effects and continuation of treatment guided by imaging. After conventional TACE, based on delivery of cytotoxic drugs emulsified in iodized oil and embolization of various types of particles, has been used for more than 20 years, the new concept of drug-eluting microspheres has been introduced. This technology effectively combines enhanced local drug delivery and ischemic embolization effects. Clinical studies showed intensified local necroses and reduced systemic toxic side effects compared to conventional TACE. Embolization of HCC with sub-100 μm particles penetrating deeply into the tumor vascular bed is another promising new option. Very effective devascularization of HCC nodules has been shown after 40 μm bland embolizations, however, potential risks like passage of particles into hepatic veins and systemic circulation have to be considered. Today the indication for TACE in intermediate stage HCC patients is widely accepted; however, there is no clear methodical standard so far. Further studies are necessary to define how to adapt various available methods to individual HCC and patients characteristics.

Key words: Hepatocellular carcinoma—Transarterial chemoembolization—Drug-eluting microspheres—Liver tumors—Regional treatment

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related death worldwide with age adjusted incidence rates of 14.7% and 4.9% per 100,000 patients for men and women, respectively [1–3]. At first presentation only 20%–30% of patients are candidates for curative treatments, including surgical resection and liver transplantation [4] with another 10%–15% suitable for potential curative thermal ablation [5, 6]. Transarterial chemoembolization (TACE) has become the standard of care for patients with HCC not amenable for surgical or ablative treatment if extrahepatic metastases and advanced liver disease are lacking [7].

Rationale for treatment of HCC by transarterial chemoembolization (TACE) is based on the dual blood supply of the liver with predominant nutrition of liver parenchyma by portal veins and arterial supply of HCC with a various degree of hypervascularization. Transarterial delivery of cytotoxic drugs combined with embolization of arterial feeders causes enhanced local cytotoxic and ischemic effects to tumor tissue, the “regional advantage” of TACE compared to systemic treatments. Regional advantages of doxorubicin, mitomycin, and cisplatin, drugs usually used for TACE in HCC, differ between 2 and 4 due to pharmacokinetic characteristics of these drugs. Depending on the technique used, drug delivery and arterial embolization can be more or less simultaneous, i.e., intermittent injections of drugs and bland particles, temporary emulsions of iodized oil and drug solutions and prolonged drug release during permanent arterial occlusion by drug-eluting microspheres, i.e., drug-eluting beads. Deriving from the rationale for TACE, the technical goal of treatment is the application of highly concentrated cytotoxic drugs over a prolonged period of time, and the complete and permanent occlusion of intratumoral arteries while maintaining the central large supplying arteries open.
HCC is associated with liver cirrhosis in most of the patients. Symptoms originating from HCC are present only in advanced stages or if complications like rupture, biliary obstruction, or portal vein thrombosis occur. Patients treated with TACE for HCC usually have no symptoms. The aim of treatment in these patients is survival benefit, improvement or maintenance of quality of life and prevention of tumor progression. Positive effects on mental status of patients had been shown up to 4 months after TACE [8].

**Patient selection for TACE**

One of the most critical points of TACE in HCC is appropriate patient selection. Following the BCLC guidelines, curative treatment by resection or transplantation and potential curative treatment by thermal ablation should be preferred in very early and early stages of disease: Child-Pugh Class A, single tumor up to 5 cm size/upto 3 tumors up to 3 cm size [7]. TACE is the treatment of choice in patients with intermediate stage of disease: Child-Pugh Class A and B, multinodular HCC and in patients with advanced stage disease (performance status 1–2) if no portal vein invasion and no extrahepatic metastases are present. So far there is no clear definition of the maximum of single tumor size, maximum number of nodules or maximum sum of diameters in multinodular disease. Also it is not clear which degree of portal vein invasion (segmental vs. main branch) should be considered a contraindication for TACE. However, with respect to the studies showing survival benefit of TACE compared to best supportive care, it seems that careful patient selection in terms of vascular criteria is mandatory. Between 88% [9] and 79% [10] of patients had been excluded in these studies due to vascular invasion, advanced disease or selection of curative treatments. Mean tumor size in these studies was 4.9 cm (4–5.8 cm) and 7 cm (4–14 cm) [9, 10], respectively. In the study by Llovet et al. [9] only 38% of patients with intermediate stage disease were included and accepted for TACE; segmental portal vein invasion was a contraindication. No patients with diffuse type of HCC were treated in these two studies. In a previous prospective randomized trial 11% of patients with diffuse type of HCC were treated by TACE; this study did not show significant survival benefit in patients treated with TACE compared to best supportive care (BSC) [11].

**General methodical aspects of TACE in HCC**

TACE in HCC should be performed as selective as possible, requiring the use of microcatheters in most cases. If multiple nodules and/or multiple feeders are present, consecutive selective catheterizations in one or more treatment sessions are necessary to obtain complete tumor coverage (Fig. 1). If incomplete response is present in tumors located near the bare area of the liver or in tumors infiltrating the liver capsule, the extrahepatic arterial supply should be considered and used for treatment (Fig. 2). In these tumors the right inferior phrenic artery, renal capsular artery, internal thoracic artery, and adrenal arteries are increasingly involved if recurrences occur [12].

Post-embolization syndrome includes abdominal pain, nausea, vomiting, and fever occurring in most of the patients. Grade and duration of these symptoms depend on the size of tumor and surrounding liver tissue affected by TACE and on the amount of embolic material applied. Concomitant medication including systemic analgesia and antiemetic drugs is generally used; intraarterial administration of local anesthetics and systemic application of antibiotics have been recommended in some studies but are not generally accepted [13].

Continuation of TACE treatment is necessary if residual or recurrent viable tumor is present or new tumor lesions appear during follow-up imaging and no contraindications arise. Evaluation of local tumor response by CT or MRI is usually performed 2–3 months after completion of TACE and requires acquisitions of both arterial and portal venous phases. If conventional TACE using iodized oil has been performed, additional plane CT study is necessary for differentiation of arterial hypervascularization in viable tumor tissue and deposits of iodized oil. This can be limited by high density artifacts favoring MRI for follow-up imaging if appropriate image quality can be obtained.

Despite the fact that overall and progression-free survival are the main goals of TACE in HCC, the evaluation of local response is of interest especially concerning the comparison of efficacy of various treatment methods. WHO- and RECIST-classification systems for evaluation of tumor response are based on changes in tumor size [14], whereas in the EASL-classification system, the extent of tumor necrosis is additionally considered independent from tumor size [15]. This different use of classification systems has to be taken into account, if results of various methods of TACE are compared. Studies performed before 2003 usually report the results based on the WHO-classification system [9, 10].

**Conventional TACE**

Deposition of cytotoxic drugs emulsified with iodized oil followed by embolization of feeding arteries using Gelfoam or PVA-particles are the steps of conventional TACE. The value of intraarterial application of cytotoxic drugs during conventional TACE is not clearly defined.
today. In a systematic review, no clear benefit has been shown so far from TACE compared to embolization alone and that there is no evidence one cytotoxic drug is more effective than another. Doxorubicin (50 mg/qam) has been used in 48%, Cisplatin (92 mg/qam) in 31% and Mitomycin (10 mg/qam) in 8% of reported series, respectively [13]. Just prior to injection, emulsion is prepared by intensive mixing of equal volumes of cytotoxic drug solution and iodized oil using the pumping method with two syringes and a three way stop cock. Injection is guided by fluoroscopy and results in dense accumulation of the emulsion within the tumor vascular bed. Injection of poor iodized oil up to a maximum volume of 10–20 cc is an option and is followed by embolization of feeding arteries with embolic particles (150–350 μm in size, PVA or bland microspheres) or by

Fig. 2. HCC treated via extrahepatic supply of right inferior phrenic artery. A CT after first TACE via hepatic artery showing incomplete filling of tumor with iodized oil. B CT after second TACE via right inferior phrenic artery showing additional uptake of iodized oil. C Hepatic arteriogram during second TACE showing no supply to residual viable tumor nodule. D Arteriogram of the right inferior phrenic artery showing hyperperfusion of viable HCC nodule.
Gelfoam cubes. Endpoints of conventional TACE are complete filling of the tumor vascular bed with iodized oil and stop-flow in subsegmental and segmental feeding arteries.

Local response rate (including complete response and partial response according to the WHO-classification system) after conventional TACE reported in the literature ranges between 15% and 55% [16]. Response after first TACE can be improved during following treatment sessions in a relevant proportion of cases. Patients with nodular-encapsulated type of HCC showed better response and longer survival after TACE compared to patients with infiltrative type of HCC [17]. Survival rates at 3 years were 29% after TACE vs. 17% after BSC (BSC) \( (P = 0.009) \) in the study by Llovet et al. [9] and 26% after TACE vs. 3% after BSC in the study by Lo et al. [10], respectively. Mean survival was significantly longer in patients after TACE (28.7 months) compared to patients with BSC (17.9 months; \( P = 0.005 \)). Portal vein infiltration was significantly reduced (17% after TACE, 58% after BSC; \( P = 0.005 \)) [9].

**TACE of HCC with drug-eluting beads**

DC Beads® (Biocompatibles UK Ltd.) are microspheres consisting of a PVA macromere backbone with hydrated shells containing negatively charged SO3-groups. Positively charged ionic molecules like the cytostatic drugs Doxorubicin and Epirubicin are loaded into the beads by coupling to the SO3 groups due to an ion exchange mechanism displacing water from the hydrated shells [18]. By catheter-directed application of beads into the arterial feeders embolic occlusion of the tumor vascular bed is caused and cytostatic drugs are delivered over a period of time by an opposite ion exchange process. 75 mg of Doxorubicin are loaded into 2 mL beads. Under in vitro conditions, it was shown that up to 98% of Doxorubicin are loaded within 5 h and up to 27% are released in saline within 1 week [19]. For treatment of HCC beads of diameters between 100–300 \( \mu \)m and 300–500 \( \mu \)m are used. Beads are of stable spherical shape and decrease in size by 20%–25% during the loading process [18]. Loading process depends on the size of beads and ranges between 60 min for 100–300 \( \mu \)m beads and 90 min for 500–700 \( \mu \)m beads. For application 2 cc of drug loaded beads are mixed with 5–7 cc of contrast material to allow flow-directed precise delivery and obviate reflux into nontarget arteries. Recommended flow during injection is 1 cc of beads-contrast mixture per minute.

Compared to conventional technique, the use of doxorubicin-eluting beads during TACE of HCC significantly reduces peak plasma doxorubicin concentration [20, 21] and drug-related side effects [23]. Doxorubicin-eluting beads cause significant necrosis of HCC nodules (Fig. 3) resulting in complete response rates of 26%–27% and partial response rates of 25%–46%, 6 months after TACE according to EASL criteria [21–23]. Twelve months after TACE complete response rate still was 20% and partial response rate 3% [22]. According to RECIST criteria a 6-month partial response rate of 44% had been measured [21]. Drug-eluting microspheres based on sodium acrylate/vinyl alcohol copolymer (HepaSphere®, Biosphere/Merrit) have also been used for TACE in HCC [24]. Drug loading and release is based on a similar ion exchange process as described for the beads. 50 mg of Doxorubicin or Epirubicin had been loaded into 50 mg dehydrated microspheres. At 6 months after TACE, complete response rate was 52% and partial response rate 26% according to EASL criteria, but only 31 of 50 patients had follow-up imaging in this study [24].
There are only limited data so far in terms of the survival benefit by the use of drug-eluting beads during TACE. Comparing consecutive series of patients who had TACE using conventional technique and drug-eluting beads, respectively, a trend to survival advantage by the use of beads was seen [25]. Significant prolongation of time to progress after TACE was demonstrated in another study (42 vs. 36 months \( P = 0.008 \)) [22]. No survival data of HCC patients following HepaSphere® TACE are available today. Further controlled trials are necessary to find out the real survival benefit of TACE using drug-eluting microspheres. In the PRECISION V study a significant increased objective response rate was seen following TACE with Doxorubicin-loaded beads compared to conventional TACE in patients with bilobar and recurrent disease and in Child-Pugh B patients [23]. Considering the high exclusion rates in the studies by Llovet et al. and Lo et al. because of advanced tumor and liver disease [9, 10], survival benefit of drug-eluting beads could be more relevant in this group of HCC patients.

**Bland embolization of HCC with <100 \( \mu \)m particles**

Potential advantages of particles of <100 \( \mu \)m size for embolization of HCC are deep penetration into the tumor vascular bed and transsinusoidal passage to the portal venous side causing more complete tumor necroses and preventing early arterial collateralization (Fig. 4). Extensive and complete ischemic necroses of HCC up to 12 cm in size have been seen following bland embolization with 40 \( \mu \)m particles [26]. In this study at 12 month follow-up, lesion based (patients based) complete response rate was 7% (15%) and partial response rate 51% (25%), respectively, according to RECIST criteria. However, only 20 of 50 patients had 12 month follow-up. Further potential benefit of 40 \( \mu \)m particles (Embozene®, Celonova BioSciences, Newnan, USA) come from small range of size calibration (±10%) and specific polyzene coating which result in a more homogeneous level of occlusion compared to other types and larger size of embolic agents [27].

On the other hand, embolization of HCC using 40 \( \mu \)m particles is associated with the risk of arteriovenous passage of particles into the pulmonary circulation. Another potential risk is pulmonary tumor embolism caused by necrotic disintegration of tumors infiltrating large hepatic veins, which can result in fatal outcome [26]. Clinical results in terms of survival data and studies comparing embolizations of HCC with 40 \( \mu \)m particles and conventional TACE are lacking.

**What is the success of TACE in patients with HCC?**

This question can be answered from different points of view: radiological view, oncological view, and patients view. Rates of complete and partial response according to RECIST or EASL-classification systems define success based on imaging findings and allow comparison of different technical variations of TACE. Survival, progression free survival, and quality of life after TACE are the most relevant outcome parameters from the oncological point of view and allow comparison of TACE to systemic medical treatments, i.e., inhibitors of angiogenesis and BSC. The patient point of view includes also mental improvement, which can be obtained by TACE as an active palliative treatment in a relevant proportion of cases [8].

**References**


![Fig. 4. HCC before and after transarterial embolization using 40 \( \mu \)m Embozene® Microparticle. A HCC evident during portal venous CT. B Complete necrosis of HCC after selective embolization using 2 mL of 40 \( \mu \)m Embozene® Microparticles.](image-url)