European Review for Medical and Pharmacological Sciences 2010; 14: 356-362

Transarterial chemoembolization (TACE) for unresectable HCC: A new life begins?

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Abstract. – *Background and Objectives:* **to provide an overview on the loco-regional therapy performed by transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC), either as sole, either as neoadjuvant to surgery or bridge therapy to orthotopic liver transplantation (OLT).**

Evidence and Information Sources: **The current review is based on an analysis of the current literature and the caseload experience of the Authors on this topic.**

State of the Art: **Chemoembolization combines de-arterialization of the tumor and selective delivery of chemotherapeutic agents into tumor's feeding vessels during angiography. Tumor ischemia raises the drug concentration compared to infusion alone and extends the retention of the chemotherapeutic drug. As locoregional therapy, TACE allows a complete local tumor control of 25-35% and permits an increase of survival in patients with intermediate HCC according to Barcelona-Clinic Liver Cancer (BCLC) classification. Excellent results were also achieved by combined therapies, such as with percutaneous ethanol injection or radiofrequency ablation, as neoadjuvant therapy prior to liver resection and in some circumstances as a bridging tool before liver transplantation.**

Perspectives: **Drug eluting beads are microspheres that can be loaded with doxorubicin and induce toxic and ischemic necrosis with the same device; that allows an increase of drug selectively exposed to tumor cells and simultaneously a reduction of systemic toxicity. Tumor embolization induces a neoangiogenic reaction with a significant growth of adiacent satellites, so the association with sorafenib has a strong rationale for a combined therapy and is currently under investigation.**

Conclusions: **today TACE is the standard of care for treatment of intermediate hepatocellular carcinoma. To get the best performance it should be tailored according to the individual patient's condition.**

Key Words:

Liver cancer, Hepatocellular carcinoma, Chemoembolization, Drug eluting beads, Sorafenib.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common causes of cancer death[1]. In Western countries, it develops in a cirrhotic liver in 80% of cases with an annual incidence of 3-5%[2]. Notabily, the incidence of HCC (626,000 cases/year worldwide) nearly matches its mortality (598,000 deaths/year worldwide)[1], underling the poor prognosis; therapeutic options are in fact limited by residual liver function and tumor extension.

Barcelona-Clinic Liver Cancer (BCLC) classification is actually the standard system for the clinical management of HCC. To determine the best therapeutic option it considers tumor burden, liver function reserve according to Child-Pugh score and patient's performance status.

Curative treatments are proposed in very early and early stage HCC (BCLC stage 0 and A) with a 5 years survival of 71-93% and 50-70% respectively. In the past, all tumor not eligible for surgical resection were grouped in the "unresectable" category. Currently, the evidence of an heterogeneous outcome among these patients led to the identification of at least three subgroups of patients with so called unresectable HCC: intermediate (BCLC stage B), with a 16 months median survival in untreated patients, advanced (BCLC stage C), with 6 months median survival and end-stage HCC (BCLC stage D) with 3-4 months survival[3,4].

In the early '90 the diagnosis of HCC was performed mainly in advanced stages: nodules less than 2 cm in diameters represented <5% of cases in Europe. Currently, surveillance programs in high risk patients allows to detect small HCC nodules and an early diagnosis is feasible in 30-60% of cases[2].

For many years, surgical resection and liver transplantation have been considered the only cu-

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rative treatments for HCC. Currently, percutaneous ablative techniques with curative intent are available as first line therapies for small HCCs (≤3 cm) in patients not eligible for surgical treatments[5]. Percutaneous ablative techniques include percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). These procedures are relatively safe and well tolerated with low rate of serious complications. RFA seems to achieve the best results in terms of tumor response, local tumor recurrence and long-term survival if compared with PEI, despite an higher rate of adverse events[6]. Today these local ablative techniques get the best results in Child-Pugh A patients bearing small single tumors[7].

Transcatheter arterial chemoembolization (TACE) is the widely used treatment for unresectable HCC. In early stages it is not recommended as first line therapy because of a effectiveness lower than surgery and percutaneous ablation[8,9]; so it represents the treatment of choice in the intermediate HCC and selected cases of advanced HCC. The main goal of this approach is to a obtain tumor necrosis, local neoplastic control, with preserving as much as possible remainder functional liver.

Transcatheter Arterial Chemoembolization

TACE was introduced in the '70s for the treatment of unresectable HCC[10]. This technique consist of angiography with selective embolization of tumor feeding artery and selective delivery of chemotherapeutic agents (Figure 1). Lipiodol, an ionized oil initially designed for diagnostic use, was introduced in '90 as a vehicle to carry and localize chemotherapeutic agents inside the tumor nodules. Although lipiodol has been widely adopted in TACE protocols, its efficacy in slowing down release of chemotherapeutic agents into neoplastic tissue has not been proven, and some concern regards the fact that lipiodol can mask assessment of residual vascularity on computer tomography imaging following local therapy[11]. Many different drugs are employed in TACE: cisplatin, doxorubicin, epirubicin, mitomycin C, mitoxantrone. Currently, which drug is more effective or which one is the best dose is unclear[11,12]. The use of embolizing agents in addition to chemio-infusion is able to induce extensive ischemic necrosis in well vascularized nodules and maximize the local concentration of chemoterapic agents. There are two kinds of available embolizing agents: sterile adsorbable gelatine sponge (Gelfoam) and polyvinyl alchool sponge (PVA), that cause a longer and distal occlusion of vessels[13,14].

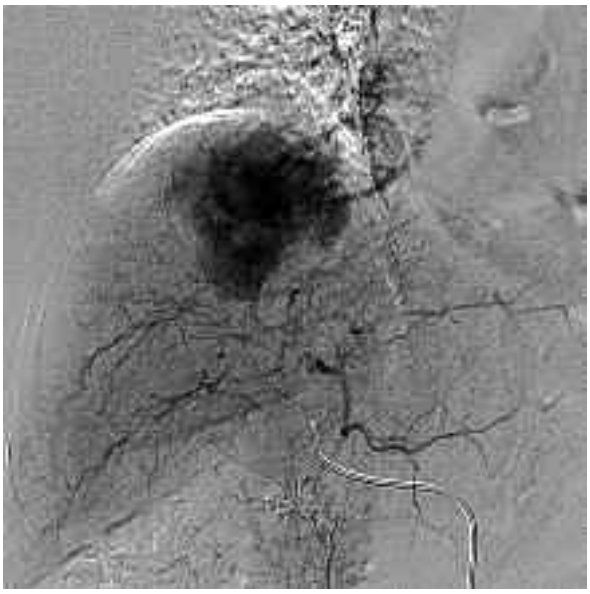

Figure 1. Large hypervascular nodule of segment VIII at diagnostic phase of angiography.

The liver appears to be an ideal organ for chemoembolization since its dual blood supply allows embolization without infarction, and HCC is almost exclusively supplied by newly formed vessels from hepatic artery. Therefore, chemo-lipiodol-infusion in tumor afferent vessels provides the highest drug concentration in the nodule with minimal diffusion in healthy parenchyma. Tumor ischemia obtained by embolization increases drug concentration compared to infusion alone, extends the retention of the chemotherapeutic agent and reduces systemic toxicity. According to catheterized vessels TACE is today referred as non-selective (lobar arteries), selective (segmental and sub-segmental arteries) and super-selective (tumor afferent vessels). In case of single tumor, a crucial issue is that chemoembolization should be super-selective into tumor afferent vessels, in order to preserve as much as possible remnant functional liver tissue and to avoid complications by sparing branches like cystic artery and right gastric artery[11]. The periphery of an HCC nodule could have a ''parasitic'' neovascularization from phrenic, suprarenal and intercostal arteries, so potential tumor's collateral vessels must be previously investigated carefully. In case of multifocal tumors involving both lobes, a two-step proceeding with at least a month interval should be preferred.

The best candidates for TACE are patients with preserved liver function (Child A) and multinodular or isolated large tumor (>3 cm), without vascular invasion, extrahepatic spread or tumor related symptoms, not eligible for surgical or percutaneous curative approaches. According to American Association for the Study of Liver Diseases (AASLD) recommendations, patients with liver functional decompensation (either Child B or C class) should be excluded because the ischemic insult can worse the functional reserve, until liver failure[15]. Nevertheless, exclusion of patients in Child B class is currently debated. Further contraindications to TACE are the hypovascular HCC (in this case TACE is completely ineffective), portal vein thrombosis (for many Authors a relative contraindication), arteroportal or porto-systemic shunts, untreated large oesophageal varices, severe renal failure, severe coagulopathy (for example, INR >1.5) and thrombocytopenia (generally, platelets count <50,000/mm^3)[16].

The post-TACE complications include post-TACE syndrome (up to 80% of patients) with fewer, abdominal pain and transient hypertransaminasemia, that requires only a supportive care. In some cases, drug-related symptoms like nausea, emesis, cytopenia and alopecia develop. Severe complications are rare and include: deterioration of liver function (encephalopathy, ascites, jaundice and increase in prothrombin time), acute renal failure, upper gastrointestinal bleeding (mainly by gastroduodenal ulceration) and ischemic complications like acute cholecystitis, necrosis or stenosis of the biliary tract, hepatic or splenic abscess. Some groups routinely employ antibiotic prophylaxis but there is no evidence of benefit. Treatment-related mortality is 2.4% (range 0-9.5%), mainly due to acute liver failure[11].

TACE Effectiveness

The evaluation of response to treatment in cancer therapy is a key aspect. In many solid tumors the response is evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST)[17]. These criteria evaluate dimensional aspects of treated lesions. The goal of locoregional therapies for HCC is to obtain the complete necrosis of the lesion which is not always followed by dimensional modification. Therefore the European Association for the Study of the Liver (EASL) proposed that the evaluation of the enhancement of the lesion using dynamic diagnostic techniques should be used as an index of the presence of viable neoplastic tissue. EASL criteria appears to be more suitable than RECIST for HCC, especially in the evaluation of locoregional therapies response[18] (Figure 2).

Overall, TACE is able to induce radiological complete response according to EASL criteria in 35% of patients[19], and to induce histological complete response, evaluated on excised tumor or explanted liver, in 25% of cases[20].

In recent years, some randomized controlled trials[21,22] and meta-analysis[19,23] have demonstrated the effectiveness of TACE on overall survival. TACE improves 2-year survival, increasing mean

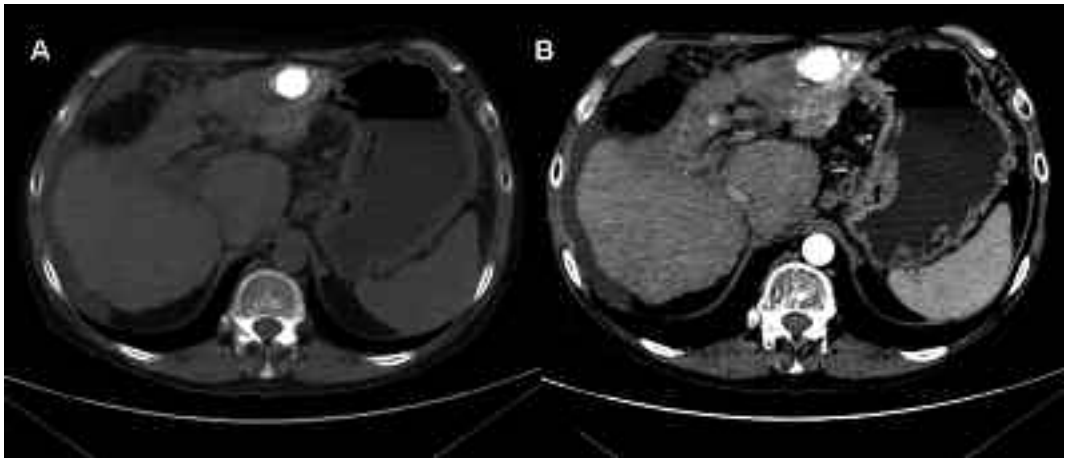

Figure 2. Computerized tomography in a patient with a nodule of HCC of 3 cm on segment III 4 weeks after conventional TACE. ***A,*** Unenhanced scan shows homogeneous lipiodol distribution intratumorally. ***B,*** Arterial phase rules out residual vascularity into the lesion.

survival from 16 to 22 months when compared to palliative care. Recently a retrospective study of the Italian Liver Cancer Group (ITALICA) has shown as, since 2003, TACE was significantly more employed in clinical practice, leading to an increased survival for these patients[24]. For these reasons, TACE should be considered the standard of care in patients with intermediate HCC with well compensated cirrhosis[25]. Instead, it's still unclear if TACE is better than embolization alone, while TACE is significantly superior to chemio-lipiodol infusion alone[11].

TACE may be part of integrated therapeutic protocols: as neo-adjuvant pre-resection treatment, refining technique after percutaneous ablation or bridge therapy for patients awaiting for liver transplantation. There is no evidence, instead, of effectiveness as adjuvant therapy post surgical resection, in terms of prevention of recurrence.

In a prospective non-randomized trial TACE plus liver resection improved disease-free survival, but not overall survival, compared with resection alone[26].

TACE is also effectively employed as combined technique in loco-regional treatment for early and intermediate HCC. In small HCC, the association between TACE and PEI was superior to PEI alone[27] and to TACE alone[28] both in reducing local residual disease and recurrence. The rationale for an association between TACE and RFA is that occlusion of arterial vascularization increases the size of the area of thermal ablation by eliminating convection by blood flow and decreasing impedance in tumoral tissue. This combination has been employed in HCC smaller and larger than 3 cm, with different results. The combination TACE-RFA seems to get equal effectiveness when compared with RFA alone for the treatment of small HCC[29], while is significantly superior than TACE alone or RFA alone for the treatment of large HCC[30].

TACE is the preferred bridging tool offered today to patients with HCC waiting for liver transplantation, since it does not expose liver transplant recipient to additional surgical risk. The benefit of TACE on reducing drop-out rate on waiting list[20] should be compared with risks of worsening liver function. Expected waiting list time is crucial when TACE is considered as bridge to transplantation: it has been proposed that TACE is useful only when the waiting list time range between 4 and 9 months[31]. TACE was also proposed as down-staging strategy for tumors exceeding Milan criteria and a sustained response to TACE seems to be a predictive positive factor for the outcome after orthotopic liver transplantation (OLT)[32].

TACE With Drug Eluting Beads

Recently, new technique have been introduced such drug eluting beads (DEBs) in order to optimize local release of chemotherapeutic agent and reduce systemic availability. DEBs are microspheres of biocompatible PVA hydrogel that has been modified with sulfonate groups of dimension between 40 e 1200 mcm (chosen according to calibre of target tumoral vessels) that can be loaded with a chemotherapic drug, usually doxorubicin (mean dose 75 mg/m^2 of body surface, maximum 150 mg per procedure)[33]. Contraindications to doxorubicin are increased bilirubin levels >3 mg/dL, white blood cell count <3.000/mm^3 and cardiac ejection fraction <50%. DEBs are water-soluble and are mixed with iodinated contrast medium. Lipiodol is avoided and the radiological response is evaluated as for RFA or PEI (Figure 3). Once injected in hepatic arterial branches, DEBs are entrapped into tumor vessels, leading to a lumen occlusion and releasing drug in sustained manner. Additional unloaded spheres were used to complete the embolization procedure, if necessary[34].

With DEBs, the same device induces toxic and ischemic necrosis; consequently the intensity and duration of ischemia are increased while the drug delivery to the tumor is enhanced. Varela et al[34] observed that the peak concentration and the area under concentration (AUC) of doxorubicin were significantly lower with use of DEBs than with classic drug infusion. The better profile of DEB-TACE allows an increase of the drug dose selectively delivered to tumor and a reduction of drug's availability rate into systemic circulation, with reduced systemic toxicity. In uncontrolled phase II trials, the radiological complete response according to EASL criteria was 12-25% and the objective response (sum of complete and partial response) was 66-80% after 2-3 procedures, with an acceptable safety profile[34,35].

Randomized trials of comparison between DEB-TACE vs conventional TACE are ongoing in Europe and Asia. Results of PRECISION V trial showed an complete response of 27% vs. 22% and an objective response of 52% vs 44% (p=0.11), according to EASL criteria[36]. Interestingly, a significant advantage was seen only in those patients with more advanced disease [Child-Pugh B, ECOG 1 (Eastern Cooperative

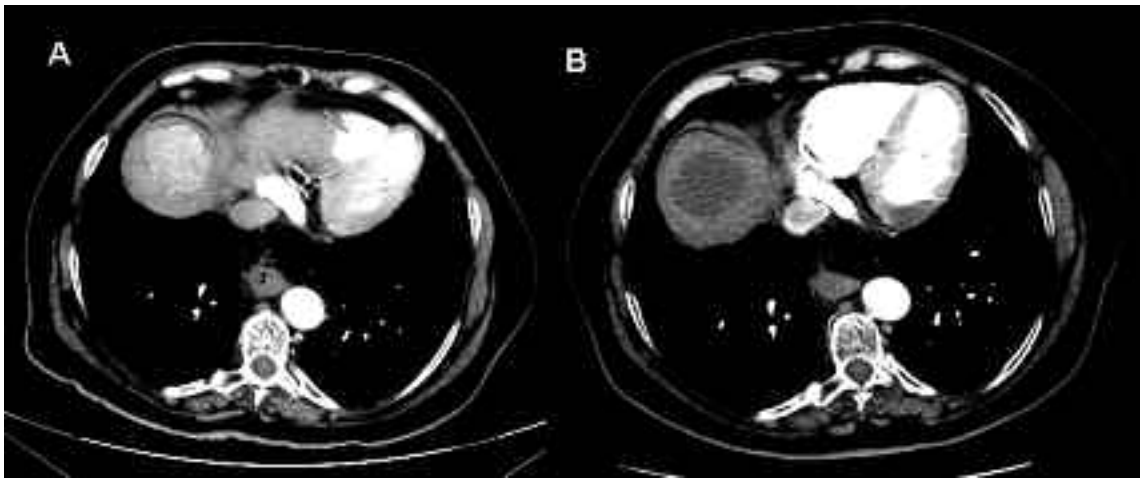

Figure 3. ***A,*** Nodule of HCC of 6 cm on segment VIII at computerized tomography before procedure. ***B,*** After TACE with DEBs (drug eluting beads), the lesion appears hypodense without viable neoplastic tissue at arterial phase of computerized tomography.

Oncology Group 1)], bilobar or recurrent disease. Promising results regarding safety are a significant reduction in serious liver toxicity and lower rate of doxorubicin-related side effects (alopecia, mucositis, and marrow suppression), but not a reduced post-chemoembolization syndrome.

While for conventional TACE the added role of the chemoterapeutic respect of alone embolization is still debated[11], a recent study of Malagari et al[37] on setting of DEB-TACE observed an higher rate of radiological complete response when compared to unloaded spheres.

In summary, TACE with DEBs is a promising tool for patients with intermediate HCC for its improved safety profile compared to conventional TACE. Furthermore, DEB-TACE opens the possibility of treatment even in patients with more severe liver disease, such as those in Child B class.

TACE and Antiangiogenic Drugs

Tumor embolization induces a central necrosis with a massive hypoxia on its border; this stimulates the cells at the edge of the lesion to produce angiogenic factors like vascular endothelial growth factor (VEGF) and beta-fibroblast growth factor (β-FGF)[38]. This neoangiogenic reaction may induce a significant growth of adiacent satellites as well as more distant tumor lesions. Recently, the multikinase inhibitor sorafenib, with both an antiangiogenic and antiproliferative effect, has been found to improve the survival of patients with advanced hepatocellular carcinoma and conserved liver function (Child A class), so it is currently the standard of care in patients with advanced HCC[39]. The combination of chemoembolization with antiangiogenic therapy has a strong rational. The antiangiogenic therapy should be introduced before the chemoembolization without interruption in order to take advantage of the antiangiogenic effect[40]. Currently, many controlled randomized trials on combination of TACE and sorafenib versus TACE alone are ongoing in Europe, Asia and United States[41].

Areas of Uncertainty

Although is a widely employed procedure, TACE doesn't appear a standardized procedure and a consensus regarding the better chemotherapeutic agent and schedule is still lacking. The recent introduction of DEBs probably will allow a better reproducibility of this technique. In case of complete response, the potential utility of multiple scheduled procedure is still unclear. Finally, it's debated if radiological response is the sole acceptable end-point for the assessment of response to therapy.

Conclusions

TACE is the main treatment indicated for the intermediate hepatocellular carcinoma, but should be tailored according to the individual patient's condition. DEB-TACE and combination TACE-sorafenib or other antiangiogenetic drugs, currently under investigation, are intriguing area of research for the next future.

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