Review

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Transarterial chemoembolization: Modalities, indication, and patient selection

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Summary

Transarterial chemoembolization (TACE) is the standard of care for patients with intermediate stage hepatocellular carcinoma (BCLC B). Further improvement of the use of TACE was the subject of intense clinical research over the past years. The introduction of DEB-TACE brought more technical standardization and reduction of TACE related toxicity. The use of dynamic radiologic response evaluation criteria (EASL, mRECIST), uncovered the prognostic significance of objective tumor response. Finally, new approaches for better patient selection for initial and subsequent TACE treatment schedules will limit the use of TACE to some extent but have the potential to improve outcome for patients at risk for TACE-induced harm.
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Introduction

Hepatocellular carcinoma (HCC), is the fifth most common cancer worldwide, and develops predominately in patients with liver cirrhosis [1]. The Barcelona Clinic Liver Cancer (BCLC) staging system [2,3] integrates tumor characteristics and performance status with liver function and links them to evidence based therapeutic options. It is the basis for the European [4] and the American [5] HCC management guidelines. Unfortunately HCC is commonly diagnosed only at intermediate (BCLC stage B) or advanced (BCLC stage C) tumor stages [6,7], where only palliative treatment options can be offered resulting in a limited overall survival (OS) of 11–20 months. Transarterial chemoembolization (TACE) is the recommended treatment modality for asymptomatic, large or multifocal HCC without macrovascular invasion or extrahepatic metastasis (intermediate HCC, BCLC stage B).

This narrative review provides a critical appraisal of the available data supporting TACE and recapitulates the recent advancements in the use of TACE in patients with intermediate stage HCC.

Key Points

- Conventional TACE is the standard of care for intermediate stage HCC
- DEB-TACE is equally effective as cTACE, but may provide a better safety profile due to less systemic absorption of chemotherapy
- Early radiologic response according to mRECIST after TACE-1 correlates with overall survival
- Patient selection for initial TACE and retreatment with TACE is key for optimal survival outcomes and may be guided by recently developed clinical scoring system

Conventional transarterial chemoembolization

Conventional transarterial chemoembolization (cTACE) using a mixture of a chemotherapeutic agent (e.g. doxorubicin or cisplatin) and lipiodol is the recommended standard of care for the treatment of intermediate stage HCC. The basis of this recommendation derived from a systematic review of randomized controlled trials [8] that tested TACE/bland arterial embolization (TAE) *vs.* best supportive care in patients with "unresectable HCC". Of note, only seven trials [7,9–14], all published between 1988 and 2002, met the inclusion criteria of this meta-analysis and only two trials reported positive results in terms of OS. Nevertheless, this systematic review found a significant improvement in 2-year survival favoring treatment (OR, 0.53; 95%CI, 0.32–0.89; $p = 0.017$). Subsequent sensitivity analysis confirmed the observed survival benefit for TACE performed with cisplatin

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or doxorubicin by analyzing 323 patients in four studies (OR, 0.42; 95%CI, 0.20–0.88) but not for TAE (OR, 0.59; 95%CI, 0.29–1.20) which failed to demonstrate significant benefit over best supportive care. While two other meta-analyses confirmed positive effects of TACE on OS (OR, 0.54; 95%CI: 0.33, 0.89; $p = 0.015$ and OR: 0.705 95%CI: 0.5, 0.99; $p = 0.0026$) compared to best supportive care, no superiority of TACE over TAE could be observed after analysis of available randomized head to head comparison trials and cohort studies, respectively [15,16] and two recent randomized controlled trials [17,18]. Given the lack of superiority of TAE over best supportive care virtually most current international guidelines [4,5,19] finally recommended TACE as the standard of care for intermediate stage HCC.

This recommendation has been recently challenged by a Cochrane review [20] which included trials published after 2002 and found no firm evidence to support or refute TACE or TAE for patients with unresectable HCC. However, this review was heavily criticized [21,22] as it included trials with inadequate patient selection and control arms, which has likely biased the results of this analysis.

Despite the fact, that the use of cTACE for the treatment of HCC is supported by 3 of 4 meta-analyses of randomized trials, some important limitations remain. One of the great problems of TACE is the huge heterogeneity of the TACE technique and schedules used in world wide clinical practice. Even the two positive randomized controlled trials [7,12] used very different technical approaches. The European study performed cTACE with the chemotherapeutic agent doxorubicin at dosages adjusted to bilirubin levels (<25.6 μmol/L: 75 mg/m^2; 25.6–51.3 μmol/L: 50 mg/m^2; 51.3–85.5 μmol/L: 25 mg/m^2) with a fixed schedule at baseline, 2 months and 6 months, while the Asian study performed cTACE with cisplatin (up to 30 mg/session), repeated every 2–3 month until disease progression, serious adverse events or hepatic decompensation. Further differences exist with regard to the selectivity of TACE (lobar *vs.* segmental *vs.* subsegmental embolization), which has been reported to be an important determinant of procedure tolerance and efficacy [23]. For all these factors no universal consensus exists and the resulting heterogeneity hinders the reliable comparison of results of different studies and complicates the conduction of high quality multicenter TACE trials.

TACE with drug eluting beads

The introduction of TACE with drug eluting beads (DEB-TACE) was primarily developed to enhance the delivery of the chemotherapeutic agent while minimizing systemic toxicity and to provide a standardized embolizing effect. DEBs are embolic microspheres loaded with a chemotherapeutic agent (mostly doxorubicin) with the ability of slow drug release, which should ensure high local and low systemic drug concentrations. Indeed, systemic levels of doxorubicin were significantly lower in patients receiving DEB-TACE compared to patients receiving cTACE with lipiodol [24]. The value of doxorubicin in this setting was investigated in a randomized, tumor size adjusted trial [17] testing DEB-TACE *vs.* bland embolization with non-loaded particles of the same diameter (BeadBlock-TAE). DEB-TACE was associated with better local response (CR: 26.8 *vs.* 14%), fewer recurrences (78.3% *vs.* 45.7%) at 12 months, and a longer TTP (42.4 ± 9.5 and 36.2 ± 9.0 weeks), than TAE with BeadBlock alone thus favoring the role of doxorubicin in the setting of TACE with microparticles, although no survival benefit was observed in this study [17]. Positive effects of doxorubicin loaded microparticles were further reported by another trial [25] showing higher rates of tumor necrosis with DEB-TACE compared to embolization with unloaded microparticles (Embosphere particles) of the same size, which was pathologically confirmed in explanted livers of HCC patients undergoing liver transplantation.

Efficacy and safety was evaluated by the randomized European Precision V phase-2 trial [26] testing DEB-TACE *vs.* cTACE in 212 patients with predominately intermediate stage HCC. Neither the primary efficacy endpoint (response at 6 months, $p = 0.11$) nor the primary safety endpoint (incidence of SAE within 30 days of the procedure, $p = 0.86$) were met in this study. However, a post hoc comparison showed a significant reduction in drug related systemic and liver toxicity in DEB-TACE group compared to the cTACE group. This better tolerability was probably responsible for better response rates of DEB-TACE at 6 months in a predefined post hoc subgroup analysis of patients with more advanced liver dysfunction (Child-Pugh B), higher tumor load (bilobular/recurrent disease) or less preserved performance status (ECOG 1). Whether this group of advanced patients should receive TACE at all is subject of repeated discussion in the scientific community, but generally discouraged by most international HCC treatment guidelines.

A potential impact of DEB-TACE on OS was further evaluated in a prospective 1:1 randomized controlled multicenter, head to head comparison trial of TACE with doxorubicin eluting beads (DEB-TACE) *vs.* cTACE using a mixture of lipiodol and epirubicin followed by occlusion of the feeding artery with gelatin sponge particles in patients with HCC [27]. This trial included 177 patients with a follow-up of at least 2 years. The study was terminated prematurely, because the second planned interim analysis revealed no significant differences between both techniques in terms of survival, radiologic response or adverse events with the exception of a significantly lower incidence of the post-embolization syndrome in the DEB-TACE group, which did not result in shorter hospital stays. Due to the equality of both TACE techniques and the higher costs of DEB-TACE the authors concluded that the routine use of DEB-TACE is debatable. However it should be noted that the maximum allowed dose of doxorubicin/epirubicin in this study was restricted to only 75 mg for both techniques. Additionally, the study predominantly included patients with low tumor load, as 46% of the population had early HCC (BCLC A) with only 11% of patients exceeding 3 nodules and only 20% with bilobular involvement and a median tumor size of only 2.6 cm. Hence, this study a priori precluded one of the major advantages of DEB-TACE namely to apply higher doxorubicin doses without increasing systemic toxicity in patients with higher tumor load as reported in the Precision V study. Therefore this study shows, that DEB-TACE is not superior to cTACE in patients with predominantly well preserved liver function and relatively low tumor load. This is important, as cTACE can obviously still be safely and effectively applied in this patient population at lower costs. Although a survival benefit still remains to be proven, DEB-TACE should be the technique of choice in the setting of clinical trials, due to its higher degree of technical standardization and the lower systemic absorption of doxorubicin with less doxorubicin toxicity. The latter facilitates potential combination trials with systemic therapies as it may reduce the risk of potential drug-drug interactions.

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