

Review

Transarterial chemoembolization using drug eluting beads for the treatment of hepatocellular carcinoma: Now and future

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Transarterial chemoembolization (TACE) using doxorubicin-eluting beads (DEBs) have been introduced as a novel device which ensures more sustained and tumor-selective drug delivery and permanent embolization compared to conventional TACE with lipiodol. Studies highlighting the use of TACE with DEBs for the treatment of hepatocellular carcinoma (HCC) have shown similar or better results compared to conventional TACE with lipiodol. TACE with DEBs is increasingly being performed interchangeably with conventional TACE. This review assessed the characteristics, clinical outcomes and future direction of TACE with DEBs compared to conventional TACE. (**Clin Mol Hepatol 2015;21:344-348**)

Keywords: Drug eluting beads; Hepatocellular carcinoma; Transarterial chemoembolization

INTRODUCTION

According to Barcelona Clinic Liver Cancer (BCLC) tumor staging and management,¹ transarterial chemoembolization (TACE) is recommended as the first-line therapy for unresectable intermediate-stage HCC (stage B). This evidence-based position has been established by the results of three studies showing that TACE significantly improves patient survival as compared with the best supportive care.²⁻⁴ TACE is one of the commonly used treatments for patients with HCC who are not suitable for curative therapy.^{5,6} And it is also considered the standard of care for patients with HCC who are not suitable for surgical treatment but limited to the liver because it can preserve liver function.^{2,7} Typically, conventional TACE involves injection of chemotherapeutic agents mixed with lipiodol followed by embolic particles into tumor feeding ves-

sel.⁸ An important limitation of conventional TACE is the inconsistency in the technique and the treatment schedules. To compensate this limitation, Transarterial chemoembolization (TACE) using doxorubicin-eluting beads (DEBs) was introduced as a novel device capable of ensuring more sustained and tumor-selective drug delivery and permanent embolization.⁹ These microspheres allow local delivery of high concentrations of chemotherapeutic agents to the tumor without elevating systemic concentrations. Therefore, adverse events which typically occur with conventional TACE can be reduced with the use of DEBs.⁹⁻¹¹ TACE with DEBs is increasingly being performed interchangeably with conventional TACE in many institutions throughout the world, it is imperative to review current status of TACE with DEBs compared to conventional TACE and anticipate the future impact as a management of HCC. This review critically assessed characteristics of each modal-

Abbreviations:

BCLC, Barcelona Clinic Liver Cancer; DEBs, doxorubicin-eluting beads; HCC, hepatocellular carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, Transarterial chemoembolization

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Characteristics of conventional TACE and TACE with DEBs

The procedure of TACE has technically and scientifically evolved since its introduction almost 30 years ago. Generally, conventional TACE involves intra-arterial infusion of a lipiodol and a chemotherapeutic agent such as doxorubicin, followed by an injection of embolic material such as gelatin sponge particles or other agents.¹² Lipiodol is a key ingredient of TACE because it has unique properties such as drug-carrying, tumor-seeking, and embolizing effects.¹³ Although the mechanism is not clearly understood, lipiodol is absorbed by a pump in the tumor cell wall and then transferred to inside of the intracellular space. After then, this pump is disabled by hypoxia within the tumor, thus lipiodol retained within the cell. Typically it could be retained by HCC for months, even up to a year, while it is washed out from normal or cirrhotic liver within 4 weeks. The embolizing agent not only helps lipiodol to be retained selectively in HCC but also reduces drug washout from the tumor and induces ischemic necrosis. An important limitation of conventional TACE is that the technique and treatment schedules can be heterogeneous¹⁴ and this makes the results reported in the literature very inconsistent. Moreover, some HCC does not exhibit lipiodol retention which may bring lower effectiveness of the treatment.^{15,16}

DEBs are microsphere which can carry calibrated doxorubicin and they can release cytotoxic drugs (e.g., epirubicin or doxorubicin) in a controlled and sustained manner.^{17,18} The microspheres can actively sequester oppositely charged drugs through an ion-exchange mechanism. Initial in vitro studies, doxorubicin can be loaded maximally by the DEBs to approximately 45 mg/ml hydrated beads, irrespective of the size of beads.¹⁹ Considering both practical therapeutic dose and optimum handling characteristics, a loading of 37.5 mg doxorubicin/ml beads is currently recommended. According to bead size, animal pharmacokinetic study showed that higher doxorubicin plasma levels were detected in the smaller-size (100–300 μm) beads group when two sizes of doxorubicin-eluting beads (DEB; 100–300 vs. 700–900 μm) loaded with same amount of doxorubicin was compared.²⁰ This result is due to increased surface area of the smaller beads, inducing a greater burst release of doxorubicin. Per treatment, the maximum recommended dose is 150 mg of doxorubicin. The primary mode of action of DEBs is to embolize the cancer vasculature, and the

second mode is to deliver doxorubicin locally to the tumor artery. After the microspheres are delivered through catheters or micro-catheters directly into the hepatic artery, doxorubicin elutes locally and is concentrated in the tumor with minimum levels in normal liver tissue. In this way, tumor concentrations are maximized and systemic concentrations are kept to a minimum limiting damage to normal liver tissue.

Clinical outcome of TACE with DEBs

Initial phase I/II TACE with DEBs performed in China tested the dose limiting toxicity and safety as well as tumor response and pharmacokinetics of doxorubicin.¹⁷ Phase I trial was a dose-escalating study from 25 mg to 150 mg doxorubicin in cohorts of 3 patients (total of 15 patients). A 150 mg doxorubicin dose was used for the phase II study. No dose-limiting toxicity was observed for up to 150 mg doxorubicin and treatment relevant adverse events were reported in 11.4%. Mean low peak plasma doxorubicin concentration was 49.4 ± 23.7 ng/ml and there was no treatment-related death. After two courses of TACE, the partial and complete response rates were 50 and 0%, respectively, according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria and 63.3 and 6.7% respectively, by modified RECIST criteria at 1 month after the second TACE. Afterward, several small sized phase II study results about TACE with DC-beads in unresectable HCC mainly with intermediate BCLC stage were reported.^{9,21} According to these studies, overall objective response was about 59.6–81.8% and 1- and 2-year survival was 65–92.5% and 55–88.9%, respectively. The rate of severe procedure-related complications was about 3.2%.

Previous comparisons between TACE with DEBs and conventional TACE with lipiodol in intermediated stage HCC demonstrated slightly conflicting results. A recent meta-analysis based on seven studies (n=693) demonstrated that the two procedures showed equivalent results, strongly suggested the lack of difference in tumor response between two procedures.²² Meanwhile, meta-analysis presented in 2014 by Han et al,²³ comparison of current conventional TACE to TACE with DEBs in the treatment of liver carcinoma showed different results. This systematic review included three randomized controlled trials and two case-control studies. In the largest randomized controlled trial by Lammer,¹⁰ overall population did not show significant difference in terms of disease control, but the subgroup analyses showed that the overall survival and disease control were statistically higher ($P=0.038$ and $P=0.026$, respectively) in TACE with DEBs group than the

conventional TACE group in patients (67%) with more advanced disease (Child-Pugh B, ECOG 1, bilobar or recurrent disease). And the incidence of severe adverse events within 30 days of a procedure was consistently lower, and elevation of AST as well as ALT was significantly less in the TACE with DEBs group. In the largest retrospective study by Song, treatment response was significantly better in the TACE with DEBs group than that of compared to the conventional TACE group ($P=0.001$) and this difference in the treatment response was shown in intermediate state from subgroup analysis according to BCLC stage ($P=0.001$).²⁴ From these result, TACE with DEBs have shown better or at least similar result in the studies between TACE with DEBs and conventional TACE with lipiodol.^{9,17,25} Furthermore, we might conclude that TACE with DEBs could improve the clinical effectiveness in patients with more advanced HCC and be safe in high-risk patients.

For advanced HCC such as BCLC stage C, the use of TACE with DEBs in advanced-stage HCC has not been well studied. According to the BCLC algorithm, patients with advanced stage HCC (BCLC-C) are recommended for systemic treatment or palliative therapy. In a small retrospective trial with TACE with DEBs for patients with advanced HCC ($n=80$), the median progression free survival and overall survival were 5.1 months [95 % confidence interval (CI): 4.1–7.7] and 13.3 months (95 % CI: 10.1–18.6) respectively.²⁶ The other retrospective study, with treatment of TACE with DEBs, the overall median survival was 13.5 months (range, 8.2–18.7 months) and severe adverse events were minimal (1%). In subgroup analysis, survival of patients with Child-Pugh A disease was 17.8 months.²⁷ Based on the results of the these studies, compared with median survivals of 10.7 months and 6.5 months for the sorafenib groups in the SHARP and Asia-Pacific trials,^{28,29} it seems that patients with Child-Pugh class A disease with advanced disease may fare better with aggressive loco-regional treatment in the form of TACE with DEBs than systemic monotherapy with sorafenib. Recently, Printer et al.³⁰ reported higher survival in patients with advanced (BCLC C) stage disease treated with conventional TACE (9.2 months) than patients treated with sorafenib (7.4 months; $P=0.377$). These results may indicate that conventional TACE as well as TACE with DEBs is also as effective as sorafenib in the treatment of advanced HCC. TACE is still commonly used in advanced HCC as palliative indication even after sorafenib is the new standard in this state, and comparable to sorafenib in some selected patients, although the mechanism of each treatment is different.

Currently, there are several trials to analyze the potential benefit by addition of sorafenib to conventional TACE or TACE with DEBs

in the patients with HCC at a more advanced stage. The rationale for this combination therapy is based on the fact that TACE induces ischemia and can stimulate tumor angiogenesis and the use of sorafenib could reduce angiogenesis. Recently, Pawlik et al. reported trial of combination therapy of TACE with DEBs and sorafenib in a group of 35 patients (64 %, BCLC stage C). In their study, the incidence of grade 3-4 toxicities are reported in 17 % and objective response rate was 58 % based on EASL criteria.³¹ The potential of this combination approach has not yet been fully verified in clinical trials, and many unanswered questions remain requesting further study.

CONCLUSIONS

To compensate limitation of conventional TACE, TACE with DEBs was introduced as a novel device capable of ensuring more sustained and tumor-selective drug delivery and permanent embolization allowing local delivery of high concentrations of chemotherapeutic agents to the tumor without elevating systemic concentrations. TACE with DEBs showed better or at least similar results compared with conventional TACE and showed increased clinical effectiveness in patients with more advanced HCC with tolerable safety. In even more advanced HCC (BCLC stage C), it showed similar results compared with sorafenib and these results support the application of TACE with DEBs in the treatment of HCC can be expandable to more advanced HCC in the future.

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Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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