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Review Article

The update on transcatheter arterial chemoembolization using drug-eluting beads: Optimization for best response

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ABSTRACT

Transcatheter arterial chemoembolization using drug-eluting beads (DEB-TACE) was developed to overcome the shortcomings of conventional TACE (c-TACE) and was expected the better clinical results. Based on the published studies so far, a clear pharmacokinetic superiority or survival benefit of DEB-TACE over c-TACE has not been established yet and clinical effect of DEB-TACE is controversy. However, previous published studies on DEB-TACE have limitations in optimizing the DEB-TACE procedure due to the lack of detailed subgroup analysis and not including the clinical data of DEB-TACE using recently and newly developed small DEB particles. Aim of this review article is to systematically analyze the published data, especially subgroup analysis, on the optimization for best response in terms of tumor response and safety profile.

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Keywords: Embolization; Hepatocellular carcinoma; Microspheres

Introduction

Transcatheter arterial chemoembolization (TACE) is commonly considered as the first line treatment for patients with intermediate unresectable hepatocellular carcinoma (HCC) or early stage HCC carrying contraindications to curative treatment.^{1,2} However, techniques of TACE are heterogenous and not well standardized, because reproducible and stable lipiodol/drug emulsions with standard droplet size are difficult to obtain and there is a lack of consensus on which embolic agent to use.^{3,4} Drug-eluting beads (DEBs) were developed to overcome the shortcomings of conventional TACE (c-TACE) and provide an opportunity to implement a more standardized approach to HCC treatment. DEB slowly releases the chemotherapeutic agent loaded at the time of injection, increasing the intensity and duration of ischemia while enhancing drug delivery to the tumor.^{5,6}

A review of prospective studies, or meta-analysis reports published so far raises controversy about the clinical effects of DEB compared to c-TACE. A meta-analysis of seven studies (693 patients) comparing the efficacy of DEB-TACE and c-TACE revealed that tumor response did not differ significantly between DEB-TACE and c-TACE.⁷ More recent meta-analyses have included multiple randomized controlled trials, prospective studies, and

retrospective studies have shown conflicting results. In a meta-analysis of seven clinical studies (700 patients), Huang et al⁸ showed that tumor response was significantly better, and that the 1- and 2-year survival rates were significantly higher for DEB-TACE than for c-TACE. Xie et al⁹ also performed a meta-analysis of four randomized controlled trials, one uncontrolled prospective study, and one prospective case control study (652 patients). They reported similar overall survival rates between c-TACE and DEB-TACE, but that DEB-TACE was associated with a significantly higher objective response rate (ORR) and a slightly lower incidence of complications.⁹ Chen et al¹⁰ performed a large meta-analysis of 1,832 patients and found that DEB-TACE had higher 1-, 2-, and 3-year overall survival rates, and higher 1- and 2-year relapse-free survival rates. Finally, a meta-analysis involving 1,449 patients found no significant differences in the 1-, 2-, and 3-year overall survival and complications rates between c-TACE and DEB-TACE.¹¹

Despite the promising results of earlier studies, a clear superiority of DEB-TACE over c-TACE has not been established yet. Only, it has been proven from previous studies that the frequency of post-embolization pain was less and the hospitalization period was shorter by about 1 day after DEB-TACE compared to c-TACE.¹² However, previous large series of studies on DEB-TACE

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have limitations in optimizing the DEB-TACE procedure due to the lack of detailed subgroup analysis according to tumor characterization, location or the size of the DEB particles used. Also, clinical data on recently and newly developed small DEB particles are not included. The current study aimed to systemically review the literature to find out tumor characteristics and DEB-TACE techniques for the best clinical outcome.

Doxorubicin Loading and Planned Dose

Each vial bead microsphere can be loaded with 50 to 75 mg doxorubicin. The maximum dose for a single treatment has been set at 150 mg, based on a study showing that this was the maximum dose for systemic infusion of doxorubicin.¹³ The better profile of DEB-TACE takes the opportunity to increase the amount of drug selectively exposed to tumor cells and simultaneously reduce systemic toxicity rather than c-TACE.¹³ However, there are few published reports analyzing the relationship between chemotherapeutic agents and tumor responses in DEB-TACE, and most of these are papers in the early stages of DEB development. Lencioni et al¹⁴ recommended in their study using DC beads (Boston Scientific, Marlborough, MA, USA) that the planned dose of doxorubicin should depend on the extent of the liver tumor burden. For limited disease within the Milan criteria, the treatment strategy needs to include escalation of the doxorubicin dose up to 75 mg per single TACE. For advanced disease exceeding the Milan criteria, the doxorubicin dose could be increased to a maximum of 150 mg.^{14,15} Univariate analysis of Urbano et al¹⁶ found a significant association between complications and the administered dose of doxorubicin. 52% of minor complications and 71% of major complications occurred in the group of patients who received the maximal dose of doxorubicin. Complications were not associated with Child-Pugh score, Barcelona Clinic Liver Cancer (BCLC) stage, selective or super-selective catheterization, co-morbidities, or treatment response.¹⁶ Galastri et al¹⁷ calculated the dose ratio in all HCCs of the chemoembolic agent/cm of viable HCC until vascular stasis is reached and concluded that the amount of chemoembolic agent increases the chance of an ORR in HCC and increases the percentage of tumor necrosis.

Overall, optimizing the dose of chemotherapeutic agents appears to be a related factor and needs to be specifically evaluated. Individual patient- and tumor-related factors play an important role in the decision of the planned dose of chemotherapeutic agent.

Drug-eluting Beads Size

The choice of microsphere size depends on many factors, including tumor size, feeding artery diameter, personal preference and experience and the presence or absence of an arteriovenous shunt that increases the risk of pulmonary complications.¹⁸ Large-caliber microspheres (> 300 μ m) that developed in the early stage showed problems such as ischemia or premature embolization of the feeding artery before the chemotherapeutic agent can be completely effective.¹⁹ Premature arterial embolism can prevent with subsequent tumor directed treatment by damaging blood vessels and promoting hypoxia-induced angiogenesis.^{19–21} In an animal model of liver cancer, infusion of 100–300- μ m microspheres resulted in the delivery of microspheres into the tumor or near its margins, and justified their use for precise drug delivery or embolization.²² In the clinical study for the DEB size, TACE with 100–300 μ m DEB is associated with better initial treatment response and fewer major complications compared with 300–500

μ m.²³ Another study demonstrated that DEB-TACE with 100–300 μ m beads was more effective in patients with BCLC stage B and small tumor (< 3 cm), and large feeding artery (> 0.9 mm). The use of 100–300 μ m sized particles is linked with significantly higher survival rate and lower complications than the employ of 300–500 and 500–700 μ m sized DEBs.¹

Recently, chemoembolization with small calibrated microspheres less than 100 μ m was introduced.^{4,5} An animal study found that beads ranging in diameter from 70 μ m to 150 μ m are associated with greater tumor coverage, more distal penetration, and higher doxorubicin concentrations in the tumor, without increasing systemic exposure, than is c-TACE.²⁴ Although smaller DEB may increase local tumor response by overcoming disadvantage of larger DEB, but it may also increase the risk of ischemic injury owing to closely related adverse events, such as post-embolization syndrome and biliary complication. A large scale of retrospective study involving 421 patients with HCC who underwent DEB-TACE using 70–150 μ m DC Bead® (M1; BTG, London, UK) showed that the overall ORRs were 94.5% and 99.5% at 3 and 6 months, respectively.⁵ These rates were higher than those in a previous multicenter randomized controlled trial²⁵ using DEB of 300–500 μ m and 500–700 μ m in diameter, where the ORR was 52% at 6 months. An Italian prospective series that conducted on 45 HCC early/intermediate patients showed favorable results with DEBs 70–150 μ m (M1; BTG).⁶ In this study, complete response (CR) was achieved in one third of them (33.3%) whereas other 20 (44.4%) reached partial response, accounting for a 77.7% ORR. In addition, the histological analysis of 28 nodules in 13 explanted livers showed 100% necrosis (complete pathologic necrosis) in 7 cases and 90% to 99% necrosis in 3 cases.⁶ Another Greek study enrolling 45 patients treated with HepaSphere microspheres 30–60 μ m/L found a CR rate of 22.2% for the target lesions and ORR of 68.9% without serious complications.²⁶

Tumor Size

The importance of tumor size on the therapeutic effect of DEB-TACE is controversial. It is necessary to analyze the clinical data by dividing by small (< 2 cm), medium (2–5 cm) and large (> 5 cm) sized HCCs. Vesselle et al²⁷ indicated that small to medium nodule size was strongly associated to CR, with 39% of CR in < 5 cm nodules versus 18% in $\geq$ 5 cm nodules. A Greek study enrolling 45 patients treated with HepaSphere microspheres demonstrated that CR rates at 1 and 6 months were lowest in tumors larger than 5 cm. The ORR at 1 month was higher in tumors 2 to 5 cm in size than in tumors < 2 cm. In the Korean registry,²⁸ the subgroup analysis for the tumor size showed that the ORR for tumors < 2 cm was lower than that of tumors with a size of 2 to 5 cm. In a single center retrospective comparison study between c-TACE and DEB-TACE, the local tumor response of DEB-TACE was lower than that of c-TACE in HCC less than 3 cm in diameter.²²

Considering the results of previous studies, DEB-TACE using 100 to 300 μ m microspheres was followed by significantly worse tumor response for smaller HCCs (1.0–2.0 cm) than for medium sized HCCs (2.1–5.0 cm).^{2,26,29} This is presumably because of the size of the feeding vessels. In a larger tumor, the feeding artery is usually well developed and large in diameter, allowing a microsphere to pass through easily to reach the capillaries within the tumor.³⁰ Irie et al² reported that tumors < 2 cm had a feeding artery of 0.1 to 0.4 mm in diameter at the tumor entry site, whereas tumors $\geq$ 2 cm had a feeding artery > 0.4 mm in diameter. Inherent disadvantage of particulate embolic material which cannot pass through vessels smaller than the DEB used

and cannot manage portal venous supply to the tumor can cause the impaired tumor response of DEB-TACE for small HCCs. In a catheter-assisted computed tomography angiography study, the main tumor feeding artery was frequently smaller than 0.2 mm in diameter when the tumor was smaller than 3 cm in size.² Thus, 100 to 300 μ m DEB may not penetrate into intratumoral vessels in sufficient quantities despite performing selective TACE in small HCCs. A previous study reported that the median diameter of vessels occluded by 100 to 300 μ m DEB was 208 μ m, and just 42% of the occluded vessels were located inside the tumor when DEB-TACE was performed for 3.9 cm tumors with 100 to 300 μ m DEBs.³ From these view points, 100 to 300 μ m microspheres can become stuck at the entry site of the feeding artery and fail to accumulate inside the lesion, resulting in poor therapeutic effect.

Tumor Location

There are a few papers analyzing the relationship between tumor location and response. Aal et al²⁹ described that peripherally located tumors had significantly higher disease control rate compared with centrally located tumors (95.5% vs 80.9%, respectively). Location in the liver had an impact on tumor response with significantly less CR when the nodules were in the median liver; 13% of CR vs, respectively, 48% and 37% in the left and right liver. Another study showed that centrally located tumor (segment 4 or 1) was a risk factor for a low therapeutic effect.³⁰ This result is probably due to the presence of collateral vessels or multiple feeders to the central located HCC.³¹ It is usually difficult to insert a catheter into multiple fine feeding arteries in a central location, resulting of incomplete embolization. Even if the feeding artery is embolized adequately using beads, a fine collateral network originating from the communicating arcade can immediately develop in the tumor and may disturb tumor necrosis in a central located tumor.³⁰

Conclusion

The advantages of DEB-TACE are better synergistic effects with embolization and cytotoxic effects and minimized system toxicity compared with c-TACE. However, DEB-TACE still have not standardized technique and there is a lack of consensus on which size or amount of embolic agent to use.

Most of published report evaluated the relationship between the dose of doxorubicin and the complication rate and there was few reports evaluating the association with the tumor response. In clinically, the dose of injected chemotherapeutic agent was determined to the amount of DEB particles required to achieve near complete stasis and the total amount of DEB particles was determined according to the tumor burden, rather than optimizing and calculating the dose of chemotherapeutic agents for a good tumor response. If near complete stasis is reached before the prepared DEB is injected, the amount of chemotherapeutic agent used is determined at this point. In a contrary, if near complete stasis is not reached until the end of the prepared DEB particle were administered, the maximal dose of chemotherapeutic agent can be injected and the complementary embolization with other embolic agent can be done until reaching near complete stasis. In addition, previous study showed that complications after DEB-TACE is not determined by the amount of doxorubicin used but is related to the position of the micro-catheter and the endpoint of the embolization (non-selective embolization, wedged embolization or forced stasis).¹⁸

Small sized DEB showed good tumor response and fewer seri-

ous adverse events compared to large sized DEB. Nevertheless, in absence of RCTs comparing these novel microspheres, no definitive indication can be released on which small sized DEB should be used in the common clinical practice, and the decision still relies on local expertise or availability of device. In the future, further prospective large-scale studies are needed to prove the effectiveness of small-sized DEBs.

Most of published large series of studies have performed using 100 to 300 μ m sized DEB particles. From these studies, the response rate was good when the tumor size was 2 to 5 cm. In the large tumor (≥ 5 cm), DEB-TACE procedures might be completed with other particle adjunction to reach complete stasis when the upper 150 mg doxorubicin limit is achieved. In the small tumor (< 2 cm), premature embolization becomes a problem due to the small size of the feeding vessel. However, recently developed smaller DEB particles have been shown to be able to penetrate into small tumors with smaller feeding arteries. In the future, it is expected that DEB TACE will show a good effect in HCC of 2 cm or less through many studies using smaller DEB particles.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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