

Classic TACE Versus Drug-Eluting Beads

Lipiodol or drug-eluting beads in the treatment of hepatocellular carcinoma?
An old question revisited.

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The burden of hepatocellular carcinoma (HCC) in the United States is steeply rising.^{1,2} Unfortunately, only a minority of these patients can undergo radical treatment at the time of diagnosis.³ Transarterial chemoembolization (TACE) was introduced more than 3 decades ago for the treatment of unresectable HCC. However, there is no consensus on the use of chemical agents, embolic materials, or technical details.

There are two frequently used methods for transarterial treatment, namely classic lipiodol TACE and drug-eluting beads. Classic TACE (referred to as “cTACE” in this article) includes the use of doxorubicin alone or together with cisplatin and mitomycin C mixed with lipiodol, followed by embolization using a gelatin sponge. Newer types of embolic agents (drug-eluting beads) have been introduced to the market and have the potential benefit of doxorubicin delivery into the target tissues over a prolonged period of time. Doxorubicin-loaded beads/spheres have been designed to deliver a high dose of drug over a longer period of time into the tumor but with much less systemic exposure to the drug.⁴

The PRECISION V study, a prospective randomized multicenter trial conducted at 19 centers in Europe, showed that drug-eluting beads and cTACE essentially have identical tumor responses. With regard to the safety of these methods, systemic side effects of doxorubicin, such as alopecia and marrow suppression, were lower in the drug-eluting bead group, as was shown in

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the post hoc analysis of the PRECISION V study. Either clinical marrow suppression or mild derangement of laboratory findings indicate that the systemic effects of drug-eluting beads are lower than with cTACE. Additionally, one of the stated advantages of drug-eluting beads over cTACE was less pain.⁵ Notably, the efficacy was significantly higher in patients with Child-Pugh B and bilobar or recurrent disease treated with drug-eluting beads (higher objective response defined as complete or partial response based on European Association for the Study of Liver Disease [EASL] criteria; 52% with drug-eluting beads vs 35% with cTACE; $P = .03$). However, the data from direct comparisons still do not suggest a survival benefit for drug-eluting beads over cTACE.⁶

CRITICAL COMPARISONS OF cTACE AND DRUG-ELUTING BEADS

The theoretical benefits and ease of use of drug-eluting beads were important factors influencing a recent surge in their utilization for HCC patients. Additionally,

the shortages in doxorubicin powders and cisplatin in the United States have led to a significant shift from cTACE to drug-eluting beads in many centers. This shift has to be reviewed carefully, as it has not been examined in a prospective controlled clinical trial that classifies patients into clinical stages of disease. Moreover, there is no cost-effectiveness analysis that demonstrates the cost benefit of this approach. For several reasons, drug-eluting beads cannot reach as distally as lipiodol, a characteristic that might be associated with lower recurrence rates with cTACE, because it has the ability to travel more distally and block the small feeders to the tumor. Importantly, hydrogel particles in LC beads (Biocompatibles, Surrey, UK) turn into hydrophobic particles once loaded with doxorubicin. This, in turn, will lead to clogging and significant bead loss inside the catheters⁷ and a more proximal level of embolization compared to unloaded beads.

In addition, incomplete doxorubicin release can also occur with mediums with low ionic strength. This phenomenon, the so-called doxorubicin self-association, happens in solutions such as 0.9% NaCl. It occurs particularly at higher loading levels and is thought to result from drug molecules being held in close proximity to each other by hydrophobic interactions.⁸ This consequently will lead to limited drug release from beads in these conditions. Moreover, the biliary damage associated with drug-eluting beads can have a major impact on the quality of life of patients and increases the length of hospital stay.⁹ Guiu et al showed in a multivariate analysis that the risk of biloma/liver infarct is nine-fold more common with drug-eluting beads compared to cTACE.⁹ The biliary damage and stricturing can result in portal vein branch narrowing, portal venous thrombosis, and eventual tissue ischemia and liver infarct.¹⁰

Meanwhile, lipiodol has been implemented as an embolic agent, as well as a carrier, since the early 1980s for the adjunctive treatment of unresectable HCCs. The advantages described in those early days that made this agent unique still hold true—the characteristics of an oily material that travels distally and remains selectively in the tumor after its administration for a long time—and deposition of lipiodol in tumor can be verified by follow-up computed tomographic imaging.^{11,12} The fact that lipiodol is radiopaque also allows the operator to monitor the flow of embolic material and look for the homogeneous lipiodol uptake in tumoral blush,¹³ a notion of utmost importance in cases of occult HCC.

Also, the viscosity of lipiodol allows it to travel along the small vessels beyond the arterial levels to the portal

vein branches.^{14,15} In fact, visualization of the portal vein during the lipiodol TACE procedure is associated with a significant reduction of local recurrence of the tumor.¹⁶ The angiographic subsegmentectomy emphasized by Iwamoto et al¹⁷ consists of the infusion of lipiodol via the draining vessels of the tumoral lesion after cTACE and is associated with complete necrosis and decreased recurrence. These two factors improve efficacy and lead to a more distal level of occlusion, more necrotic tissue, and hence more fever, nausea, and abdominal pain.

The review of our own series with LC beads and cTACE confirms identical tumor response rates according to EASL classifications. We have attempted to further analyze the patients with failure/recurrence after the use of LC beads to identify which subgroup of patients may benefit more from cTACE or drug-eluting beads. Patients with extensive disease or high-risk patients seem to tolerate the procedure better when treated with drug-eluting beads. The need for re-embolization, however, was higher in the drug-eluting bead group. We have found that patients with lesions situated between two segments, lesions with a high probability of more than one arterial feeder (eg, segment-4 lesions), or lesions with small-size feeder vessels are more amenable to cTACE therapy.

The biliary damage associated with drug-eluting beads should be weighed against their use in selected patients with longer life expectancies. Biliary damage resulting from the procedure can endanger liver function, especially in the long-term. Therefore, we do not recommend the use of drug-eluting beads in patients with liver metastases due to neuroendocrine tumors. On the contrary, because cTACE embolizes more distally, it should be attempted in patients who have a higher liver function reserve and lower stages in the Child-Pugh system. On the same grounds, the use of lobar embolization with drug-eluting beads is preferred. Similarly, cTACE may be ideal in conditions in which superselective embolization of the feeding branches of the arteries and small feeders is possible.

CONCLUSION

Drug-eluting beads are considered by many to be a significant advancement in technology, and with further improvement, they may indeed represent the future of tumor therapy. However, at this point, there is a role for both cTACE as well as drug-eluting beads in the treatment of unresectable HCC. We believe that lipiodol is still an important embolic/career agent that can be used in the treatment of carefully selected patients. cTACE remains the best adjunctive therapy, especially in lesions with very small feeders that are

anatomically located in adjacent segments and when there is an angiographically occult HCC. ■

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