Drug-eluting Beads in the Treatment of Hepatocellular Carcinoma and Colorectal Cancer Metastases to the Liver

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Abstract

Drug-eluting beads (DEBs) may become a standard of care in the treatment of unresectable liver cancers. DEBs have a significant advantage by offering simultaneous embolisation, and sustained release of antineoplastic agents in a controlled manner, resulting in a localisation of the drug in the targeted tumour, while minimising its systemic exposure. This article reviews current treatment options for liver cancer and concentrates on the benefits of DEBs for patients with unresectable liver cancer. Preclinical and clinical studies suggest smaller microspheres and extended release characteristics as key properties that will enable DEB device technologies to become a standard of care for unresectable liver cancer. A new, tightly size-calibrated DEB ≤100 µm, Embozene TANDEM™, was designed to meet these requirements.

Keywords

Drug-eluting bead, microspheres, transarterial chemoembolisation, hepatocellular carcinoma, colorectal cancer metastases

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Hepatocellular carcinoma (HCC) is the most common primary liver malignancy (70–85 %)[1] with an associated mortality of >600,000 per year.[2,3] Underlying cirrhosis is the major risk factor,[2] with an estimated annual risk of developing HCC of 4–8 %.[2,4] Hepatitis B is responsible for 53–80 % of all cases.[2] Hepatitis C is the major cause of HCC in Japan, the US, Latin America and Europe.[3] Untreated HCC patients have a median survival of 3–8 months.[5]

Nearly one million patients are diagnosed with colorectal cancer (CRC) worldwide every year.[6] Thirty to fifty percent of them develop hepatic metastases (hmCRC);[6–8] hmCRC is responsible for two-thirds of CRC deaths.[8] One- and five-year survival rates for untreated hmCRC patients are <30 % and <5 %, respectively.[2] Untreated hmCRC has a median survival of 5–10 months.[2]

Treatment Options

The Barcelona Clinic Liver Cancer (BCLC) staging system is commonly used for HCC.[9] It takes into account underlying liver disease, tumour characteristics and general performance status.[4,10] About 30 %[4] of patients in Western countries identified as having BCLC stage 0 or A HCC are eligible for curative treatments, including liver transplantation (LT), liver resection (LR) and various ablation techniques (ATs).[11]

LT provides excellent outcomes applying the Milan criteria, with five-year survival rate of 70 % and recurrence rates below 15 %.[12] LT is the only curative option for the underlying cirrhosis.[13,14] However, because of the shortage of potential liver donors and progression of the HCC, the risk of dropout from liver transplantation waiting lists is up to 4 % per month.[15]

LR is the treatment of choice for HCC in non-cirrhotic patients (~5 % of cases in Western countries, ~40 % in Asia).[15] In the case of underlying cirrhosis, candidates need to be carefully selected to diminish the risk of post-operative liver failure with increased risk of death.[15,16] In HCC patients after LR, the risk of tumour recurrence exceeds 70 % at five years.[15]

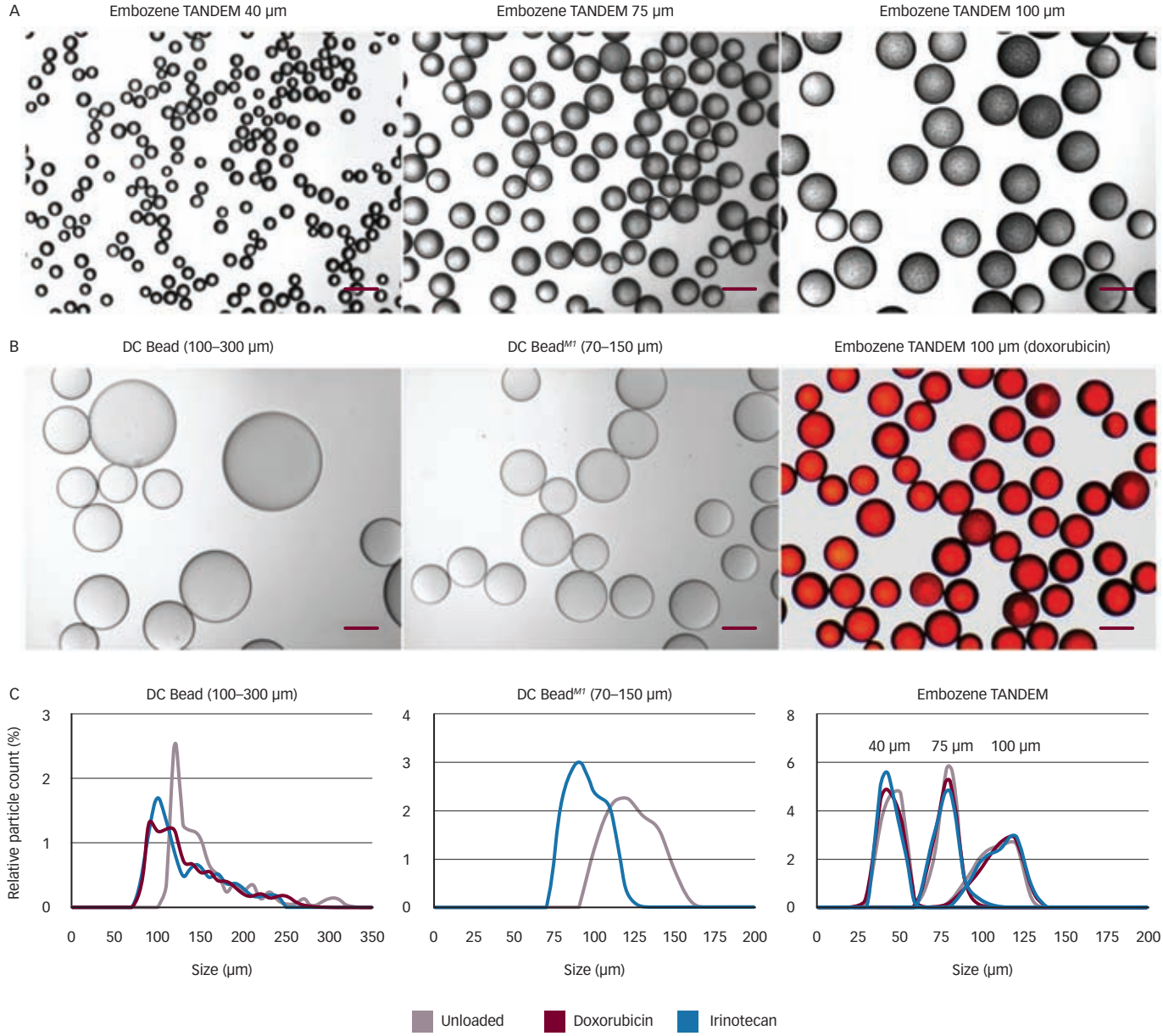
ATs include chemical (e.g., percutaneous ethanol injection [PEI]) and thermal (e.g., radiofrequency ablation [RFA]) ablation. PEI results in five-year survival rates of 47–53 % (Child–Pugh class A, early-stage tumours).[17] PEI has high local recurrence rates of 33–43 %.[17] For RFA, depending on Child–Pugh class and location of lesions in the liver in early-stage HCC patients, five-year survival rates of around 60 % have been reported.[17]

In hmCRC, unlike HCC, LR is the only potential curative standard treatment.[18–20] In patients with hmCRC, LR provides five-year survival rates in the range of 25–58 %.[18] However, only 10–20 % of patients are suitable for LR.[2,21] Recurrence rates for hmCRC after LR range from 60–70 %.[22]

Drug-eluting Beads

Conventional chemotherapy should not be recommended for HCC treatment.[4,23] Most patients with HCC are not suitable for curative treatments. Patients with end-stage disease have a median survival of only three months and should receive symptomatic treatment.[24] Sorafenib has been found to improve the survival of patients with advanced-stage HCC (10.7 months versus 7.9 months for placebo).[25] Dual blood supply of the liver and almost exclusive arterial blood

Figure 1: Optical Micrographs and Size Distribution of Embozene TANDEM™, DC Bead® and DC Bead®M1

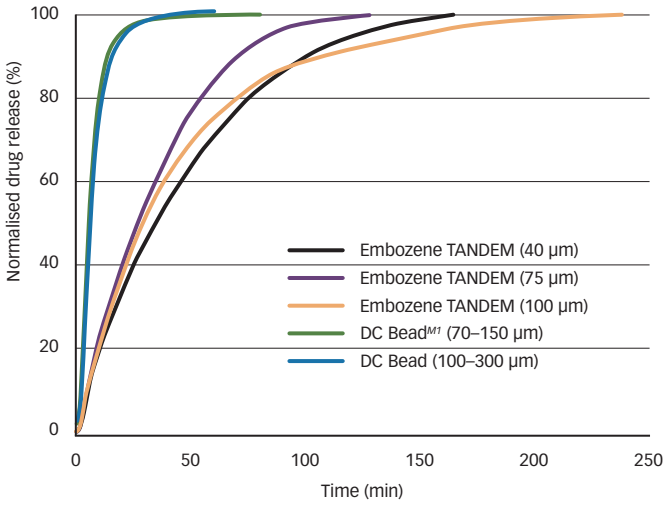


A = Optical micrographs (scale bar 100 µm) of Embozene TANDEM 40 µm, 75 µm and 100 µm. B = Optical micrographs of DC Bead (100–300 µm), DC Bead^{M1} (70–150 µm) and doxorubicin-loaded Embozene TANDEM 100 µm. C = Size distribution of DC Bead, DC Bead^{M1} and Embozene TANDEM: unloaded and loaded with irinotecan or doxorubicin (with irinotecan only in the case of DC Bead^{M1}, which is not intended for use with doxorubicin).

supply of tumours[26] allow intra-arterial approaches for the treatment of intermediate-stage HCC. Transarterial techniques include at least transarterial chemoembolisation (TACE) and transarterial embolisation (TAE).[27] TACE has been shown to improve survival compared with best supportive care.[28–31] TACE has not been proven to be superior to TAE.[27,32] For TACE, there is no clear consensus on, or established standard for, material choice and procedural technique.[33] Drug-eluting beads (DEBs) have the potential to standardise and simplify the TACE procedure.[33] In Europe, commercially available DEBs include DC Bead® (Biocompatibles UK Ltd), HepaSphere™ (Merit Medical) and the newly available Embozene TANDEM™ (CeloNova BioSciences, Inc.).

DEBDOX™ (DC Bead loaded with up to 37.5 mg doxorubicin per ml microspheres) was shown *in vivo* to reduce systemic doxorubicin exposure compared with TACE.[33–35] *In vitro* drug-elution showed a low total release (up to 27 %).[36–38] However, *in vivo*, 89 % of the initially loaded drug was released within 90 days in a pig model.[39] Histological examination showed a higher degree of necrosis for DEBs (loaded with either doxorubicin or epirubicin) compared with TAE.[40,41] A randomised trial comparing DEBDOX with TAE showed a statistically significant longer time to progression with DEBDOX.[42] However, there was no difference in survival rates within 12 months between both groups.[42] Although a survival benefit for DEBDOX over TACE was shown in a small retrospective case-controlled study,[43] a large multicentre study showed no significant difference in overall response between DEBDOX and TACE (51.6 % versus 43.5 %, respectively).[44] For patients with more advanced disease (Child–Pugh class B or Eastern Cooperative Oncology Group [ECOG] score 1, with recurrent HCC or bilobar involvement), a statistically significant higher objective response with DEBDOX was shown and that response was sustained in larger number of patients.[44]

Figure 2: Release Profiles of Different Irinotecan-loaded Drug-eluting Beads (50 mg/ml Microspheres)



Release monitored in process via ultraviolet-visible spectroscopy in SOTAX CE 1 elution system at 37 °C using isotonic medium, 5 ml/min flow rate.

Table 1: Time to Release 10 mg of Doxorubicin for DEBDOX™ and Embozene TANDEM™ (in Minutes)

DEBDOX (37.5 mg/ml Microspheres)		Embozene TANDEM (50 mg/ml Microspheres)		
100–300 µm	500–700 µm	40 µm	75 µm	100 µm
90 ± 20	510 ± 60	190 ± 30	175 ± 25	195 ± 25

Release monitored in process via ultraviolet-visible spectroscopy in SOTAX CE 1 elution system at 37 °C using isotonic medium, 5 ml/min flow rate.

HepaSphere is available as a dry formulation and can load similar amounts of doxorubicin to DC Bead.[45,46] Drug-loading efficiencies of 82–100 % have been reported.[36,45,46] *In vivo* preclinical trials showed sustained drug delivery over a couple of days[46,47] and reduced peak plasma concentrations for doxorubicin versus TACE.[47] A randomised Phase II trial comparing doxorubicin-loaded HepaSphere with TACE showed a lower peak plasma concentration and smaller area under the curve for the former.[48] A multicentre trial resulted in high objective response rates with doxorubicin-loaded HepaSphere at one-month and six-month follow-up.[49]

Since LR is the only potential curative treatment allowing long-term survival in hmCRC patients, many strategies have been developed to achieve downstaging of initially unresectable tumours.[50] Irinotecan-loaded DEB is quite a novel treatment approach when LR is not feasible and chemotherapy has failed or is ineffective.[2,33] DC Bead, DC Bead^{M1}, HepaSphere and Embozene TANDEM can be loaded with irinotecan up to 50 mg per ml hydrated microspheres. Drug-loading degrees range from 90 to >99 % depending on microsphere size, microsphere type, drug concentration and loading time.[37,51,52] DEBIRI™ (DC Bead loaded with irinotecan) showed anticancer activity after chemoembolisation of rat hmCRC (reduction of tumour burden treated versus control [T/C] 42–47 %, reduction of liver weight T/C 54–62 %).[53] Furthermore, in a rabbit VX2 liver tumour model, DEBIRI resulted in lower early serum levels of irinotecan, high and prolonged intratumoural irinotecan level and a higher rate of tumour necrosis at 24 h compared with intra-arterial and intravenous injection.[54] The clinical performance of DEBIRI has been reported in several studies.[55–59] The median survival has been shown to be 23–25 months, a statistically significant improvement compared with FOLFIRI (folinic acid plus fluorouracil plus irinotecan).[60,61]

Embozene TANDEM™ – The Next Step in Drug-eluting Beads Technology

Better tumour penetration of small (100–300 µm) versus larger (300–500 µm) microspheres has been demonstrated in VX2 liver tumour.[62] Potential benefits of small microspheres have been reported in a prospective multi-institutional non-randomised registry for HCC patients[63] and are also suggested for hmCRC patients.[64–67] In a recent study, increased benefit with decreased size has been shown, with an approximately twofold improved drug coverage in swine kidney (70–150 µm versus 100–300 µm).[68] Thus, microparticles should be small[69] (approximately 50 µm)[2] and tightly size-calibrated with a narrow size distribution.[69]

Embozene TANDEM is designed to fulfill the need for:

- size consistency;
- high drug-loading capacity;
- deeper penetration into peripheral tumour vessels; and
- controlled drug release.

Embozene TANDEM is tightly calibrated (40 ± 10 µm, 75 ± 15 µm and 100 ± 25 µm) (see *Figure 1*) and can load 50 mg irinotecan or doxorubicin per ml microspheres with high loading efficiency (98 ± 2%) in short periods of time (30 and 60 minutes for the two drugs, respectively). Different from other DEBs, Embozene TANDEM typically maintains its size after drug loading to allow consistent performance (see *Figure 1*). Size decrease of up to 30 % upon drug loading has been reported for other DEBs depending on the size of microspheres and amount of loaded drug.[38,51,70,71]

The high loading capacity of Embozene TANDEM allows to deliver the desired dose and to reach the stasis endpoint by design. The risk of reduced dosage due to premature stasis during intervention is lowered. Embozene TANDEM is available in pre-filled syringes with 2 and 3 ml microspheres. Embozene TANDEM is specifically designed to penetrate into medium/large (35–80 µm) arterioles before blocking blood flow and releasing drug at controlled rates. It offers the smallest microspheres and the tightest calibration on the market.

Release results depend on test set-up and parameters.[36,38] It has been reported that, under the same conditions, the use of 100–300 µm DEBs resulted in 15-times higher maximum plasma concentrations and in statistically significant lower mean tissue concentrations of doxorubicin compared to 700–900 µm DEBs in a porcine liver model.[39,40] The expected clinical benefits of controlled drug release are to reduce systemic exposure (improved safety) and increase tumour concentration of doxorubicin (enhanced efficacy). By adapting the structural and chemical compositions of Embozene TANDEM, the desired release rates can be achieved (see *Table 1*).

For irinotecan-loaded DEB, one additional challenge is to reduce drug side effects.[58,72] Some of the adverse events are related to the initial, fast, and premature release of 5-10 % of the loaded irinotecan for DEBIRI.[58,73] The release rate of irinotecan is faster than that of doxorubicin.[37,39,74] Furthermore, the published *in vitro* release data demonstrate that the release rate of DEBIRI is size-dependent (see *Table 2*).[51,52] Consistent with the reported data,[75] investigations in our

Table 2: $t_{75\%}$ Values (in Minutes) for Irinotecan-loaded DC Bead®, HepaSphere™ and Embozene TANDEM™

	DC Bead				HepaSphere	Embozene TANDEM		
Source	70–150 µm (DC Bead^{M1})	100–300 µm	500–700 µm	700–900 µm	400–600 µm	40 ± 10 µm	75 ± 15 µm	100 ± 25 µm
Jordan et al., 2010[37]*			66		7			
Taylor et al., 2007[51]‡		25	60	160				
Tang et al., 2008[52]†		23		205				
CeloNova BioSciences#	9 ± 1	9 ± 1				67 ± 12	49 ± 5	60 ± 8

$t_{75\%}$: time to reach 75 % of release plateau level.
All releases monitored in process via ultraviolet-visible spectroscopy.
** 50 mg/ml microspheres (DC Bead) or per 25 mg dry microspheres (HepaSphere); 37 °C in SOTAX CE 6 elution system using isotonic medium, 5 ml/min flow rate.*
‡ 50 mg/ml microspheres; 37 °C in T-cell apparatus using phosphate buffered saline as release medium, ~50 ml/min flow rate; $t_{75\%}$ estimated from given graphs.
† 47 mg/ml microspheres; 25 °C in T-cell apparatus using phosphate buffered saline as release medium, 136 ml/min flow rate; $t_{75\%}$ estimated from given graphs.
 # 50 mg/ml microspheres; 37 °C in SOTAX CE1 elution system using isotonic medium, 5 ml/min flow rate.

laboratory showed that DC Bead (100–300 µm) and DC Bead^{M1} (70–150 µm) had similar release profiles for irinotecan. Under the same *in vitro* test conditions, Embozene TANDEM demonstrated 5–8 times slower irinotecan release than DC Bead and DC Bead^{M1} (see *Table 2* and *Figure 2*). It is important to point out that the release rate of Embozene TANDEM is expected to be even lower *in vivo*, due to its deep penetration into peripheral tumour vessels with a smaller flow rate. Embozene TANDEM is therefore expected to reduce irinotecan-related side effects.

Conclusion

DEBs are a well established palliative therapy for the treatment of HCC. In the treatment of hmCRC, the role of DEBs is increasing, either as palliative treatment or as downstaging therapy. The trend has been towards smaller microsphere sizes and the need for DEBs ≤100 µm featuring size consistency, high drug-loading capacity, deeper penetration into peripheral tumour vessels and controlled drug-release has emerged. Embozene TANDEM, a new embolic microsphere, is designed to respond to this need. ■

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