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Review article

Drug-eluting embolic microspheres for local drug delivery – State of the art☆

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ABSTRACT

Embolic microspheres or beads used in transarterial chemoembolization are an established treatment method for hepatocellular carcinoma patients. The occlusion of the tumor-feeding vessels by intra-arterial injection of the beads results in tumor necrosis and shrinkage. In this short review, we describe the utility of using these beads as devices for local drug delivery. We review the latest advances in the development of non-biodegradable and biodegradable drug-eluting beads for transarterial chemoembolization. Their capability to load different drugs, such as chemotherapeutics and anti-angiogenic compounds with different physicochemical properties, like charge and hydrophilicity/hydrophobicity, are discussed. We specifically address controlled and sustained drug release from the microspheres, and the resulting *in vivo* pharmacokinetics in the plasma *vs.* drug distribution in the targeted tissue.

1. Introduction: locoregional drug delivery in transarterial chemoembolization (TACE)

Liver cancer is the second most common cause of death from cancer worldwide, which led to an estimated 746,000 deaths in 2012. The most common primary malignancy of the liver is hepatocellular carcinoma (HCC) [1].

For patients with multinodular hepatocellular carcinoma and preserved liver function (intermediate-stage B according to the Barcelona Clinic Liver Cancer (BCLC) classification), transarterial chemoembolization (TACE) is the standard of care [2–4]. During TACE, the tumor-feeding arteries are selectively catheterized. Conventional TACE (cTACE) is carried out by the infusion of an emulsion composed of a chemotherapeutic agent and iodized oil (Lipiodol®), followed by bland embolization (absorbable gelatin, unloaded beads). For TACE with drug-eluting beads (DEB-TACE), beads are loaded with a chemotherapeutic drug prior to their transarterial delivery. DEB-TACE is considered a more standardized and reproducible methodology in terms of delivered drug dose compared to cTACE, whereas for the latter several regimens exist without a universally accepted protocol [5–8].

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; cTACE, conventional TACE; CT, computed tomography; MRI, magnetic resonance imaging; DEB, drug-eluting bead(s); APTA, (3-acrylamidopropyl) trimethylammonium chloride; HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; DSM, degradable starch microspheres; PLGA, poly(lactide-*co*-glycolide) or poly(lactic-*co*-glycolic acid); PEG, Poly(ethylene glycol); PEGMA, Poly(ethylene glycol) methacrylate; PLA, poly(D,L-lactic acid); PBS, phosphate buffered saline; SDS, sodium dodecyl sulfate; MW, molecular weight

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Site-specific drug delivery from the beads to the targeted tumor tissue leads to a controlled pharmacokinetic profile [6,9–11]. Al-Abd et al. [12] recently summarized the unique advantages of embolization to increase local drug levels and concomitantly decrease systemic toxicity by entrapping the drug in the tumor-feeding vessels. As such, local drug delivery is achieved by the synergistic combination of local administration of drug-eluting beads (DEBs) and the prevented wash-out of the drug due to interrupted arterial blood flow [13]. Importantly, drug delivery in the tumor proximity was reported to effectively result in high drug concentration in the targeted tumor tissues [14].

In case embolization with micron-sized beads is not indicated for treatment (patients beyond BCLC stage B), intra-arterially administered nanocarriers are explored to target specifically advanced-stage HCC lesions. Possible biochemical targets and currently developed drug delivery nanosystems were summarized in an excellent recent review by Zhang et al. [15].

The present review aims to highlight the latest advances in the design of embolic drug-eluting beads for DEB-TACE of HCC. With this, it also covers temporary embolizing agents, which show less serious post-embolization side effects [16] and are therefore currently in the research focus [17–27]. Drug loading and release of relevant drugs for HCC treatment from established and novel, among them biodegradable, bead formulations are discussed. Besides chemotherapeutic drugs, anti-angiogenic and immunotherapeutic drugs are beneficial in HCC treatment [12,28–31], which are not necessarily easy candidates for drug loading on beads by ion exchange such as doxorubicin [32] or irinotecan [33].

Due to different mechanisms of drug loading or due to different affinities to the bead surface, different drugs show different release profiles *in vitro*[34]. This translates in turn into unique pharmacokinetic profiles *in vivo*, and little is known about the local drug distribution in the targeted tissue. We discuss here whether there is an “ideal drug release profile”, and whether sustained drug release is required to achieve long-term exposure of the tumor to the drug.

2. State of the art of drug-eluting microspheres

Embolic beads have been used since the 1970s [31] and were compared in experimental [32,34,35], pre-clinical [36–39] and clinical settings [40]. Massmann et al. [41] provided a complete tabular overview of clinically established and more recent FDA-approved embolic agents. The features of clinically established agents as well as some novel embolic agents were summarized in recent reviews [31,42]. In this section, we focus on advances in drug-eluting bead development, *i.e.* beads that are still under preclinical evaluation and were specifically designed to deliver anti-cancer drugs to tumors. Advances in non-biodegradable and biodegradable embolic beads are summarized in Tables 1 and 2, respectively.

2.1. Non-biodegradable beads for drug delivery and in vitro drug release

Clinically used DC Bead (BTG, London, UK), HepaSphere (Merit Medical, South Jordan, UT, USA), Embozene TANDEM (CeloNova BioSciences, San Antonio, TX, USA), and LifePearl (Terumo, Tokyo, Japan) are non-biodegradable beads, which are capable of drug loading *via* an ion exchange mechanism [32]. This elegant method does not interfere with drug activity, ensures drug release in contact with physiological fluids [43,44], and is therefore also mainly employed for bead-drug combinations in development.

Lewis et al. [45–52] and Jordan et al. [53,54] have recently developed a series of non-biodegradable beads with “special features” for drug delivery (Table 1). Beads for the loading of anionic drugs [45], and X-ray image-able beads with doxorubicin loading capacity [46–49,52,55] were presented. DC Bead were also loaded with two drugs at the same time, *e.g.*, doxorubicin was loaded *via* ion exchange and rapamycin *via* drug precipitation into the bead [50], or DC Bead were combined with different anti-angiogenic drugs [51,53,54].

Table 1
Recently developed non-biodegradable drug-eluting beads.

Bead (brand name if available, matrix)	Size (μm)	Drug	Mechanism of loading and/or release	Maximal drug loading	Release rates (*in vitro*, PBS pH 7.4, 37 °C)	Reference
Cationic quaternary (3-acrylamidopropyl) trimethyl ammonium chloride (APTA)	100–300	Anionic pyrene model drugs	Ion exchange	Up to 30 mg/mL depending on drug and bead formulation	Monovalent pyrene dye: 80% release, plateau reached at 1 h, for 8.6 μmol/mL loading	[45]
Lipiodol-loaded DC Bead	70–150, 100–300	DOX	Ion exchange	37.5 mg/mL	Radiopaque beads eluted DOX slightly more slowly than non-radiopaque beads	[46]
iBeads (DC Bead modified by iodinated moieties)	100–300, 300–500	DOX	Ion exchange	40–80 mg/mL	Slightly increased released drug dose compared to non-iodinated beads, $t_{50\%}$ = 0.5 h (100–300 μm), $t_{50\%}$ = 0.8 h (300–500 μm)	[47]
DC Bead (methacryloyl-polyvinyl alcohol (PVA) polymerized with 2-acrylamido-2-methylpropanesulfonate sodium salt (AMPS))	500–700	DOX + rapamycin	Ion exchange (DOX) + (non-solvent-induced) rapamycin precipitation	40 mg/mL DOX + 30 mg/mL rapamycin	Not different from single drug-loaded bead at max. Loading: 5% DOX release, 27% rapamycin release	[50]
DC Bead, DC Bead LUMI	70–150	Vandetanib	Ion exchange	30 mg/mL for DC Bead, 135 mg/mL for DC Bead LUMI	PBS pH 7: 85% drug release from DC Bead, 50% drug release from DC Bead LUMI at plateau at 2 h	[51]
DC Bead	100–300	Sunitinib	Ion exchange	30 mg/g	PBS: $t_{50\%}$ = 0.8 h, 94% release at plateau; NaCl 0.9%: $t_{50\%}$ = 1.0 h, 100% release at plateau)	[53,56]
DC Bead	70–150	Bevacizumab	Ion exchange	38 mg/mL	Extended by layer-by-layer technique to 3 days with a 41% release at plateau	[54]

DOX: Doxorubicin.