Toward a better understanding of the mechanism of action for intra-arterial delivery of irinotecan from DC BeadTM (DEBIRI)

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DC Bead is designed for the embolization of liver malignancies combined with local sustained chemotherapy delivery. It was first demonstrated around a decade ago that irinotecan could be loaded into DC Bead and used in a transarterially directed procedure to treat colorectal liver metastases, commonly referred to as drug-eluting bead with irinotecan (DEBIRI). Despite numerous reports of its safe and effective use in treating colorectal liver metastases patients, there remains a perceived fundamental paradox as to how this treatment works. This review of the mechanism of action of DEBIRI provides a rationale for why intra-arterial delivery of this prodrug from an embolic bead provides for enhanced tumor selectivity, sparing the normal liver while reducing adverse side effects associated with the irinotecan therapy.

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Transarterial chemoembolization of colorectal metastases

The treatment options for liver-dominant colorectal metastases (CRLM) have become significantly more varied with the introduction of locoregional approaches such as percutaneous ablation and hepatic arterial-directed therapies

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including hepatic arterial infusion pumps, selective internal radiation therapy and transarterial chemoembolization (TACE). Although conventional Lipiodol-based TACE (cTACE) has been used extensively in the treatment of hepatocellular carcinoma (HCC) with positive data on overall survival (OS) from randomized studies [1,2], there has been no such demonstration of efficacy in the setting of CRLM. One reported study followed 564 CRLM patients over a 10-year period that were treated with various chemotherapy regimens together with Lipiodol and/or starch microspheres and reported 1-, 2- and 3-year survival rates of 62, 28 and 7% respectively with a median survival of 14.3 months [3]. In a meta-analysis of hepatic arterial therapies comparing outcomes from hepatic arterial infusion, radioembolization and TACE in CRLM patients, 14 TACE studies were identified totalling 1038 CRLM patients, with a similar median OS of 15.2 months reported [4]. Hepatic arterial therapies have therefore been shown to be effective in controlling disease in CRLM patients and recently there has been increasing interest in the locoregional delivery of irinotecan (IRI) from embolic drug-eluting beads (DEBs) through hepatic arterial administration, collectively termed DEBIRI. A number of recent excellent reviews discuss the current clinical evidence for DEBIRI and its place in the treatment of CRLM, evaluating data from 13 published studies consisting of around 850 patients, including two randomized control trials, six prospective Phase I/II trials and five retrospective studies [5–7]. Consistent throughout these reviews is the discussion of the fundamental paradox that exists with the rationale of DEBIRI, given that DEBs are usually targeted to the tumor, but the IRI is a locally delivered prodrug that is designed for activation in normal liver parenchyma. In this article we discuss this mechanism of action in more detail, with reference to data from nonclinical and clinical studies that sheds more light on why lobar administration used in this procedure makes sense and how the DEB-based delivery leads to appropriate pharmacodynamics, high tumor selectivity and high rates of pathological tumor response for this disease state.

DC Bead loading with irinotecan

DC Bead™ was the first DEB to receive regulatory approval, in this case for loading doxorubicin (Dox) for treatment of HCC (DEBDOX) and has been commercially available in Europe since 2004. DC Bead is made by the reverse suspension polymerization of aqueous droplets containing polyvinylalcohol macromer and 2-acrylamido-2-methylpropane sulfonic acid, suspended in butyl acetate by rapid stirring and copolymerized by application of initiator and heat [8]. This gives rise to spherical hydrogel microspheres of around 96% water content that are subsequently tinted blue with Reactive Blue 4 for visualization and sieved through a sieving tower to produce different size fractions. In 2009, the CE mark approval for DC Bead was extended to include loading with IRI for the treatment of CRLM. When the beads are placed in a solution of irinotecan hydrochloride (commercially available as Campto formulated with lactic acid), the drug can easily and rapidly diffuse into the bead structure and interacts with the negatively charged sulfonate groups by ion-exchange (Figure 1A) turning the beads slightly turquoise (Figure 1B & C) [9]. Drug entering the bead structure displaces some water causing a dose-dependent shrinkage in diameter up to 25–30%, with a small increase in the stiffness of the bead toward compression (Figure 1D & E) [9]. The most common approach in the clinic is to load DC Bead with IRI in the hospital pharmacy before the procedure (performed by an interventional radiologist [IR]), although a number of publications have reported on a preloaded version of the product known as PARAGON Bead (Figure 1F) [10–13]. The properties of the two are exactly the same at the point of use and data generated from these two approaches can be considered interchangeable.

Whether loaded in the pharmacy or preloaded, the IRI interaction within the bead can be demonstrated using Fourier transform infra-red spectroscopy (Figure 2) [14,15]. The IRI exists in a closed-ring lactone and open-ring carboxylate form governed by a pH-dependent equilibrium. Only the lactone (the bioactive form) carries an overall positive charge owing to the protonation of the nitrogen of the piperidino side chain in acid conditions. This form therefore binds to the sulfonate groups in the bead, depleting the solution of lactone (Figure 2A) and driving the equilibrium in the favor of more lactone formation until all the drug is loaded within the bead (maximum capacity being 50 mg/ml of hydrated beads for DC Bead) [16]. The lactone form is confirmed by FTIR (Figure 2B) and a dose-dependent shift in the S=O stretching band of the sulfonate demonstrates the ionic interaction between drug and bead (Figure 2C) [14]. Uniform loading of IRI can therefore be imaged throughout the bead using FTIR microscopy on bead sections (Figure 2D). The procedure for loading in the hospital pharmacy is straightforward, whereby the saline packing solution is removed to leave a bead slurry and 5 ml of Campto solution (20 mg/ml of IRI) is added to the slurry. The beads are agitated and stored for 30–60 min to load depending upon their size and transferred into a syringe. At the end of the loading period, excess supernatant is removed and the syringe is transported to the interventional radiology suite where the procedure is performed. Nonionic contrast agent is

Figure 1. Loading of DC Bead with irinotecan by ion-exchange and the subsequent effects on bead properties. (A) Schematic of irinotecan (IRI) loading in DC Bead; **(B)** optical micrographs of unloaded DC Bead and **(C)** IRI loaded DC Bead (50 mg/ml); effect of IRI loading in DC Bead on **(D)** bead size and **(E)** bead stiffness to compression; **(F)** Comparison of DC Bead loaded with IRI in the pharmacy with the preloaded and lyophilized PARAGON bead.

DEBIRI: Drug-eluting bead with irinotecan.

Created using data from Taylor *et al.* [9].

added to the suspension immediately prior to administration to reduce the amount of drug that is displaced by the mixture [17] and the beads are then injected through a microcatheter directly into the hepatic artery under fluoroscopic guidance.

Locoregional delivery of irinotecan & mechanism of action

The mechanism of action and metabolism of IRI (also known as CPT-11) are complex (Figure 3). Although a derivative of camptothecin, it is designed as a prodrug in which the bulky piperidino side group is enzymatically hydrolyzed by carboxylesterase (predominantly CES-2) which exists within various compartments within the body, including the blood, liver and gut [18]. This forms 7-ethyl-10-hydroxycamptothecin, or SN-38, which is known to be 1000-times more potent in binding the drug target, TOPO-1, a protein present within the cell that is responsible for relieving torsional strain during DNA replication (Figure 3A) [18,19]. The SN-38 binds irreversibly to TOPO-1 to form a complex that interferes with DNA replication, inducing single strand breaks in DNA and leading to apoptosis of the cell. The drugs' metabolism is not straightforward as the fused ring structure of IRI and its metabolites exist in pH-dependent closed ring lactone and open-ring carboxylate forms [20], whereby only the lactone is active (Figure 3B inset) [21]. The IRI is further deactivated within the cell by CYP3A4 to inactive 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) and 7-ethyl-10-[4-N-

Figure 2. Investigation into drug-bead interactions using Fourier transform infra-red spectroscopy and imaging microscopy. (A) pH-dependent interconversion between open-ring carboxylate and closed-ring lactone, showing interaction of net positively charged lactone with negatively charged sulfonate groups of DC Bead (red-dashed highlight); (B) fourier-transform infrared spectroscopy (FTIR) spectra of carboxylate, lactone and DC Bead bound IRI confirming lactone structure persists; (C) FTIR spectra of S = O stretching absorption peak shift with increasing dose of IRI demonstrating interaction through interaction with the sulfonate of DC Bead; (D) microscopy showing section through DC Bead and corresponding FTIR intensity map for characteristic drug peak showing relatively uniform loading throughout.

IRI: Irinotecan.

(A) Created using data from [16]; (C) created using data from [14].

(1-piperidino)-1-amino] carbonyloxycamptothecin (NPC) or if converted to SN-38, may be glucuronidated to SN-38 G by UGT1A1. All forms of the drug and its metabolites can be actively eliminated from the cell by various ABC transporter systems such as ABCB1, MDR-1 and MOATc. The latter is predominantly responsible for excretion of the compounds into the bile, whereby once in the gut, the IRI can be converted by bacterial carboxylesterases into SN-38 or the SN-38 G converted back to SN-38 by the action of β -glucuronidase (β -Gluc in Figure 3), the upshot being severe dose-limiting toxicity in the gut and subsequent high grade diarrhea [22]. Carboxylesterase present in the blood generates SN-38 which manifests itself as dose-limiting toxicity on white blood cell count.

Traditionally IRI is delivered by a series of scheduled 30–90 min intravenous (iv.) infusions [23], whereby the drug is diluted within the systemic circulation, passing through the liver where its activity depends upon its ability to be taken up by the tumor versus distant deactivation and excretion by the healthy liver. Locoregional delivery of IRI from drug-eluting beads (DEBIRI) has significant impact on both the pharmacokinetics and the pharmacodynamics of the drug, as a much lower overall dose is delivered but targeted at high concentration in and around the vicinity of the tumor. Studies in the rabbit VX2 model demonstrated significantly lower serum peak levels and greater tumor tissue levels of IRI at 24 h when treated with DEBIRI compared with hepatic intra-arterial (IA) or iv. delivery [24]. The vast majority of DEBIRI data has been generated using DC Bead as the DEB, whereby the loading and release of the drug from this device is well characterized and widely recognized as a much faster release than that of Dox for the corresponding DEBDOX procedure for treating HCC [25]. The current technical recommendation for DEBIRI using DC Bead involves a minimally invasive image-guided intra-arterial administration of DEBs directly into the hepatic artery that feeds the main lobe in which the tumor metastases exist. The lobar delivery ensures the DEBs

flow into both the tumor vessels (given its rich vascularity relative to the normal liver parenchyma, despite perhaps being classified as hypovascular) and into the normal liver surrounding the tumor masses [26]. Despite such proximal administration of DEBIRI, the procedure's effectiveness has been confirmed with high rates of pathological tumor destruction in a small patient series [27]. This is distinctly different to the recommendation for super selectivity to target HCC tumors with DEBDOX [28] and is a consequence of the different mode of action of IRI versus Dox at a locoregional level.

Lobar delivery of IRI from DC Bead results in a rapid release of the drug into the surrounding tumor and normal tissues. Here we see the first significant difference versus the conventional iv. infusion, as the peak plasma levels are significantly reduced for DEBIRI versus a similar iv. dose as drug targeted to the tissue (Table 1). Importantly, lobar infusion results in occlusion of tumor and normal liver hepatic arterial vessels. Tumors, however, are predominantly supplied by the hepatic arterial supply [29], whereas normal parenchyma from the portal vein. Embolization therefore creates selective ischaemia in the tumors relative to the normal tissue which is largely unaffected. We see evidence for this in studies of healthy porcine hepatic artery embolization with DEBIRI, where the normal liver parenchyma in the embolized lobe shows only minor effects from the procedure [9] compared for instance with DEBDOX where the drug causes widespread necrosis of normal tissue [30]. In a study of DEBIRI in a rat colorectal liver metastases model, however, embolization with beads alone had no effect on tumor burden, compared with a dose-related response with DEBIRI, signaling that both embolization and drug are important for tumor efficacy (Figure 4) [31].

Studies involving hepatic pedicle clamping demonstrate that ischaemia is associated with a rapid drop in liver tissue pH with just 10–20 min of inflow occlusion [36]. As embolization with particles results in a similar degree

Figure 3. Irinotecan chemical structure changes by metabolism or pH change and mode of anti-tumor action. **(A)** Metabolism of IRI and its anticancer action; **(B)** pH-dependent interconversion between the active lactone (closed ring) and inactive carboxylate (open ring) forms of IRI and its metabolites (X = various groups shown in 3A).
β-Gluc: β-glucuronidase; IRI: Irinotecan.

Table 1. Key pharmacokinetic parameters from selected studies including an example intravenous irinotecan study compared with preclinical and clinical data from drug-eluting bead with irinotecan across several referenced studies.

Study (year)	Species	Method	Number treated	Dose (mg)	Time point	IRI plasma level (ng/ml)	SN38 plasma level (ng/ml)	IRI AUC (ng/ml.h)	SN38 AUC (ng/ml.h)	Ref.
Forni <i>et al.</i> (1994)	Human	iv. irinotecan	6	122	Cmax	1552 ± 86	16 ± 6	3453 ± 305	69 ± 24	[23]
Brooks <i>et al.</i> (2007)	Pig	DEBIRI	3	100	Cmax	1493 ± 432	1.7 ± 0.9	7307 ± 2129	505 ± 3.6	[32]
Levy <i>et al.</i> (2015)	Human	DEBIRI	11	86	Cmax	194 ± 124	16.7 ± 11.3	1680 ± 1200	281 ± 352	[33]
Chiche <i>et al.</i> (2010)	Human	DEBIRI	10	100	1-h post	281 (207–484)	16.4 (11.4–27.8)	ND	ND	[34]
Jones <i>et al.</i> (2013)	Human	DEBIRI	8	200	1-h post	188.3 (80.0–352.7)	10.2 (6.9–31.2)	ND	ND	[12]
Levy <i>et al.</i> (2019)	Human WT	DEBIRI	3	100	Cmax	405.2 ± 3.5	20.5 ± 2.5	3227.7 ± 857.7	164 ± 11.7	[13]
	Human VAR	DEBIRI	2	100	Cmax	200.0 ± 40.0	39.7 ± 13.1	1998.5 ± 345.3	558.6 ± 52.6	
Warburg <i>et al.</i> (2018)	Human	DEBIRI (M1)	10	100	Cmax	1299 ± 2276	41.5 ± 26.1	5020 ± 2138	305 ± 206	[35]

AUC: Area under the curve; DEBIRI: Drug-eluting bead with irinotecan; IRI: Irinotecan; iv.: Intravenous.

Figure 4. Efficacy of DEBIRI in a rat colorectal metastases model. Showing the effect of drug-eluting bead with irinotecan in a rat model of colorectal metastases versus embolization alone with DC Bead.

DEBIRI: Drug-eluting bead with irinotecan.

Created using data from Eyol *et al.* [31].

of hypoxia generation [37], it is reasonable to assume that embolization-induced hypoxia in the tumor results in acidosis, and hence a decrease in the extracellular pH environments compared with the normal liver parenchyma. Moreover, hypoxia induces a shift from oxidative phosphorylation to glycolytic metabolism within the tumor cells that further promotes acidosis [38]. It is well recognized from evidence gathered over many years that electrodevaluated human tumor pH is on average lower than that of normal tissue [39] and that pH gradients do exist between adjacent tumor and normal tissues [40]. This is of fundamental importance when considering the mechanism of selectivity for IRI, given the pH-dependent interchange between the inactive and active forms of the drug and its metabolites (Figure 5). For instance, SN-38 has been shown to demonstrate a several-fold potentiation in anticancer activity (IC_{50} decrease across multiple cell lines) at pH 6.8 relative to pH 7.4 [41,42]. Those metabolites present in

Figure 5. pH-dependent equilibrium between the lactone and carboxylate forms of IRI and its metabolites. Showing the pH-dependent interconversion of lactone and carboxylate forms of irinotecan (left axis) and corresponding rate constant of hydrolysis (right axis), with the gray area representing the change in pH from normal to tumor tissue based upon reported pH gradient measurement [40] and arterial stump ligation-induced acidosis in the liver [36]. Created using data from Araki *et al.* [22].

the hepatocytes in the normal liver at approximately pH 7.2 are therefore predominantly present in the inactive carboxylate forms, compared with the more acidic tumor environment, where even a modest drop of just fractions of a pH unit have a significant impact on the percentage of lactone form that exists. Moreover, there is also a concomitant decrease in the rate of lactone hydrolysis to the carboxylate, ensuring the lactone form prevails for longer.

It is also known that intracellular levels of CES-2 are far higher in normal liver tissue compared with that of colorectal tumors [43,44] and hence lobar delivery in the vicinity of the tumor means that drug delivered into these cells is likely to be more efficiently converted into SN-38 relative to that in the tumor [45]. Jones *et al.* clearly showed, in analysis of tumor explants, the correlation between CES-2 levels and levels of microsomal SN-38 [12]. The TOPO-1 target for SN-38 however is five to 35-fold overexpressed in colorectal cancer cells relative to normal tissue [46], and hence SN-38 should be consumed more efficiently within the tumor cell relative to the normal hepatocyte. In this scenario it could be envisaged that a diffusion gradient could be established, whereby high levels of SN-38 (largely inactive form) in surrounding normal parenchyma may diffuse into the tumor environment, being interconverted to the active form by the decrease in pH by a process driven by SN-38 consumption by the much higher levels of the TOPO-1 target in the more rapidly dividing tumor cells (Figure 6) [47]. Again, Jones *et al.* saw a correlation between the SN-38 levels and the degree of fibrosis that resulted in the tumor, which has been noted as an indicator for long-term tumor response [12]. These phenomena ensure a high level of selectivity between healthy and tumor tissue and explains the high levels of tumor necrosis reported on explanted tumor samples (Figure 7) [10,12,48].

High locally delivered levels of IRI result in its conversion to SN-38 being rate limiting, probably by saturation of the tissue levels of CES-2 (as supported by the lack of impact of CYP3A4 expression on microsomal activation of IRI observed by Jones *et al.* [12]). This promotes accumulation of high intracellular levels of IRI in both normal and tumor tissue as confirmed by biopsy in a recent pilot study conducted by Levy *et al.* [13], which consequently overloads the ABC transporters responsible for the active elimination of the drug and metabolites from the cell, overcoming one mechanism of tumor drug resistance [49,50]. Levels entering the systemic circulation are therefore

reduced relative to the iv. route of administration as supported by [Table 1](#), in which it is clear that a $C_{\max}$ of around 200–400 ng/ml has been consistently observed in multiple DEBIRI PK assessments (at 100 mg/ml target dose). Moreover, in one study double the dose was administered (200 mg/ml), yet also resulted in a similar $C_{\max}$ for both IRI and SN-38 [12], further supporting these rate-limiting steps in the metabolism. Interestingly, the $C_{\max}$ observed in the DEBIRI treatment of healthy porcine liver results in a much higher $C_{\max}$ more akin to iv. administration (typically ~1200–1500 ng/ml for a 100 mg/ml dose) ([Table 1](#)) [9,32]. This phenomenon could be due to differing

Figure 7. Pathological response to drug-eluting bead with irinotecan compared to systemic chemotherapy. Showing the comparison of pathological response from patients treated with neoadjuvant drug-eluting bead with irinotecan or several cycles of FOLFOX/FOLFIRI prior to resection.

Created using data from Jones *et al.* [8].

DEBIRI: Drug-eluting bead with irinotecan; FOLFOX/FOLFIRI: Folinic acid/5-fluorouracil/oxaliplatin.

levels of CES-2 in blood and plasma compared with man, or perhaps because there is a lack of tumor in the model to drive the consumption of SN-38 by TOPO-1.

Levy *et al.* also noted in their limited patient cohort that UGT1A1 mutation resulted in a lower level of SN-38 G formation and relatively higher levels of SN-38, as expected for these patients [13]. This might suggest a greater efficacy of the treatment in these patients without the associated toxicity observed for those treated by iv. IRI. This effect, however, was not observed in similar patients in the Jones *et al.* patient cohort for reasons that are unclear [12]. Excretion of the drug and metabolites into the bile is similarly influenced by saturation of the transporter proteins and indeed, the relatively low overall dose administered during DEBIRI is below that required to damage the gut wall. Severe diarrhea is therefore not an observed dose-limiting toxicity for DEBIRI as it is for iv. delivery of IRI. This is illustrated by comparing the observations from Forni *et al.* who found that 50% of patients receiving $>115 \text{ mg/m}^2$ (total iv. dose of $>213 \text{ mg}$) of IRI suffered grade 3–4 diarrhea versus 22% for lower doses between 50 and 98 mg/m^2 (92–181 mg total iv. dose of IRI) [23]. Hence, DEBIRI is associated with a very different toxicity profile compared with iv. IRI administration and is why the combination of DEBIRI with systemic IRI may be possible given the lack of overlapping toxicities. Further research is required to validate this approach.

Implications of DEBIRI mechanism of action on clinical practice

Bead size selection

Most of the clinical evaluations of DEBIRI conducted since the first report by Aliberti *et al.* in 2006 have been with the 100–300 μm DEB size [51]. In general, CRLM are more hypovascular than HCC and smaller DEB sizes were adopted fairly early on in clinical practice in order to deliver the entire planned dose before reaching occlusion. Indeed, this prompted the manufacturer to release DC Bead M1, a subfraction of the 100–300 μm size

with a range from 70–150 μm [52]. The premise was that the removal of the larger sizes from 150–300 μm would provide for significantly more distal penetration, which was confirmed in evaluations using radiopaque versions of these products [53]. In a study reported by Kelly *et al.* comparing 70–150 μm beads with 100–300 μm DEBIRI in patients with hepatic metastatic disease, they demonstrated that when using the 70–150 μm beads there was less premature vessel occlusion and hence more of the drug dose administered, together with a lower adverse event rate [54]. This finding was confirmed in a prospective analysis of registry data propensity score matching analysis of small versus large DEBIRI showing an increase in target dose delivered (96 vs 79% for small vs big beads, $p = 0.005$) and a lower percentage of treatments terminating in complete stasis for smaller beads ($p = 0.0035$) [55]. Additional support for this drug dosing advantage and procedural safety was also demonstrated in an analysis of 15 consecutive patients with unresectable CRLM that underwent treatment with DEBIRI (M1) [56]. A recently reported prospective single-center Phase I study of DEBIRI (M1) included a pharmacokinetic study in the first ten patients and showed the smaller beads to give rise to a higher IRI C_{max} than seen previously with the 100–300 μm size DEBIRI (Table 1) [35]. This is presumed to be due to the higher burst effect expected with the smaller beads due to their increase surface area to volume ratio. There was no observed increase in adverse effects and it was also demonstrated for the first time that the procedure significantly reduced the levels of VEGFR1 at 24 h post, which is associated with a better treatment prognosis [57].

Other DEB platforms

The vast majority of the clinical literature pertaining to DEBIRI is related to the use of DC Bead as the DEB platform. There are some sporadic reports of nonclinical studies that demonstrate various DEB platforms and different drug–bead interactions and hence in loading and release of IRI [58–60], and some that report on the pharmacokinetics and mode of action of the combination in rabbit VX2 tumor models [61,62]. There is also a comparison of TandemTM (75 μm) with DC Bead M1 in a pig model which showed there was a difference between their pharmacokinetic profiles [63]. Ranieri *et al.* reported on a 25 patient single center study of patients with CRLM in <50% liver and no extrahepatic spread treated with DEBIRI using 100–300 μm HepaSphereTM (Merit Medical) 100 or 200 mg IRI + folinic acid/5-fluorouracil/oxaliplatin (FOLFOX/FOLFIRI) + antiangiogenic therapy. Tumor response and toxicity profile was favorable prompting the need for larger studies to confirm the findings [64]. In a similar study, 50 patients with unresectable CRLM were treated with 100 μm LifePearl[®] + 100 mg IRI but with no combination systemic chemotherapy [65]. Results showed mild toxicity, good quality of life measurements with overall noninferior outcomes to previous studies with other DEBs. Given that the different DEB platforms have been shown to release IRI at different rates, the mechanism of action and clinical outcomes for described for DC Bead may not necessarily be translatable to these other DEBs (Table 2).

Toxicities associated with DEBIRI

The mechanism of action described above for DEBIRI combined with the low overall dose of drug administered via this procedure somewhat explain the clinical observations [10,66,67] of the lack of dose-limited toxicities usually associated with systemic IRI, such as diarrhea and neutropenia. Early reports of the use of DEBIRI in a palliative setting however, although generally well tolerated, did report on a unique adverse effect of upper quadrant abdominal pain, particularly during the injection phase of the beads [68]. The reasons for this are still unknown, but as there are no pain nerves within the liver itself and the pain presumably originates from the Glisson's Capsule, it could be associated with osmotic swelling effects induced by the aqueous-based loading solution used to prepare the DEBIRI. This is in contradiction, however, to observations from several clinical studies on intrahepatic infusion of high dose IRI, for which there are no recorded instances of right upper quadrant pain [69–73]. While the exact cause of pain following DEBIRI has not been clearly established, follow-up studies have shown that pain can be reduced to those levels expected from postembolization syndrome by the application of a pain management regimen, such as iv. hydration, morphine and antibiotics [66] or iv. opioids and IA 1% lidocaine [33]. Narayanan *et al.* suggest camptothecin derivatives can cause pain and irritation on contact and recommend, in addition to IA lidocaine and morphine before and after DEB delivery, that iv. hydromorphone at 1 mg increments for a total of 4 mg be included to reduce the severity of abdominal pain [74]. There has been isolated reports of bradycardia associated with DEBIRI [75] and thought to be a consequence of a cholinergic surge induced by the IRI [76]. This is easily treated with iv. atropine administration if symptoms are severe.

Table 2. Comparison of key characteristics of commercially available drug-eluting bead platforms.

DEB platform	DEB core chemistry	Drug-binding group	IRI release rate relative to DC Bead [†]	Comments	Product appearance under optical microscopy (scale bar = 200 μ m)
DC Bead™ (Bicompatibles UK Ltd)	Sulfonate-modified polyvinyl alcohol hydrogel	Sulfonate (AMPS)	-NA-	Blue colored handling tint (70–150 μ m)
DC Bead LUMI™ (Bicompatibles UK Ltd)	Sulfonate-modified polyvinyl alcohol hydrogel with triiodobenzyl moieties	Sulfonate (AMPS)	Slower	Radiopaque PVA hydrogel matrix, higher density, golden color (70–150 μ m)
HepaSphere™ (Merit Medical Systems Inc)	Polyvinyl alcohol-co-sodium acrylate hydrogel	Carboxylate: (AA)	Much faster	Highly deformable, no color tint, provided dry (30–60 μ m/120–240 μ m when reconstituted)
Embozene TANDEM™ (Boston Scientific Corp)	Polymethacrylic acid coated with polyphosphazene	Carboxylate: (MAA)	Much slower	White color, more crosslinked structure, thin degradable coating (100 $\pm$ 25 μ m)
LifePearl® (Terumo Corp)	Sulfonate-modified polyethylene glycol hydrogel	Sulfonate (SPA)	Similar	Green colored handling tint (100 $\pm$ 25 μ m)

[†] [58–60].

AA: Acrylic acid; AMPS: Acrylamide-2-methylpropane sulfonate; DEB: Drug-eluting bead; IRI: Irinotecan; MAA: Methacrylic acid; SPA: Sulfopropyl acrylate.

Imaging considerations with DEBIRI

A neoadjuvant study of 22 easily resectable patients with 37 CRLM lesions was carried out with DEBIRI, followed by CT imaging and then resection at 4 weeks with pathological analysis of the tumors [11]. There was an impressive pathological response observed following just one DEBIRI treatment (comparable with those reported following several cycles of systemic FOLFOX/FOLFIRI [77]), as now somewhat anticipated from the proposed mechanism of action previously discussed (Figure 4). Importantly however, these findings were not accurately reported by CT assessment at 4 weeks, as radiologic response reported by RECIST was found to be inadequate for DEBIRI. This can be linked again to the mode of action of DEBIRI and is likely due to ischemic and edema-related swelling of the embolized tumors over the first few weeks post-therapy prior to their subsequent contraction; this is in contrast to the relatively early response observed with DEBDOX. Early evaluation by CT may therefore underestimate DEBIRI efficacy and could lead to a premature and unnecessary halt to treatment if wrongly interpreted. This is not an uncommon observation in the treatment of CRLM by liver-directed therapies, as previously reported for Yttrium-90 radioembolization where imaging findings even 3 months post-treatment lead to misinterpretation [78].

Combination of DEBIRI with systemic therapies

One aspect of the mechanism of action of DEBIRI is that IRI release and metabolism is relatively rapid, which means that it should be possible to combine this locoregional approach with additional systemic chemotherapy

where there is a desire to treat potential disease outside of the targeted liver lobe. Proof of concept for this approach was demonstrated in a preclinical swine safety study, where administration of sequential DEBIRI followed by systemic chemotherapy was safe with no adverse toxicity issues [32]. Indeed, Martin *et al.* have extended this into a ten patient study with concomitant DEBIRI and FOLFOX $\pm$ bevacizumab demonstrated as being safe with no dose-limiting toxicities, minimal adverse events and an enhanced overall response [34]. In a prospective Phase II trial to further study DEBIRI with a concomitant systemic FOLFOX regimen (the FFCD 1201 trial), there has been an intriguing case report of a 48-year-old male with six bilobar unresectable liver metastases [48]. Following two cycles of DEBIRI and five cycles of FOLFOX, the tumor response was sufficient for resection, which when analyzed showed a complete pathological response, the first report of its kind following DEB-TACE in multiple CRLM. Kekez *et al.* combined DEBIRI with FOLFIRI with a similar conclusion [79], although all seven patients suffered right upper quadrant pain due to the lack of an effective pain regimen. In a single institution Phase II study of 40 patients with CRLM who had failed two previous lines of chemotherapy, multiple DEBIRI procedures were performed on a schedule depending on whether it was single or bilobar disease and in combination with capecitabine (1000 mg/m² twice daily on days 1–14 every 3 weeks). Modest disease control rates of 47.5% were seen with the incidence of grade 3 adverse events at just 15%, making this a valid treatment option in this heavily pretreated patient population [80].

Future perspective

The past decade has seen significant advances in the management of CRLM, with the combination of existing chemotherapeutic regimens with targeted liver therapies such as DEBIRI pushing median survival out beyond 30 months with the possibility of cure by patient downstaging to resection [81]. Indeed, a Phase III randomized control trial of 74 first- and second-line patients treated with either DEBIRI or FOLFIRI achieved its primary end point of 40% improvement in OS (56 vs 32%, $p < 0.032$) and median survival of 22 versus 15 months respectively, which underpins just how effective this locoregional therapy can be [66]. Further Phase III trials in larger patient groups, however, are needed to substantiate these promising results and enable DEBIRI to become a more mainstream choice in the treatment paradigm for CRLM.

As an alternative to combining DEBIRI with systemic chemotherapy, it has been demonstrated that it is possible to combine more than one drug into DEBs, or to codeliver DEBs loaded with different drugs with complimentary modes of action. For instance, in a study evaluating cytotoxicity of DEBs containing two different drugs on the viability of HEPG2 and PSN1 cancer cells, it was found that there was significant synergy in DEB-mediated codelivery of irinotecan and rapamycin [82]. Rapamycin is an inhibitor of mTOR which is responsible for downstream activation of many pro-survival pathways in cancer cells and upregulated in hypoxic conditions, and hence a potentially ideal agent to add to DEBIRI. This could further increase tumor efficacy, while continuing to minimize adverse systemic effects of the combined DEB-drug cocktail. In order to elucidate further on DEBIRI mechanism of action, different topoisomerase-1 inhibitors that are not prodrugs and therefore do not need to be converted by the normal liver into an active species, could also be interesting to investigate by DEB-mediated locoregional delivery. Topotecan is one such drug and has already been shown to be loadable into DC Bead and more potent than IRI on pancreatic cancer cell lines using *in vitro* cytotoxicity assays [83]. Comparison in an appropriate tumor model or perhaps pilot clinical investigation is required, where the combined effects of local delivery and embolization effects can be evaluated to determine if ultimately there may be any advantage in the remote activation of the IRI in healthy liver compared with a targeted delivery directly in the tumor of the active drug, as is the case for conventional DEB-TACE.

Author's contributions

AL Lewis conceived of the concept and preparation of the figures. AL Lewis and B Hall both contributed to the review of the literature, data analysis and manuscript writing.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This article is based around a review of the current literature pertaining to the study of DEBIRI in nonclinical and clinical studies, together with literature related to irinotecan and its mechanism of action. A balanced, unbiased and objective review of this literature has been undertaken to provide the insights into how this therapeutic procedure works.

Executive summary

- DC Bead loaded with irinotecan (IRI; drug-eluting bead with irinotecan) is a promising locoregional approach that can be performed alone, or in combination with additional iv. systemic chemotherapy, to provide local control of metastases from colorectal cancer to the liver.
- Only the lactone form of IRI is loaded into DC Bead via reversible ion-exchange interactions, ensuring 100% of the drug can be eluted at the target, all of which will initially be in its active form.
- Drug-eluting beads are designed to afford targeted delivery to hepatocellular carcinoma tumors via super-selective microcatheterization, ensuring site-specific drug dosing while minimizing the cytotoxic effects of Dox in the liver and systemic circulation. Drug-eluting beads-based delivery of IRI, however, appears to present a fundamental paradox in terms of mechanism of action and how efficacy is achieved.
- The IRI is a prodrug that requires activation to its more potent metabolite SN-38, which occurs more efficiently in the normal liver parenchyma than in the tumor. Consumption of SN-38, however, is higher in the tumor where the cells are replicating more rapidly and there are much high levels of topoisomerase-1 (the target for SN-38 activity). This creates a concentration gradient between normal and tumor tissues that drives the diffusion of SN-38 into the cancer cells.
- The drug and its metabolites also exist in either open (lactone) or closed (carboxylate) ring forms, the interconversion being a pH-dependent process. The lactone is the only form with anticancer activity. Differences in pH between the normal liver and adjacent tumor create a pH gradient that favors the generation and stability of the active lactone form in the more acidic tumor environment, providing a degree of selectivity for tumor over normal cells.
- The pH-dependent nature of the activation of the drug/metabolites, together with the selective tumor hypoxia induced by the embolization procedure, combine to produce a unique mechanism of action that warrants adjustments to procedural technique, evaluation of response and patient management.

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