Expert Opinion

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A new tool to enhance the efficacy of chemoembolization to treat primary and metastatic hepatic tumors

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This editorial focuses primarily on a paper that presented the clinical applications of a new material, named DC Bead embolic drug-eluting bead (DEB), which is used to modulate the blood flow in conjunction with chemotherapy in primary and metastatic hepatic tumors. DEB appears to have several advantages over alternative embolization agents, not least of which is its effective capacity of drug diffusion in tumors, thereby making it suitable for ideal treatments.

Keywords: chemoembolization, doxorubicin, drug-eluting bead, liver cancer

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1. Introduction

This editorial focuses primarily on a paper that presented the clinical application of a new material, called DC Bead embolic drug-eluting bead (DEB) [1]. Owing to an ageing population, the number of cancer patients is on the rise. The total number of tumor cases diagnosed annually will increase 50%, from 10 million to 15 million, by 2020 according to the World Health Organization (WHO).

Multidisciplinary teams of physicians are taking new approaches in the fight against cancer. Cancer cure is moving away from extensive surgical removal of tumors and chemotherapy or radiotherapy and is expanding into new areas. One of those areas is interventional oncology, which is opening up new opportunities to palliate oligonodular metastases or relapsed tumors with minimally invasive techniques. When looking at liver hepatocellular carcinoma, for example, surgery is feasible in only 25% of these patients; and half out of the remaining, classified as intermediate stage, are candidates for minimally invasive cure such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE). The advantage of these new approaches is that these procedures are much less invasive than open surgery. Hospital stays are therefore shorter and patients can go home and continue with their daily life much earlier than after undergoing surgery.

Regional treatment of liver tumors leads to a more selective drug distribution and a higher drug concentration in the target area than systemic cytotoxic administration, but, owing to the rapid blood flow of the hepatic artery, suboptimal tumor drug concentrations in liver tumor cells still result [2,3]. Therefore, a temporary regional reduction of arterial blood flow during intra-arterial drug administration might act to enhance further the therapeutic effect. In the past few years several methods have been utilized in an attempt to reduce the hepatic arterial blood flow, so as to induce tumor necrosis through ischemic damage and/or increase the efficacy of intra-arterial chemotherapy.

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2. Rationale for liver regional chemotherapy

Basically, regional chemotherapy aims to provide high chemotherapeutic agent concentrations within the tumor and low drug concentrations in the body vascular compartment. Compared with intravenous delivery, higher drug concentrations can be achieved at the target site. This regional drug exposure advantage (i.e., the ratio of drug exposure after intra-arterial infusion to drug exposure following intravenous administration of the same dose) is related to the rate of drug clearance by the rest of the body and the rate of blood flow into the target organ [4-6]. The relationship has been described as shown in Equation 1.

$$\text{Regional advantage} = 1 + \frac{Cl_{TB}}{Q_T\,(1 - E_T)} \quad (1)$$

where Cl_{TB} is total body drug clearance, Q_T is blood flow through the regional artery being infused and E_T is the extraction ratio of the drug by the target region. As is evident from this equation, regional advantage is greater for a drug with a relatively high total body clearance that is infused into an artery with relatively slow blood flow.

In attempting to exploit the advantages of regional administration of anticancer drugs for the treatment of hepatic tumors, it must be remembered that the liver has a large blood supply (> 1000 ml/min), albeit that two-thirds is of portal origin and, thus, fails to influence drug extraction [2-4]. The benefits of such administration may therefore be compromised. If, however, the blood flow to this target organ is reduced by mean a vascular occlusion, as is possible when co-administering DEB, then the regional advantage can be optimized.

2.1 Chemoembolization (TACE): development and pharmacokinetic considerations

TACE represents a combination of two partially effective therapies with the aim of improving on both. There are multiple variations on the technique and ingredients, but it has evolved into a common procedure in many institutions worldwide to palliate patients with previously untreatable malignancies. The expression TACE connotes a bipartite anticancer effect elicited through occlusion of the tumor vascular bed coupled with cytotoxic drug administration. Such vascular occlusion provides a greater cytotoxic drug concentration in tumor regions, which can now be defined as chemosaturation. Early studies demonstrated that extensive tumor necrosis could be produced, with radiographic tumor response rates of up to 83% [7-11]. Tissue levels of chemotherapy were found to be up to 40 times higher in the tumor than in the surrounding liver, and to persist for several months.

Nutrient flow from the hepatic artery to a tumor is twice that from the portal vein, and experiments that gave chemotherapy during surgery showed a 10 times higher intratumoral concentration when it was given through the artery rather than the portal vein [5,6,12-16]. This makes arterially directed treatment especially attractive from both the delivery and safety points of view, as the tumor can be made hypoxic while uninvolved liver is spared. Moreover, the pharmacokinetic advantage of locoregional drug administration enhances the theoretical benefit [5,6]. Many drugs show preferential extraction when delivered intrahepatically and they can achieve quite favorable liver/systemic drug concentration ratios, thus minimizing the systemic toxicities associated with chemotherapy (**Table 1**). For example, hepatic drug exposure has been estimated to be double for doxorubicin, sevenfold greater for cisplatin, 8 times greater for mitomycin, 10 times greater for 5-fluorouracil, and up to 400-fold higher for 5-fluorodeoxyuridine (FUDR) when delivered intrahepatically rather than intravenously [6]. Moreover, there is reason to hypothesize that the hypoxia resulting from the embolization component might actually enhance the cytotoxic action of the chemotherapy. Many drugs, such as doxorubicin, are actively expelled from tumor cells owing to the action of the transmembrane pump P-glycoprotein, the product of the multi-drug resistance (*MDR*) gene. P-glycoprotein is an ATP-dependent pump, and it is conceivable that the tissue hypoxia induced by chemoembolization inhibits the active efflux of the drug [12,13]. Further reports emphasized that TACE is relatively well tolerated in this group of patients with advanced cancer and may lead to prolonged survival [14-20], despite local side effects [7,8,21].

3. Expert opinion

3.1 Drug-eluting bead technology

The authors of the DEB review [1] describe DEB as being composed of a polyvinyl alcohol hydrogel hybrid polymer with 2-acrylamido-2-methylpropanesulfonate sodium salt formed in microspherical shape. In these microspheres there are a lot of sulfonic acid groups that are capable of ion-exchange between the sodium counter ions and other positively charged ions in the solution in which the beads are immersed. Doxorubicin or irinotecan are suitable charged drugs and they diffuse into the structure, displace the sodium ions and bind through electrostatic interactions to the sulfonate groups.

The concept of new materials for TACE has existed since Helmut Ringsdorf proposed a generic drug-polymer conjugate consisting of a targeting group, a solubilizing agent and a drug to enable its release at the site of action once targeted. Then many systems of drug delivery were expanded until the DEB system was developed, in which the drug carrier is delivered intra-arterially through catheters that can be positioned close to the main arterial supplies that feed tumors, causing primarily a physiological blockage of the artery in combination with a local chemosaturation of the tumors.

DEB is in the field of targeted drug delivery and is a new embolization system with drug delivery capabilities optimizing the concept of regional advantage where $E_T = 0$.

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Table 1. Regional drug delivery advantage (*Rd*) for selected anticancer drugs at various regional blood flow rates (*Q*).

Cl_{TB} (ml/min)	Drug	*Rd*			
		Q = 1 (ml/min)	*Q* = 1 (ml/min)	*Q* = 100 (ml/min)	*Q* = 1000 (ml/min)
40,000	Thymidine	40,001	4001	401	41
25,000	FUDR	25,001	2501	251	26
4000	5-Fluorouracil	4001	401	41	5
3000	Cytosine arabinoside	3001	301	31	4
1000	BCNU	1001	101	11	2
900	Doxorubicin	901	91	10	1.9
400	AZQ	401	41	5	1.4
400	Cisplatin	401	41	5	1.4
200	Methotrexate	201	21	3	1.2

AZQ: Diaziquone; BCNU: Bischloroethylnitrosourea; FUDR: Fluorodeoxyuridine.

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DEB can be considered the best application of ideal attributes for TACE that Kerr described in 1987 [22]: a biocompatible material capable of carrying a drug and releasing it locally in a controlled manner at therapeutic levels in the tissue.

So far a competitive embolic agent does not exist because they cannot be loaded with drugs and are used only for the final embolization step of the TACE procedure.

3.2 Drug-eluting bead clinical activity

The article that follows is an interesting clinical review of TACE where the embolic material to block nutrient flow is a substantially new one: DEBs that were designed to be loaded with doxorubicin and irinotecan to deliver the drug locally in an intensive fashion. The efficacy of DEB is reported in primary liver cancers (hepatocellular carcinoma [HCC], the seventh most common cancer in the world), which represent the best choice for intermediate disease alone or in combination with new drugs such as sorafenib.

The principal application of TACE, including DEBDOX, is in patients with unresectable intermediate or advanced HCC in order to control symptoms and prolong survival. DEBDOX may allow patients to move to other curative treatment options for which they are initially unsuitable owing to tumor size or site. Of interest is the position of DEBDOX in 'bridge to transplant'; the aim is to control the HCC until such time as a transplant becomes available. It has been recognized that the measure of improved outcome is the extent of tumor necrosis before transplant, as incomplete necrosis may increase the risk of tumor spread post-transplant [10].

Lammer *et al.* report results of a Precision V study, the only randomized controlled trial so far for an embolic drug delivery bead in HCC, for a direct comparison of DEBDOX with conventional TACE. Even if the incidence and frequency of post-embolization syndrome are comparable in the two treatments arms, this study indicates that liver toxicity is lower following treatment by DEBDOX than the conventional arm [11]. The results of this large randomized study seem to confirm and correlate well with the previous pharmacokinetic analysis done by Varela *et al.* [23].

The rate of occurrence of HCC is lower in Western countries, where metastatic liver cancer from colorectal origin and other gastrointestinal tumors is predominant. Such tumors of the liver are generally less vascular than HCC and are not commonly treated by TACE, as the core for therapy is intravenous chemotherapy to contrast the metastatic nature of the disease; but for colorectal cancer there is a step during 'metastatic cascade' where the liver is the unique site and if it is possible to operate, 20% more of the patients are cured. So TACE will in the near future be considered more as a fruitful combination with systemic chemotherapy considering the high potential of locoregional control of the disease, reducing metastatic spreading from the liver to the rest of the body.

Of note is that in the case of DEBIRI, it has been demonstrated that irinotecan is preferentially bound and released from DC in its active lactone form. The drug diffuses from the beads several hundred micrometers from the bead edge, generating a chemosaturation of the tumors. This is probably one of the keys of clinical activity of DEB in liver metastases from colorectal cancer. The author and co-workers reported results on the first randomized study comparing DEBIRI versus systemic chemotherapy (FOLFIRI) in patients with liver metastases from colorectal cancer where there is evidence of increase in responses, quality of life and survival for the DEBIRI arm [24]. They also cite a new field of clinical activity as the first report on liver metastases from ocular melanoma; confirming clinical evidence of activity is also reported and discussed [25].

The author and co-workers present further perspectives of clear clinical relevance. They propose exploring small size-range products (300 – 500 and 100 – 300 μm) to deliver the beads more distally into the tumor bed, although there is as yet no clear evidence of a better clinical outcome considering the risk of embolizing the venous part of the liver, generating portal hypertension and enlargement of the spleen, as has been reported with other products of small size

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(50 – 100 μm). They stress the interest of loading DEBs with radiopaque contrast in order to make them visible under CT scan; showing the different special distribution seems to be of interest in planning retreatment of untreated areas.

In HCC, DEBDOX is the mainstay treatment for intermediate HCC and may be combined with other interventional techniques such as RFA to better effect. Combination of DEBDOX with sorafenib, designed to prevent tumor proliferation, has been identified as a promising strategy that needs to be defined in further randomized study.

The treatment of metastases of colorectal cancer is moving to combination therapies whereby the TACE will be provided as an adjunct to existing systemic IV regimens in order to provide local control of the liver-dominant disease in addition to the treatment of more distant metastases.

Declaration of interest

The author declares no conflict of interest and has received no payment in preparation of this manuscript.

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