

Extravascular use of drug-eluting beads: A promising approach in compartment-based tumor therapy

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Author contributions: Binder S and Keese M analyzed the data and wrote the paper; Lewis AL wrote the passage about intrapancreatic therapy; Lewis AL, Löhrl JM and Keese M designed and performed the research.

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Received: August 11, 2013 Revised: September 5, 2013

Accepted: September 16, 2013

Published online: November 21, 2013

Abstract

Intraperitoneal carcinomatosis (PC) may occur with several tumor entities. The prognosis of patients suffering from PC is usually poor. Present treatment depends on the cancer entity and includes systemic chemotherapy, radiation therapy, hormonal therapy and surgical resection. Only few patients may also benefit from hyperthermic intraperitoneal chemotherapy with a complete tumor remission. These therapies are often accompanied by severe systemic side-effects. One approach to reduce side effects is to target chemotherapeutic agents to the tumor with carrier devices. Promising experimental results have been achieved using drug-eluting beads (DEBs). A series of *in vitro* and *in vivo* experiments has been conducted to determine the suitability of their extravascular use. These encapsulation devices were able to harbor CYP2B1 producing cells and to shield them from the hosts im-

mune system when injected intratumorally. In this way ifosfamide - which is transformed into its active metabolites by CYP2B1 - could be successfully targeted into pancreatic tumor growths. Furthermore DEBs can be used to target chemotherapeutics into the abdominal cavity for treatment of PC. If CYP2B1 producing cells are proven to be safe for usage in man and if local toxic effects of chemotherapeutics can be controlled, DEBs will become promising tools in compartment-based anticancer treatment.

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Key words: Compartment based therapy; Intraperitoneal; Drug-eluting beads; Carcinomatosis; Hyperthermic intraperitoneal chemotherapy; Glioblastoma; Pancreatic cancer; CYP2B1; Ifosfamide

Core tip: Intraperitoneal carcinomatosis occurs with several tumor entities and prognosis is usually poor. Besides standard therapy, only few patients may benefit from hyperthermic intraperitoneal chemotherapy. The treatment may cause severe systemic side-effects. One different approach to target chemotherapeutic agents to the tumor employs carrier devices. Contemplable carriers are drug-eluting beads (DEBs). DEBs can be used to transfer drugs or pro-drug converting enzymes directly to the tumor. Furthermore, DEBs can successfully target chemotherapeutics into the abdominal cavity for *ip* treatment. When local toxic effects are controlled, DEBs are effective tools in compartment-based therapy.

Binder S, Lewis AL, Löhrl JM, Keese M. Extravascular use of drug-eluting beads: A promising approach in compartment-based tumor therapy. *World J Gastroenterol* 2013; 19(43): 7586-7593 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i43/7586.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i43.7586>

CLINICAL BACKGROUND

Peritoneal carcinomatosis (PC) is a disseminated tumor stage, which is observed in patients with ovarian, pancreatic, gastric and colorectal cancer. With median survival rates of 3.1 mo for gastric cancer and 5.2 mo for colorectal cancer, respectively^[1], the prognosis is usually poor^[2].

Survival is prolonged by new agents used in palliative chemotherapy. With the availability of oxaliplatin, irinotecan, bevacizumab, and cetuximab the 5-year survival has significantly increased over the last decade^[3-7].

Although some patients seem to benefit from these drugs, the physical and psychological strain for patients suffering from PC remains high. In addition to the commonly known side effects of chemotherapy^[8], patients show a variety of symptoms originating from PC itself, ranging from abdominal pain, nausea and obstipation up to bowel obstruction and obstructive uropathy^[9].

EVALUATION OF PRESENT TREATMENT

The treatment of peritoneal carcinomatosis requires an interdisciplinary and multimodal approach. Modern therapy combines cytoreductive surgery (CRS), radiation therapy and systemic chemotherapy, depending on the origin of the tumor^[10-12]. Unfortunately survival rates remain low^[1,13] at the cost of frequently observed dose limiting side-effects^[8].

Since tumor spread into the abdominal cavity may also be considered as an early step of dissemination - comparable to liver metastasis in colorectal carcinoma - and not as a state of generalized systemic disease^[14-16], one approach may be to resect all detectable tumor nodules and target drugs directly to the peritoneal cavity^[17].

The surgical procedure removes all macroscopic tumor manifestations by combination of different peritonectomy procedures, including greater omentectomy, splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy, cholecystectomy with stripping of the omental bursa, pelvic peritonectomy with sleeve resection of the sigmoid colon, and antrectomy^[18-21], as well as parietal peritonectomy^[22,23]. After the resection, the dissolved chemotherapeutic agent and carrier solution are heated up to 42 °C and pumped through the abdominal cavity for 40-90 min^[24]. Since the abdomen remains opened, it is possible for the surgeon to support the circulation in the abdominal cavity manually^[25]. This procedure is followed by thorough lavage, anastomosis of resected bowel segments and closure of the abdominal wall^[24].

A survival benefit using CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown^[26]. Verwaal *et al.*^[27] reported a 3-year survival of 38% in their patients. A more recent follow up of the same cohort shows similar survival rates^[28]. Median progression-free survival was 7.7 mo in the control arm and 12.6 mo in the HIPEC arm. A 5-year survival of 45% was found in patients, in which R1 resection could be achieved. This

indicates that CRS combined with HIPEC is superior to systemic chemotherapy alone. Nevertheless the findings of Franko *et al.*^[29] suggest, that CRS combined with HIPEC as well as systemic chemotherapy alone have their roles in the multidisciplinary approach treating peritoneally disseminated cancer.

In selected patients even a long term survival may be possible, with CRS and HIPEC being a curative approach in disseminated colorectal carcinoma^[28,30].

The HIPEC procedure itself is demanding for most of the patients. Even though the median survival rates increased, the 30-d mortality rate of 4.8% and a morbidity rate reaching up to 55% are high^[31]. The surgery itself and severe systemic side-effects may lead to deterioration of health or death^[32,33]. Given that, the inclusion criteria to receive CRS and HIPEC remain strict. The peritoneal surface has to be the only site of disease dissemination^[27] and the preoperative assessment^[34] should suggest a high likelihood of achieving complete cytoreduction (CC-0)^[35]. Therefore only patients with medium-sized intraperitoneal tumor nodules and a limited distribution within the abdomen are selected^[36]. Patients have to be physically fit to endure this extensive procedure. Considering that peritoneal carcinomatosis only becomes symptomatic in advanced stages, where CC-0 or CC-1 can rarely be achieved, only few highly selected patients have access to this approach^[37]. Excluded patients are left with systemic chemotherapy.

Alternative techniques have been investigated to target chemotherapeutic agents to the body cavities without the strain of surgery. These are promising approaches to circumvent both the systemic side effects and the hazard of an extensive surgical procedure.

DRUG-ELUTING BEADS

Bead characteristics

Promising carriers for contemplable agents such as doxorubicin, irinotecan or mitoxantrone are drug-eluting beads (DEB).

By far the most commonly used product in clinic is DC Bead™, which are microspheres comprised of a sulphonate-modified polyvinyl-alcohol hydrogel. They are available in sizes from 70-700 µm^[38] and can be loaded with doxorubicin (DOX), irinotecan (IRI) or mitoxantrone (MTX)^[39]. When drug-loaded, the product provides an accurate dosage of drug per unit volume of beads *in vitro*^[38], which they release *via* ion exchange constantly over weeks^[40,41]. *In vitro*, the beads are robust and maintain their size and shape after drug loading^[42]. This is a prerequisite for DEBs, since damage of the beads may cause rapid liberation and significant systemic distribution of the encapsulated drug or adverse effects by the debris itself.

The surface of the DEBs itself is inert and did not cause any immune reaction in control groups treated with unloaded beads^[39,43]. Furthermore the biomechanical engineered material is able to shield its content from the immune system^[44,45].

Present field of application

DEBs are used in clinical practice for trans-arterial chemoembolisation (TACE) of hypervascularized tumors^[46], such as hepatocellular carcinoma (HCC) and liver metastasis. By administering them selectively into the tumor-feeding vessels, the route for essential nutrients is obstructed and high levels of antineoplastic drugs can be reached within the tumor^[47].

As the procedure itself can be carried out under local anesthesia, morbidity and complication rates are low^[48], TACE has become the standard palliative approach in patients with unresectable HCC^[49-51]. The objective response rates range from 70%-75%^[52,53] at a low rate of complications^[53]. This suggests a good risk-benefit ratio.

For both associated side effects^[54] and progression free survival^[55] as well as overall disease control^[54,55], doxorubicin-loaded DC beads (DOXDEB™) produced the most promising results.

DEBS IN EXTRAVASCULAR USE

Since DEBs are able to liberate agents continuously *in vitro*^[56] they can also serve as drug carriers for extravascular application if the beads are directly instilled into the compartments.

Intracerebral therapy

The median survival of rats with experimental glioblastoma multiforme (GBM) could be successfully prolonged using doxorubicin polymers^[57]. This demonstrated a superior effect of chemotherapeutic carriers as compared to *iv* administration of the free drug. The most efficient drug - namely doxorubicin - caused the most severe side effects. Intracerebral hemorrhage and edema as well as hemiparesis were observed^[57]. A significantly longer median survival could be achieved in patients with GBM using carmustine warfers^[58], but they did not affect the recurrence-free survival times^[59]. These findings justified the idea of compartment-based therapy, but also called for new delivery systems and alternative antineoplastic drugs in return.

Baltes *et al.*^[60] showed that the intracerebral administration of DEBs is safe for use depending on the loaded drug. Both doxorubicin- and irinotecan-loaded DEBs significantly improved survival time in a rat BT4Ca GBM model. Doxorubicin again caused severe side effects^[57] whereas irinotecan seemed to selectively affect only the cancer cells and not healthy brain tissue^[61,62]. These findings could be confirmed in follow-up experiments where alginate was used as a viscosity modifier to secure the administration of the beads into the tissue^[63].

Intrapancreatic therapy

The efficacy of irinotecan- and topotecan-loaded DEBs have been evaluated by use of a modified MTS assay and in a PSN-1 mouse xenograft model of pancreatic cancer by direct injection at the tumor site. Topotecan was shown to be more potent than irinotecan in the *in*

vitro cell assay, had reasonable efficacy and tolerability at 0.2-0.4 mg doses but was lethal at doses of 0.83-1.2 mg. Irinotecan however, was well tolerated even with repeated injections of doses from 3.3-6.6 mg and displayed good efficacy^[64]. A similar study evaluated combinations of doxorubicin, irinotecan, topotecan and rapamycin DEBs and demonstrated synergistic activity for certain drug combinations, in particular doxorubicin and rapamycin^[65].

Feasibility for the clinical application of the direct intratumoral delivery of a compartment-based therapy was first demonstrated by delivery of a reservoir of a thermosensitive gel containing paclitaxel (Oncogel®) into the pancreas by use of ultrasound-guided endoscopic needle injection^[66,67]. This approach has been subsequently adapted for the administration of irinotecan-loaded DEBs suspended in alginate into the tail of the pancreas of a healthy pig. The therapy was well tolerated up to doses of 300 mg of irinotecan, with only localized pancreatic tissue reactions on histopathologic review^[68].

Intraperitoneal therapy of peritoneal carcinomatosis

An elegant approach to target drugs to a tumor is to administer them as pro-drugs and activate them intratumorally. The active metabolites are formed by enzymes which are selectively injected into the tumor.

Routinely, ifosfamide has been used *via iv* application in pancreatic cancer treatment^[69,70]. After administration cytochrome P450 2B1 (CYP2B1) produced by hepatocytes, transforms ifosfamide into 4-OH-ifosfamide, which results in the active compounds phosphoramidate mustard and acrolein^[71]. *In vitro* preparation and direct administration of the active compounds are limited due to their short half life (45 min)^[72].

Löhr *et al.*^[73] used encapsulated feline kidney cells, engineered to produce CYP2B1^[74], to target activated ifosfamide into pancreatic carcinoma^[73]. Therefore, cells were encapsulated in cellulose sulphate^[75] for immobilization and to protect them from the immune system when injected into the tumor. To model a pancreatic cell-like carcinoma PaCa-44 human pancreatic tumor cells were injected subcutaneously into nude mice. All mice received ifosfamide *iv*, one group received intra-tumorous injection of encapsulated CYP2B1 producing cells and one group received nonencapsulated cells. Tumor growth was impaired in all mice receiving ifosfamide. However, the most significant tumor reduction was detectable in the group that had received encapsulated cells. Complete macro- and microscopic tumor remission could be achieved in 20% of the animals. Although the same dosages of ifosfamide were used in both groups, the apoptotic rate of tumor cells was three times higher in the group receiving encapsulated cells. Furthermore these animals appeared healthier than the ones receiving nonencapsulated cells. Müller *et al.*^[43] were able to reproduce these results using a CYP2B1 producing cell line of human origin. This cell line did not produce potentially harmful retroviruses^[76] and is immune resistant^[77].

The approach worked for other tumor entities as

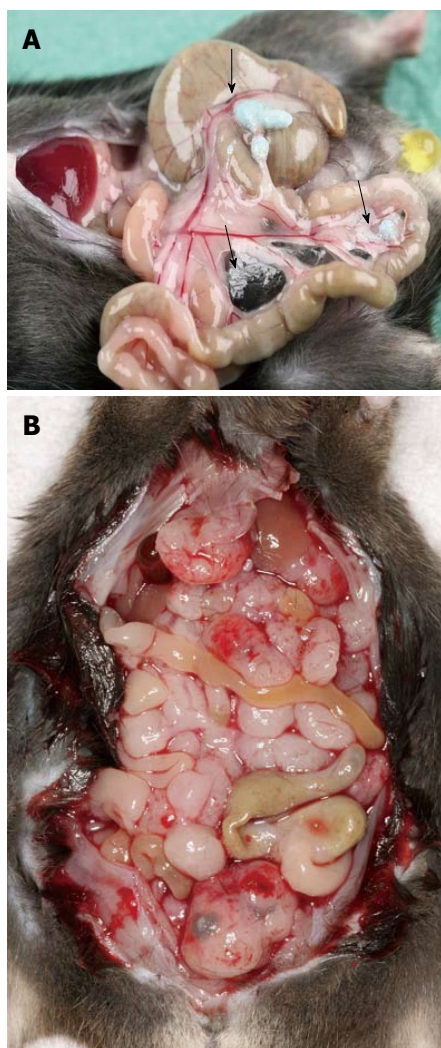


Figure 1 Peritoneal metastasis. A: Beads accumulate in the mesentery of the small bowel (arrows). Animals show a complete tumor remission; B: Control animal with disseminated peritoneal carcinomatosis induced by EGFP-C-26 cells.

well. Samel *et al.*^[78] showed, that similar results could be achieved in Balb/c mice carrying peritoneal tumor nodules, induced by syngenic C-26 cells injected into the abdominal cavity. This cell line is highly malignant and rapidly forms tumor nodules on the peritoneum. Again, in some animals a complete response was achieved. One major drawback of this approach is the use of genetically engineered cells. These cells may maintain a malignant potential. It remains to be shown if they can be safely applied to patients.

Therefore, an easier approach directly employs encapsulated chemo agents. *In vitro* tests with wild-type C-26 murine colon-carcinoma cells showed potent tumor toxicity for free DOX, IRI and MTX and the encapsulated drugs when combinations of the chemotherapeutic agents and DEBs were tested^[39]. For free IRI and MTX the inhibition of cell growth was superior to their encapsulated forms. The proportion of apoptotic cells was significantly higher for free DOX as well as for DOXDEB™ when compared to the other two agents. Both DOX and MTX showed a dose-depending induction of apop-

tosis, whereas IRI did not show any significant effect.

In vivo tests followed after determining appropriate concentration levels^[39]. For better detection of micro-metastases and for tumor load quantification, C-26 cells had been transfected with the marker protein enhanced green florescent protein as described^[78,79]. All animals developed disseminated PC (Figure 1A). Thereafter, animals were treated with free and encapsulated DOX and MTX. Best tumor reduction was obtained when splitting the DEB application into three sessions. Complete tumor remission could be obtained (Figure 1B). Weight loss and mortality of the subjects was significantly higher in the groups which were treated with the corresponding free drugs, suggesting a lower toxicity in the DEB groups.

The results obtained in this model of colorectal tumor, could be reproduced for pancreatic carcinoma dissemination. Yagublu *et al.*^[80] used a model of peritoneally metastasized panc02 pancreatic carcinoma cells in C57 black6 mice. Treatment was performed with free and encapsulated DOX, IRI and MTX. The free drug was more potent in decreasing tumor cell growth and inducing apoptosis than the encapsulated drugs *in vitro*. Again, *in vivo* free drug administration caused more weight loss and significantly higher lethality than the encapsulated drug, while no relevant differences in antitumoral activity could be observed.

To test the safety of the intraperitoneal injection and therapy using the DOXDEB™ a large animal trial was carried out^[81]. Black-headed meat-sheep received an application of DOXDEB™ into the abdominal cavity. Up to 50% of the maximal cumulative dose suggested for male humans were used in one single intraperitoneal injection^[82]. DEBs were injected using a verres needle. Upon autopsy, no DEBs were distributed *via* blood or lymphatic vessels. Beads remained on the peritoneum, immobilized by a fibrin layer (Figure 2A and B). No evidence for organ-related damage or systemic toxicity was observed. This is remarkable, as cardio toxicity^[83-87] and myelosuppression^[88-91] are frequently described with the systemic use of doxorubicin, along with less severe side effects such as stomatitis, alopecia, nausea and vomiting^[90]. The systemic distribution of DOX followed a three-compartment-model omitting a rapid and high peak, in comparison to *iv* administration. Serum levels reached a steady-state 360 min after application with a half-life of 615 h. Some sheep did not reach the end point and developed a chemical peritonitis^[82,92,93] (Figure 3). By circumventing the systemic administration and its accompanying side effects, local toxicity was the only limiting factor. This underlines the importance of drug choice when it comes to DEB therapy within the intraperitoneal compartment.

CONCLUSION

There is convincing evidence that drug-eluting beads can be employed in an extravascular environment for a compartment-based therapy. In several tumor models, the carrier devices showed convincing tumor control and

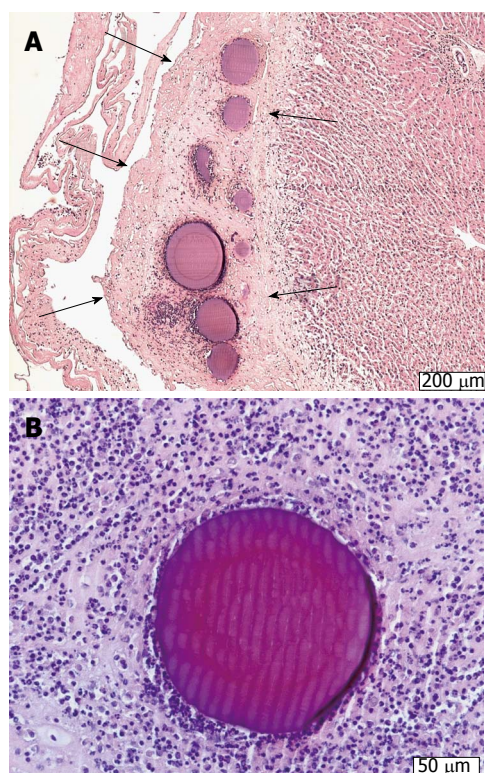


Figure 2 Doxorubicin-eluting beads. A: HE-stained, magnification $\times 50$: A layer of fibrin (between arrows) immobilizing the doxorubicin-loaded DC beads (DOXDEB™) on the livers surface; B: HE-stained, magnification $\times 100$: DOXDEB™ in layer of fibrin and surrounded by lymphocytes immobilizing it on mesenteric connective tissue.



Figure 3 Chemical peritonitis. Autopsy of an animal 28 d after installation of *ip* doxorubicin-loaded drug-eluting beads: Situs with greater omentum and intestinal loops with fibrinous adhesions, amber-colored ascitic fluid.

side-effects were less likely to occur. Also, encapsulation devices can be used to transform pro-drugs into their active metabolites within or in vicinity of the tumor. Here, drug-eluting beads successfully immobilized transforming-enzyme producing cells and protected them from the host immune system. However, the application of genetically engineered cell lines remains a major safety concern.

Intraperitoneal application of DEBs is a small procedure which can be safely performed under local anesthesia. Within the abdominal cavity DEBs show predictable liberation characteristics, remain inert and do not distrib-

ute *via* blood or lymphatic vessels.

Compartment-based therapy could be considered as a favorable treatment option for palliative patients with a deteriorated general condition, who are not eligible for HIPEC. Local toxicity is a limiting factor. Other drugs - for example irinotecan - have to be tested in a large animal model to further investigate local reactions.

If the adverse effects of the loaded substances are controlled, the extravascular use of drug-eluting beads is a promising future approach in compartment-based tumor therapy.

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P- Reviewers: Ding MX, Filep JG, Tan XR **S- Editor:** Gou SX
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ISSN 1007-9327

