Locoregional cancer therapy using polymer-based drug depots

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Locoregional delivery of anticancer drugs is an attractive approach to minimize adverse effects associated with intravenous chemotherapy. Polymer-based drug depots injected or implanted intratumorally or adjacent to the tumor can provide long-term local drug exposure. This review highlights studies in which drug-eluting depots have been applied locally in the treatment of cancer. In many cases such drug depots are used for prevention of tumor recurrence after surgery to eradicate remaining tumor cells. Clinical success has been reported for the treatment of brain cancer and liver cancer, and preclinical studies showed proof-of-concept for inhaled drug depots in lung cancer and intraperitoneally injected depots for the treatment of abdominal cancer.

Introduction

Cancer remains one of the world's most overwhelming diseases and, according to WHO, cancer is about to overtake cardiovascular disease as the main cause of death worldwide, accounting for more than eight million deaths annually (http://www.who.int/). Systemic chemotherapy has an important place in the clinical management of cancer. However, owing to exposure of normal tissues to anticancer drugs, which are typically administered at high drug doses, severe dose-dependent toxicities are unavoidable [1]. Moreover, inefficient treatment of tumors using systemic chemotherapeutics (e.g. exposure of tumor to sub-lethal drug concentrations) will result in the selection of drug-resistant tumor cells, making effective anticancer therapy even more problematic [2].

Surgery is the preferred treatment for most solid tumors. However, complete surgical resection is not possible in many cases because occult tumor nodules can remain undetected, eventually resulting in tumor recurrence. Consequently, locoregional recurrence of tumors after surgery has been reported for many cancer types including brain [3], colon [4] and lung [5]. Therefore, to overcome the lack of specificity of conventional chemotherapeutic drugs and to prevent tumor recurrence after surgery, localized chemotherapy using polymeric drug depots is considered a valuable approach. Drug-loaded microparticles offer several advantages over conventional dosage forms, such as improving duration of action for short-half-life drugs, bypassing different biological barriers in the body by direct administration into the target organ (e.g. via intratumoral implantation or adjacent to the tumor) and sustaining action of the drug over a long period of time [6–9]. Most of the examples in this review are drug depots based on polymeric microparticles that can be either injected or inhaled as such, or compressed into polymeric wafers. Figure 1 shows the rationale for locoregional chemotherapy over conventional systemic chemotherapy for the treatment of solid tumors. High drug concentrations at the site of disease and lower drug distribution to the surrounding healthy tissues are basic concepts behind intratumoral injection or implantation of a drug depot close to the cancerous lesions [10,11]. In this review, clinical and preclinical studies on local drug delivery for the treatment of cancer types are discussed. Four types of cancer have been treated in this manner (i.e. brain cancer, lung cancer, intraperitoneal cancer and liver cancer; Fig. 1). Table 1 provides

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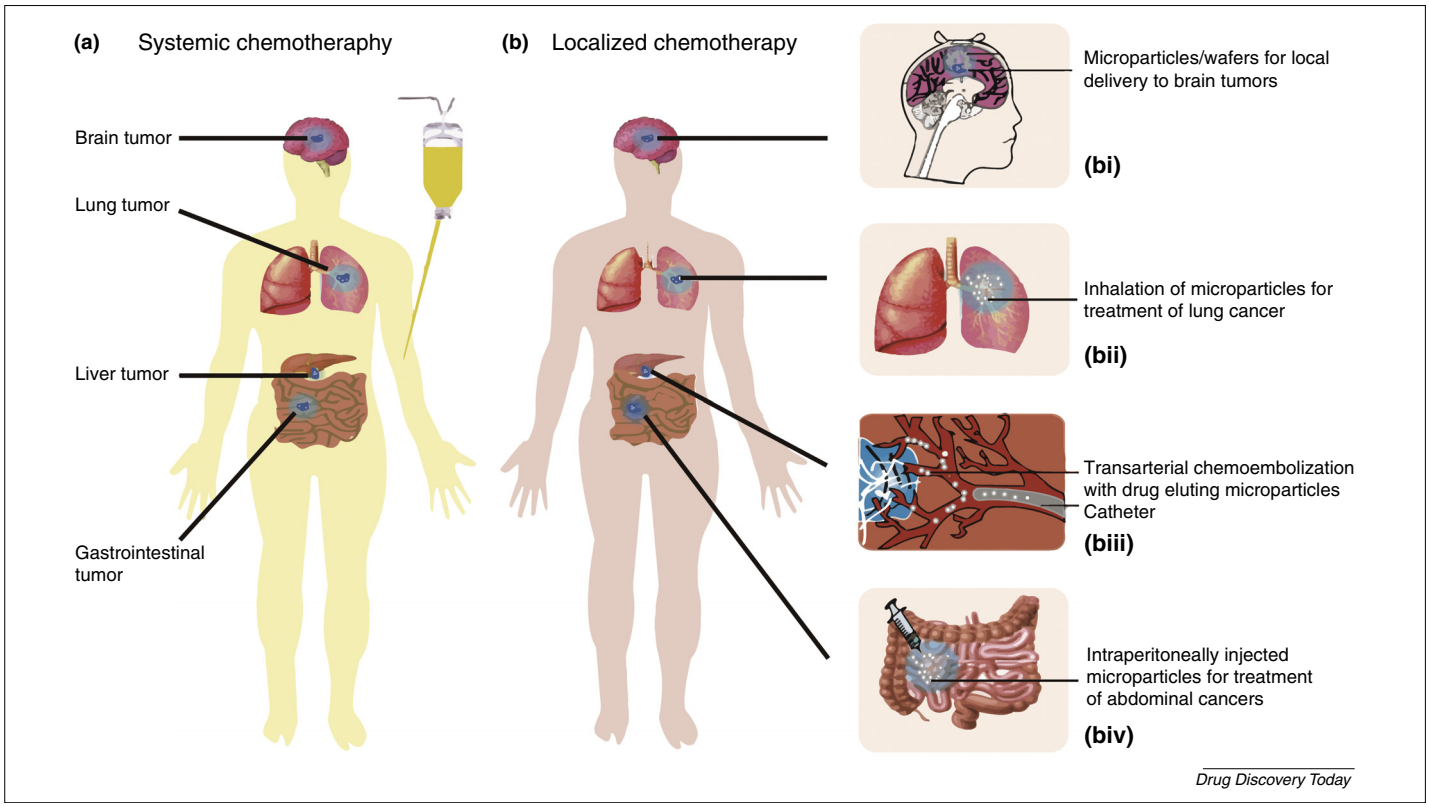

FIGURE 1

Local treatment of cancer by drug depots. **(a)** Types of cancer discussed in this review. **(b)** Local chemotherapy. High drug concentrations in the tumor nodules are effectuated by the local depot and less chemotherapeutic is distributed to other tissues. **(bi)** Local drug delivery for the treatment of brain cancer by drug-loaded polymeric wafers. **(bii)** Local drug delivery for the treatment of lung cancer by inhalation of drug-loaded microparticles. **(biii)** Transarterial catheter chemoembolization with drug-loaded microparticles for the treatment of liver cancer. **(biv)** Intraperitoneal chemotherapy using drug-loaded microparticles for the treatment of abdominal cancers.

an overview of the different types of drug-eluting depots that are discussed.

Localized anticancer therapy of brain cancer by intratumorally implanted depots

The blood–brain barrier (BBB) is a huge obstacle for treating brain tumors, because it prevents drugs from entering the brain parenchyma by its tightly connected cell layers that express a multitude of multidrug-resistance proteins [12,13]. Surgical resection, radiotherapy and chemotherapy are current treatments for malignant gliomas [12]. Resection is not efficient for long-term tumor control because recurrences often happen within centimeters of the original resection cavity, suggesting that tumor cells have invaded deep into the surrounding brain tissue. Carmustine is a frequently used drug to treat brain cancer. However, upon intravenous administration carmustine has a circulation half-life of only 12 min and its systemic levels cause damage to other, nontarget organs [14]. Therefore, locally controlled release of carmustine was investigated by Langer and Brem in the early 1980s. They developed Gliadel® wafers which are drug depots based on a matrix of a biodegradable polymer poly[1,3-bis(carboxyphenoxy)propane-*co*-sebacic-acid (PCPP-SA 20:80) loaded with carmustine [14]. The drug was first loaded into PCPP-SA microspheres using spray-drying, and subsequently the drug-loaded microspheres were compression-molded to form wafers for filling the resection cavity.

Gliadel® wafers released carmustine *in vitro* (buffer 37°C) and *in vivo* (rat brain) over a period of approximately 7 days [15,16]. Domb *et al.* [16] investigated the degradation of radiolabeled Gliadel® wafers in rabbit brain. It was shown that 74% of carmustine and 80% of SA was released from the polymer matrix in about 7 days, leaving behind the water-insoluble 1,3-bis(carboxyphenoxy)propane (CPP) copolymer. After a lag phase of about 9 days, the CPP copolymer started to degrade, and about 60% of the CPP was cleared from the implantation site within 3 weeks. It was suggested that the anhydride linkages in the more hydrophilic SA-containing blocks degrade faster than the anhydride linkages in the blocks containing the more hydrophobic CPP diacids. It was further shown that PCPP-SA was completely eliminated *in vivo* over a period of 6–8 weeks [15,16]. Following surgical removal of the primary brain tumor, about eight Gliadel® wafers can be deposited in the brains of patients within the resection cavity [17]. In a clinical study, Gliadel® wafers (along with surgery and in some cases radiotherapy) showed 29% death risk reduction in the patients ($n = 240$) with high-grade glioblastoma multiforme (GBM), the most aggressive form of brain cancer [18]. Median survival improved from 11.6 months in placebo-treated patients to 13.8 months in patients treated with Gliadel®. The survival advantage compared with the placebo was maintained at the first (59% vs 49%), second (16% vs 8%) and third (9% vs 2%) year and was statistically significant at the third year. Of all patients, two

TABLE 1

Examples of polymeric drug depots for the loco-regional treatment of cancer

Types of cancer	Drug	Type of carrier	Route of administration	Clinical trial or animal model	Remarks	Refs
Brain cancer	Carmustine	Gliadel® wafer	i.c.	Clinical trial	Improved survival from 11.6 months (placebo) to 13.8 months	[18]
	Carmustine + temozolomide	Gliadel® wafer	i.c. and oral	Clinical trial	Combination of local Gliadel® with oral temozolomide was more effective than monotherapy	[19]
	Minocycline + temozolomide	PCPP-SA wafer	i.c. and oral	Sprague–Dawley rats	Combination of local minocycline with oral temozolomide was more effective than monotherapy	[20]
	Paclitaxel + radiotherapy	Polilactofate Ms	i.c.	Sprague–Dawley rats	Paclitaxel was an effective radiosensitizer	[3]
	Imatinib	PLGA Ms	s.c. and i.c.	Swiss nude mice	Significant reduction in tumor size without any signs of toxicity	[7]
Lung cancer	Doxorubicin	PLGA Ms	Inhalation	C57BL/6 mice	Reduced the tumor mass and number of metastases	[30]
	Doxorubicin and TRAIL	PLGA Ms	Inhalation	Balb/c nu/nu mice	Synergistic effect by combination therapy using doxorubicin microspheres coated with Apo2L/TRAIL	[35]
Liver cancer	Doxorubicin	DEB	TACE	Clinical trial	Higher survival compared with conventional TACE	[46]
	Sunitinib	DEB	TACE	Rabbits	High local drug concentration until 24 hours	[51]
	Norcantharidin	Gelatin Ms	TACE	Sprague–Dawley rats	Higher survival rate compared with either free drug or embolization by blank microspheres	[41]
Abdominal cancer	Cisplatin	Gelatin Ms	i.p.	Balb/c mice	Higher survival compared with treatment with free drug	[11]
	Cisplatin	PLGA Ms	i.p.	Balb/c nu/nu mice	Significant tumor growth inhibition	[55]
	Paclitaxel	PLGA Ms	i.p.	Balb/c nu/nu mice	Higher drug concentration in peritoneal tumors and lower toxicity compared with paclitaxel/cremophor	[57]
					Slow drug distribution into systemic circulation	[59]

Abbreviations: i.c., intracranial; s.c., subcutaneous; i.p., intraperitoneal; DEB, drug-eluting beads; TACE, transarterial chemoembolization; Ms, microspheres; PCPP-SA, poly[1,3-bis(carboxyphenoxy) propane-*co*-sebacic-acid; PLGA, poly(lactide-*co*-glycolide); TRAIL, tumor-necrosis-factor-related apoptosis-inducing ligand.

patients from the Gliadel®-treated group survived after 56 months of follow-up study.

The efficacy of Gliadel® can be further improved by the combination with either radiotherapy or chemotherapy [19]. McGirt and colleagues compared the combination of Gliadel® plus radiation with that of Gliadel® plus radiation plus oral administration of temozolomide (TMZ) after primary resection of the brain tumor. It was found that the combination therapy with TMZ prolonged the median survival of patients ($n = 30$) up to 21 months whereas the control group ($n = 70$) showed 12 months median survival [19]. The authors suggested that systemic TMZ, an alkylating antineoplastic agent, is most effective in the vascularized regions of the tumor, whereas local delivery of carmustine using Gliadel® wafers allows direct access of the drug to the tumor, independent of vascularization. In another study, PCPP-SA wafers loaded with minocycline, an antibiotic that also showed antiangiogenic activity *in vitro*, were combined with either oral TMZ or radiotherapy [20]. Local delivery of minocycline in this combination therapy approach improved the median survival in rats bearing 9L gliomas by 38% and 139%, respectively, compared with oral TMZ and radiotherapy alone.

Recently, in rats implanted with intracranial 9L gliosarcoma, local delivery of paclitaxel using microspheres based on polylactofate (a copolymer of polylactide and a phosphoester), following radiotherapy, demonstrated a synergistic improvement in survival compared with other treatments including radiotherapy alone,

paclitaxel-loaded microspheres alone and radiotherapy followed by treatment with paclitaxel-loaded microspheres. It was concluded that pretreatment with locally injected paclitaxel-loaded microspheres is effective as a radiosensitizer for malignant gliomas [3].

Some studies indicated that platelet-derived growth factor receptor (PDGFR) contributes significantly to angiogenesis associated with malignant gliomas, and inhibition of PDGFR results in tumor growth arrest [21]. Imatinib mesylate (Gleevec®) is a molecularly targeted drug known to block the activity of PDGFR and has been approved by the FDA for the treatment of chronic myeloid leukemia as well as gastrointestinal stromal tumors [22]. To show the feasibility of a local release formulation of imatinib for the treatment of brain cancer, Benny *et al.* [7] prepared imatinib-loaded poly(lactide-*co*-glycolide) (PLGA) microspheres. PLGA is a frequently used biodegradable polymer for the development of sustained release drug depots because of its biodegradability and biocompatibility [23–25]. Imatinib-loaded PLGA microspheres were evaluated in subcutaneous (s.c.) and orthotopic human glioblastoma xenografts and syngeneic murine tumor models [7]. Five days after tumor inoculation, a single dose of microspheres with a dose of 1.25 mg imatinib was injected at two sites into the tumor. This local administration of imatinib microspheres resulted in a significant reduction of tumor size: 88% and 79% in s.c. human (U87-MG) and murine (GL261) glioma tumors in mice, respectively. Apart from s.c. tumor models, intracranial administration of imatinib microspheres resulted in 79% reduction in tumor (human U87-MG cells inoculated in mice) size 14 days post injection. In addition, no signs of toxicity were observed in harvested organs (liver, kidney, brain, heart, muscle, spleen) upon administration of PLGA–imatinib microspheres. A significantly lower total dose of imatinib microspheres (1.25 mg single dose of imatinib (in microspheres) after local delivery vs 30 repeated doses of approximately 1.5 mg imatinib/day after systemic dosing) achieved similar antitumoral effects in comparison to systemic intraperitoneal injections [26]. From these studies it can be concluded that possible systemic toxicity can be minimized by local drug delivery.

A major hurdle regarding local treatment of brain cancer is the limited drug penetration into the cancerous tissue. Fung *et al.* [27] noted only a short diffusion distance (<0.3 mm) for carmustine encapsulated in a monolithic implant in rat brains. Wang *et al.* [28], using a mathematical model, established that carmustine gets drained out of the implantation site before being able to diffuse to an appreciable distance; this was ascribed to the high transvascular permeability for the drug. Roullin *et al.* [29] studied the distribution of the antimetabolite 5-fluorouracil in the brain tissue of rats implanted with ^{3}H-labeled drug that was loaded into PLGA microspheres. They showed that drug diffusion was limited to the vicinity (~3 mm) of the implantation site. One way to compensate for the short diffusion distance of drug molecules from their injection site is multipoint administration of drug-loaded microparticles to maintain a therapeutic concentration of the drug within the resection margin.

Treatment of lung cancer by inhalable drug depots

Accounting for about 27% of all cancer deaths, lung cancer is by far the leading cause of cancer-related deaths among men and women (http://www.cancer.org), and ≥90% of lung cancer death is attributed to metastases [30]. In addition, lung cancer is associated with a high percentage of local recurrence after surgical resection [31]. Therefore, local pulmonary delivery of anticancer drugs by inhalation could offer important advantages including high local drug concentration and better patient compliance compared with systemic administration.

Frequent drug administration via the pulmonary route can be inconvenient for lung cancer patients who normally encounter problems with breathing. Thus, the development of inhalation delivery systems that prolong the release of a cytotoxic drug is of great importance. For deposition in the lungs, microparticles should have special characteristics such as a suitable mass median aerodynamic diameter and a proper fine particle fraction [32]. Particles with low density (<0.4 g/cm^3) and mean particle size of approximately 3 μm show deep lung deposition [33]. However, such particles can be easily taken up by lung macrophages [32]. For these reasons, large porous particles with mean particle size of 5–30 μm are preferred for pulmonary delivery [34].

Recently, Kim *et al.* [30] developed highly porous doxorubicin-loaded PLGA microparticles (Dox-PLGA-Ms) with good aerosolization characteristics. The mean particle size was 14 μm, and mass median aerodynamic diameter was 3 μm. Ammonium bicarbonate was used as a gas-forming porosigen in the formulation [30]. An *in vitro* study showed that these microspheres released doxorubicin over 14 days (Fig. 2a). When administered to mice, the deposition of the particles in the lungs and the subsequent redistribution of doxorubicin were visualized using a Maestro 2 *in vivo* imaging system by making use of the intrinsic fluorescence of doxorubicin. The microspheres were deposited in the central lungs (i.e. bronchi to bronchioles), and then gradually spread throughout the lungs of C57BL/6 mice and remained there over 14 days (Fig. 2d). However, it is debatable whether the observed fluorescence belongs to the drug-loaded microparticles or the released drug from the microparticles. Pulmonary administered Dox-PLGA-Ms significantly reduced the tumor mass and the number of metastases in a mouse model of B16F10 melanoma metastasis [30]. It should, however, be mentioned that the authors did not evaluate the effect of free doxorubicin administered systemically as a positive control group.

Kim *et al.* [35] also developed Dox-PLGA-Ms coated with tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL). TRAIL initiates apoptosis by binding to proapoptotic receptors named as death receptors, which are expressed in several malignant cell types [36]. TRAIL, a positively charged protein at pH 7, was adsorbed onto the surface of PLGA particles by ionic interactions. For this purpose, the microspheres were prepared using poly(ethylene-*alt*-maleic anhydride) as the emulsifier, resulting in particles with a negative zeta potential because of the hydrolyzed anhydride groups. It was shown that Dox-PLGA-Ms (11 μm) coated with TRAIL released this protein faster than Dox; about 90% of TRAIL was released within 3 days whereas 60% of doxorubicin was released at the same time. Tumors in H226-implanted mice treated with TRAIL-coated Dox-PLGA-Ms were significantly smaller and fewer in number than those in groups treated with TRAIL or P-Dox-PLGA-Ms alone. This improved efficacy was ascribed to the synergistic apoptotic effects between TRAIL and doxorubicin.

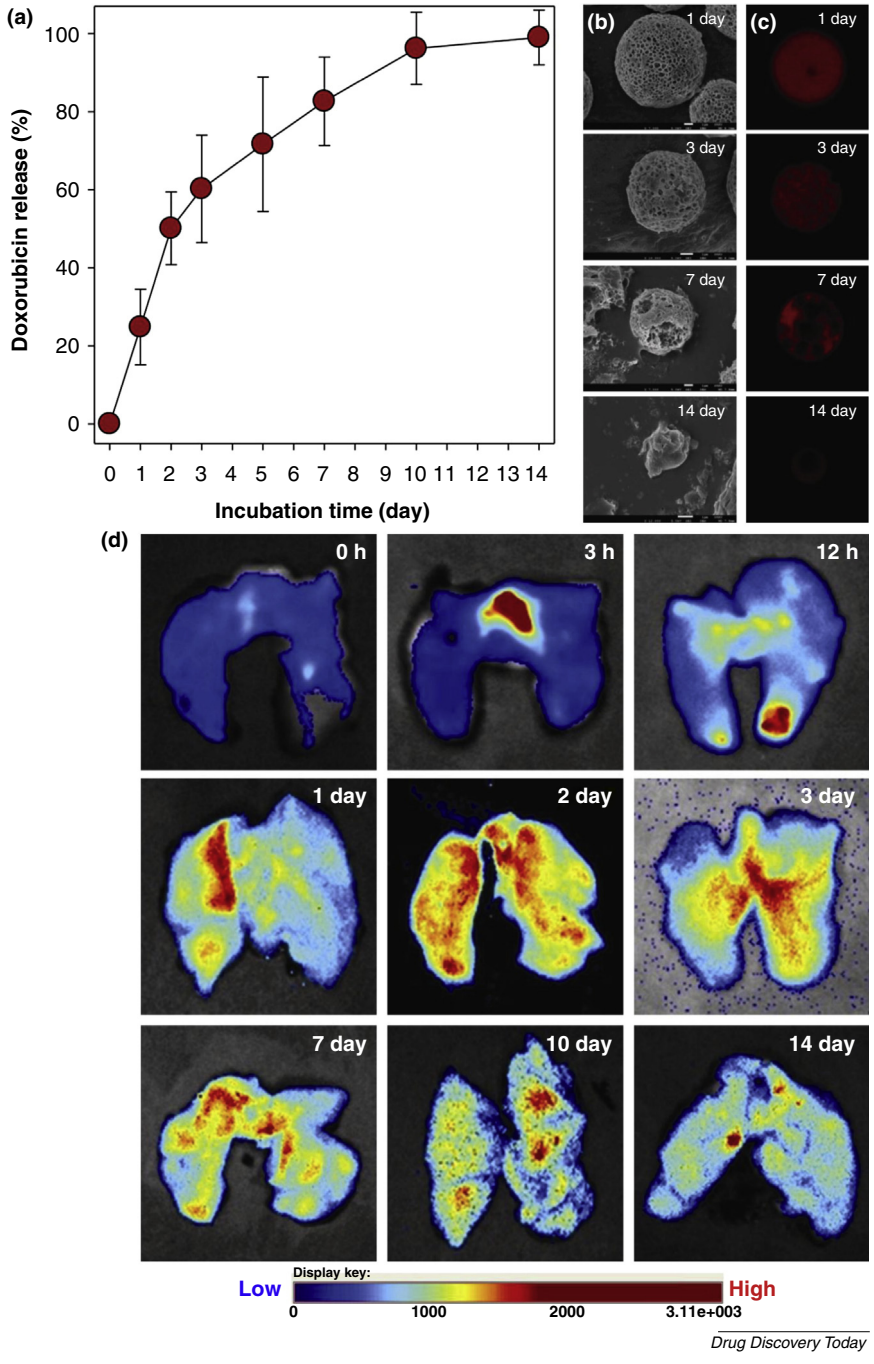

FIGURE 2

Doxorubicin-loaded porous microparticles for pulmonary delivery to lung cancer. **(a)** *In vitro* doxorubicin release from porous microparticles. **(b)** Scanning electron microscopy images of porous doxorubicin–poly(lactide-*co*-glycolide) (PLGA) microspheres at different times of the release study. **(c)** Confocal laser scanning fluorescence microscopy images of the same microspheres showing doxorubicin in the microparticles. **(d)** Lung deposition of doxorubicin-PLGA microspheres in C57BL/6 mice visualized by *in vivo* imaging using a red-green-blue (RGB) spectrum until 14 days post-administration. At 3 hours after administration, microspheres appeared to be located at the center of lungs, and then spread throughout the lungs.
Reprinted, with permission, from [35].

Treatment of liver cancer by transarterial chemoembolization

Hepatocellular carcinoma (HCC) accounts for approximately 5% of all cancers. Liver transplantation is considered as the best treatment option for HCC. However, when patients are not good candidates for curative surgical therapy, they can also be treated with transarterial chemoembolization (TACE) [37,38]. TACE is a minimally invasive targeted therapy for the treatment of various types of liver tumors [39,40]. In the conventional setting, using a thin catheter and X-ray imaging for guiding, a mixture of chemotherapy (e.g. doxorubicin or epirubicin) and a radio-opaque contrast agent (lipiodol) are injected into the vessels that supply the tumor. This is followed by injecting embolic particles (40–1000 μm) to induce hypoxia of the tumor by blocking its

blood supply [37,39,41]. Polymers such as polyvinyl alcohol, starch, gelatin, PLGA, chitosan and hydroxyethylacrylate are currently used for the preparation of embolic particles in preclinical studies and clinical studies [42].

Recently, drug-eluting beads (DEBs), which are embolic particles loaded with cytostatic drugs, have been developed to improve the efficacy of conventional TACE. Commercially available DEBs (DC Beads®, Biocompatibles UK) are microgels (100–1000 μm) based on a cross-linked copolymer of vinyl alcohol and 2-acrylamido-2-methylpropanesulfonate sodium salt, prepared using an inverse suspension polymerization method [43]. These negatively charged microspheres can load protonated drugs such as doxorubicin by displacing the sodium ions and binding through electrostatic interactions to the sulfonate groups. Once localized in the liver, the loaded drug is eluted from the beads to locally exert its cytostatic activity [44]. Dox–DEB released 43% of their initial payload after 28 days and 89% after 90 days in a pig model [45]. It has been demonstrated that treatment with Dox-DEB-TACE provided a survival advantage over conventional TACE (C-TACE) combined with free doxorubicin [38,46]. For example, in a clinical study by Dhanasekaran *et al.* [46], patients with unresectable HCC were treated with either doxorubicin-eluting Dox-DEB-TACE or drug-free beads that only occlude the tumor blood vessels (C-TACE). The beads varied in size (from 300 to 500 and 500 to 700 μm) depending on the tumor burden, vascular supply and macrovascular invasion. Median survival times of patients in the Dox-DEB-TACE-treated group and those in the group treated with C-TACE were 610 and 284 days, respectively, indicating that the Dox-DEB-TACE formulation was superior to C-TACE. Furthermore, in another clinical study by Nicolini *et al.* [38] on 38 liver transplant candidates with HCC, the three-year recurrence-free survival after liver transplantation was higher in patients who were treated with Dox-DEB-TACE compared with C-TACE (87.4% vs 61.5%). By contrast, a randomized clinical study (177 HCC patients divided into two groups) performed by Golfieri *et al.* [47] showed that C-TACE and Dox-DEB-TACE were equally effective: 1- and 2-year survival rates were 86% and 56% after Dox-DEB-TACE and 83% and 55% after C-TACE treatment. In this study, compared with the previous studies of Dhanasekaran *et al.* [46] and Nicolini *et al.* [38], the number of patients was higher. Moreover, a recent meta-analysis based on seven studies (total 693 patients) revealed that there was no difference in tumor response between the two procedures [48]. Therefore, the routine use of Dox-DEB-TACE in clinical practice is debatable, and further studies are, consequently, needed to show the advantage of Dox-DEB-TACE over C-TACE.

Incomplete killing of the tumor cells and hypoxic conditions induced by embolization can transform cancer cells into even more aggressive types [49,50]. Therefore, administration of DEBs that release antiangiogenic drugs might be an option for the treatment of liver cancer. Recently, sunitinib, an inhibitor of tumor vessel growth, was loaded into negatively charged PVA-based DC Bead® (100–300 μm) by charge interaction (sunitinib $pK_a \sim 9$) [51]. Drug loading was almost 100%, and the DC Bead® released sunitinib for about 8 hours in an *in vitro* study in saline. As expected, after administration of the sunitinib-loaded PVA beads via a catheter to hepatic artery of healthy rabbits, sunitinib concentrations in the liver were relatively high for 6 hours (14.9 μg/g) and 24 hours (3.4 μg/g) when compared with orally administered sunitinib (4.2 μg/g after 6 hours and 2.6 μg/g after 24 hours). The therapeutic efficacy of sunitinib-loaded PVA beads in liver cancer models has to be evaluated in future studies.

Future advances in material science and pharmaceutics will open new avenues for research in the field of chemoembolization. For example, imageable DEB–TACE (using contrast agents that are chemically attached or physically loaded into the beads) could provide a better understanding of the distribution of the bead in the target organ (tumor) and, therefore, allow tailoring of the procedure to a specific patient. It has been reported that tumor blood vessel diameters are different suggesting a need for tailoring bead size to the tumor arterial anatomy [52]. Furthermore, combination of other novel chemotherapeutics such as idarubicin, which was more potent than Dox on HCC cell lines [53], or antiangiogenic agents (to reduce hypoxia-induced angiogenesis by embolization), in combination with cytostatic drugs, can be possible options to improve the treatment of liver cancers further.

Treatment of abdominal cancer by intraperitoneally injected depots

In recent years, physicians have used intraperitoneal chemotherapy for better treatment of peritoneal carcinomatosis, which is the local recurrence of primary abdominal cancers such as colorectal, ovarian, gastric and pancreatic carcinoma [11]. For the treatment of peritoneal carcinomatosis in the clinic, chemotherapy of cisplatin, paclitaxel or carboplatin is often performed by administration of the drugs via intraperitoneal perfusion [54]. Intraperitoneal perfusion has major limitations including infection complications as well as mechanical bowel obstructions [55,56]. Therefore, researchers have focused on developing drug-loaded polymeric microparticles that can be administered as an intraperitoneal single injection [11,57,58]. The ideal drug delivery system for intraperitoneal chemotherapy must expose all cancerous areas or residual tumor cells to sufficient drug levels for a prolonged period of time. Recently, Gunji *et al.* [11] developed cisplatin (CDDP)-loaded gelatin microspheres (GM–CDDP) with a size of 20–70 μm. These microspheres were prepared by cross-linking (using glutaraldehyde) gelatin in a water-in-oil emulsion method [11]. Because cisplatin is a small molecule drug with good aqueous solubility, its release from strongly hydrated gelatin microspheres is expected to be governed mainly by diffusion. However, the release of cisplatin from these gelatin microspheres (after the small burst) was governed mainly by collagenase-triggered gelatin degradation. Most likely, there were strong physical interactions between the drug and the matrix. Mice with peritoneal carcinomatosis that had been injected with GM–CDDP intraperitoneally lived longer than mice treated with free cisplatin (median survival of 74 vs 40 days). Furthermore, the mice treated with GM–CDDP showed no weight loss and reduced nephrotoxicity compared with control mice treated with free cisplatin, which lost approximately 20% body weight. The lower systemic toxicity of the GM–CDDP formulation was attributed to its lower peak drug concentration in the kidney and blood. In another study, Lu *et al.* [57] showed that the intraperitoneal treatment with paclitaxel-loaded PLGA microspheres in a mouse model of ovarian cancer overcame the limitations of free paclitaxel therapy. In comparison with the commercial paclitaxel/cremophor formulation, the microspheres

showed 16-times higher drug concentration in peritoneal tumors, lower toxicity to intestinal crypts and less body-weight loss with longer survival at equal milligram doses [57].

The sizes of microparticles are crucial for the treatment of peritoneal carcinomatosis because small particles (<5 μm) can be phagocytized by macrophages or can be drained from the peritoneal cavity through the lymphatic capillaries because subdiaphragmatic lymphatic openings are about 3 μm in mice [59]. To illustrate this, Lu *et al.* [57] studied the effect of particle size of PLGA microspheres (4 and 30 μm, labeled with acridine orange) on their distribution after intraperitoneal injection in tumor-free mice. They found that 4 μm particles deposited over mesentery, omentum, diaphragm and lower abdomen, whereas the 30 μm particles were mainly localized in the lower abdomen near the injection site. Kohane *et al.* [60] investigated the effect of size on residence time of PLGA particles (265 nm to 250 μm) upon injection into the peritoneum of mice. They found that PLGA microparticles (>5 μm) remained there for at least 2 weeks, whereas nanoparticles of 265 nm were cleared from the peritoneum within 2 days and transported to the liver and spleen, where they were found in foamy macrophages. Based on these observations, larger microparticles seem most suitable for sustained drug release within the peritoneum because they are big enough to stay in the peritoneal cavity and are not drained via the lymphatics.

Tsai *et al.* [59] showed the advantages of paclitaxel PLGA microspheres (6 μm) over paclitaxel gelatin nanoparticles (0.9 μm) and the paclitaxel/cremophor formulation after intraperitoneal injection in mice. In comparison with cremophor and gelatin nanoparticles, the microparticle formulation showed slower drug clearance from the peritoneal cavity and slower absorption into the systemic circulation [about five-times lower peak plasma concentration and area under curve (AUC) at 24 hours post i.p. injection]. Moreover, the median survival (after i.p. injection of equal dose of 40 mg/kg) of mice that received microparticles was significantly higher than mice treated with gelatin nanoparticles, cremophor formulation or nontreated animals [59]. These preclinical studies suggest that polymer drug depots are efficient in delivering chemotherapeutics after intraperitoneal injection. In this respect, drug carriers that cause less tissue reaction with good biocompatibility and longer residence time after intraperitoneal administration are preferred.

Concluding remarks

This review shows that different cancers including lung, brain, peritoneum and liver can greatly benefit from local delivery of chemotherapeutics by sustained release depots. Locoregional chemotherapy, in clinical and preclinical studies, has been proven to enhance therapeutic efficacy and to diminish systemic toxicity associated with chemotherapeutics. Local drug administration can kill cancer lesions remaining at the resection margins thus reducing the rate of tumor recurrence. Further clinical studies are, however, needed to establish approaches for accurate and preferably minimally invasive implantation to reach desired sites.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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