Local Drug Delivery Strategies for Gastric Cancer Treatment

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Qin Liu and Baorui Liu

15.1 The Clinical Need for Localized Gastric Cancer Therapy

Gastric cancer is associated with poor patient prognosis and, as a result, is the leading cause of cancer-related death worldwide [1]. Systemic chemotherapy is the major treatment for locally advanced and metastatic gastric cancer, despite the fact that satisfactory clinical outcomes have not been reached with this approach. As such, exploring more effective modalities for gastric cancer management is necessary. Increasing evidence has shown that the most advanced gastric cancer patients ultimately die from local recurrence or metastasis. To this end, it has been reported that positive peritoneal washing cytology is a negative prognostic factor in patients with gastric cancer [2]. According to a phase II study, the 1-year survival rate after receiving treatment with modified FOLFOX-4 for 48 gastric cancer patients with malignant ascites was 27.2% [3]. Many advanced gastric cancer patients have died from local metastasis, especially peritoneum metastasis. Additionally, intraperitoneal chemotherapy has been proven to improve survival rates as well as decrease peritoneal recurrence in gastric cancer patients with peritoneal dissemination [4, 5].

Both systemic and local administrations of nanoparticles (NPs) have been shown to increase the sensitivity and effectiveness of gastric cancer management. Typically, NPs accumulate at the targeted solid tumor(s), either by passive diffusion via an enhanced permeability and retention (EPR) effect or through an active targeting moiety. Of these, actively targeted NPs are superior to those that are passively targeted NPs. This is due to their conjugation to the ligand of tumor cells overexpressed and/or a unique marker such as folic acid, a monoclonal antibody, and/or transferrin. These environment-responsive nanocarriers are then triggered to release the loaded drugs in response to tumor cell differences in pH and/or temperature. Generally, the ability of the nanomaterial to accumulate at the tumor site is the primary driving force behind the selected therapeutic drug concentrations, particularly for intravenous administration. That being said, the reticuloendothelial system can take up and remove most drug-loaded nanoparticles when given intravenously. Larger amounts of therapeutic drugs can also accumulate within several normal organs, especially the liver, spleen, and kidney. This limits the amount of drug that can actually accumulate at the tumoral sites. As

Q. Liu (✉) • B. Liu
The Comprehensive Cancer Center
of Drum-Tower Hospital, Medical School
of Nanjing University & Clinical Cancer
Institute of Nanjing University,
Zhongshan Road 321, Nanjing 210008,
People's Republic of China
e-mail: liuqinxh@126.com

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such, it is difficult to achieve sufficient chemotherapeutic drug concentrations within the targeted sites. Furthermore, satisfactory antitumor effects and reduced side effects are difficult to achieve due to the drug distribution and bioavailability. For example, when given intravenously, nearly 50% of paclitaxel is removed from the body 24 h post-administration with only 0.5% of the drug capable of accumulating at the targeted tumor. Importantly, intraperitoneal delivery of docetaxel has a pharmacokinetic advantage hundreds of times higher than when it is given intravenously [5].

The local administration of drug-loaded carriers is superior to systemic delivery in the following aspects: [1] easy loading of water-insoluble drugs and high loading efficiencies; [2] maintaining high local drug concentrations and allowing for controlled drug release; [3] prolonging drug retention and uptake into cancer cells; [4] decreasing administration times, thus improving patients' convenience; and [5] reducing side effects due to the less drug distribution in nontargeted organs. After intravenous administration, a large percentage of drug-loaded nanoparticles are taken up by several healthy organs, such as the liver, spleen, and kidney. Afterwards, only a small amount of drug will be distributed to the tumor site(s) themselves. However, the EPR effect can significantly influence the distribution of nanomedicine deposition in tumors and normal organs. Several other factors can influence the antitumor efficacy of nanodrugs, such as their inherent characteristics including size, shape, surface charge, hydrophilicity, and targeting functionality. The tumor microenvironment can also contribute to treatment toxicity and influence tumor blood vessels, interstitium penetration, and retention time at the site.

In order to minimize the systemic side effects posed by such drugs, it is necessary to allow for local delivery of the chemodrug. A series of studies have examined this issue, showing that such local delivery of drug carriers is highly effective at controlling recurrence or metastatic tumor growth in various local tumor recurrent animal models.

15.2 Intraperitoneal (IP) Delivery of Therapeutic Agents

Advanced gastric cancer patients usually die from peritoneal metastasis, which itself has a reported association with poorer patient prognosis. Given this, it is a pressing concern that systemic chemotherapy has only limited effectiveness on the control of gastric cancer metastasis. With this concern, intraperitoneal (IP) chemotherapy has emerged as a promising drug delivery approach, as it achieves high local drug concentrations for an extended period of time. Moreover, its route of delivery minimizes systemic exposure. Taxanes have a large molecular weight and high fat solubility. Noticeably, taxanes are absorbed through the openings of the lymphatic system, which are important locations for peritoneal dissemination formation. Given its promise for use in drug delivery, IP injections have been widely used in a variety of cancers. For instance, IP paclitaxel significantly increased local drug concentration 1000 times that than of systemic administration. For this reason, NCCN recommends that patients with metastatic cancer should receive intraperitoneal chemotherapy.

The peritoneal barrier includes blood capillary endothelium and cellular-interstitial matrix. Collectively, these barriers provide the major form of physical resistance to drug penetration. Several recent studies have confirmed that both the interstitium and capillary endothelium are major barriers in peritoneal carcinoma patients undergoing partial or total peritonectomy. Flessner et al. [6] explored peritoneal transport physiology in detail (Fig. 15.1). The residence time in the peritoneal cavity for systemically injected, small-molecular-weight agents is too short to allow for absorption through the peritoneal capillaries [7]. Therefore, this drug delivery approach does not allow for high or long-lasting therapeutic agent concentration at the targeted sites [8]. Thus, there has been a global research push to develop new techniques to overcome these biological limitations to yield efficient therapeutic results.

Keeping high and long-lasting local drug concentration is necessary for successful and efficient IP therapy [7]. Drugs with a small molecular weight (<20 kDa) enter circulation through peritoneal capillary absorption. The drug is then quickly removed

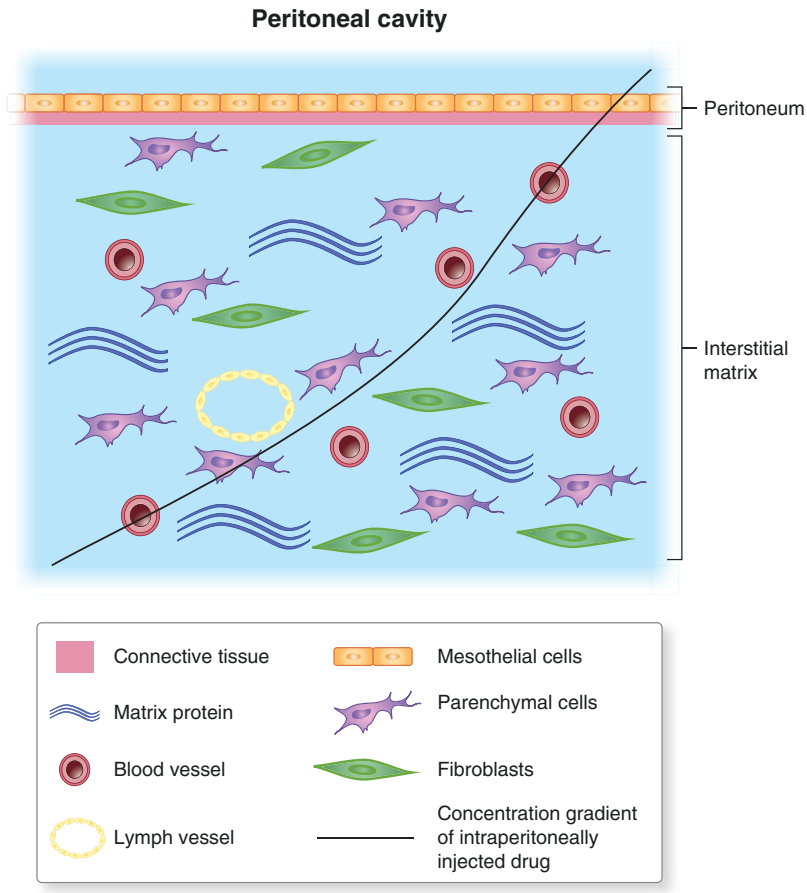

Fig. 15.1 The blood capillary endothelium and the cellular-interstitial matrix are major barriers to efficient drug transport. When compared with the mesothelium, the interstitium and capillary barriers play greater roles in possessing insignificant barrier properties (Adapted from Intraperitoneal delivery of nanoparticles for cancer gene therapy (2013), Hallaj-Nezhadi S et al. [6])

from circulation, and its residence time in the peritoneal cavity is not sufficient to get either high or long-lasting drug concentrations. In order to get satisfactory cytotoxicity, frequent or continuous dosing is required. However, this increased frequency can lead to catheter-related problems, increased risk of infection, and bowel complications in patients. Small molecular weight drugs do show systemic circulation. Pharmacokinetic studies in animals have shown that IP taxane (docetaxel or paclitaxel) was quickly cleared within 24 h from the peritoneal cavity. In addition, many free drugs are usually coupled with severe side effects. For example, Cremophor EL (Cr-EL) and dehydrated ethanol are usually used to increase paclitaxel solubility to get solvent-based PTX (Sb-PTX: Taxol®). Due to the large amount of Cr-EL added as well as the nonspecific drug biodistribution in other healthy organs, Sb-PTX has been reported to have moderated antitumor efficacy and severe side effects including hypersensitivity reactions, bone marrow suppression, and neurotoxicity.

With this in mind, nanoparticle albumin-bound paclitaxel (nab-paclitaxel, Abraxane®) [9] has been designed to address the aforementioned problems. Since it is an albumin-bound, 130-nm particle, neither ethanol nor Cr-EL is required. In animal models, Abraxane exhibited superior antitumor advantages and a more favorable safety profile when compared to free PTX. In the clinic, a randomized Phase II study investigated the overall response and the disease control rates for unresectable or recurrent gastric cancer patients treated with nab-paclitaxel. Results indicated responses of 27.8% and 59.3%, respectively [10]. Interestingly, one patient had a response rate of 100%. The median progression-free survival was 2.9 months, and overall survival time was 9.2 months. Recently, Kinoshita et al. [11] evaluated the therapeutic efficacy of

nab-paclitaxel and free drug Sb-PTX on gastric cancer cell-bearing nude mice xenografts. Using this peritoneal metastatic xenograft model, nab-paclitaxel showed greater efficacy than Sb-PTX at equal doses when given as an IP injection. Compared with IP Sb-PTX, nab-paclitaxel treatment exhibited a better tumor suppression on both subcutaneous tumor size and ascites burden ($p < 0.05$).

Recently, thermosensitive hydrogel has attracted attention as a drug delivery method since it is a stimuli-responsive material. This is particularly true for local region administration [12]. At specified temperatures, thermosensitive hydrogel undergo a sol-gel transformation. Moreover, thermosensitive hydrogels are easy to load either with hydrophilic or hydrophobic drugs. This loading occurs with high loading efficiency, and the gel allows for controlled drug release behavior. In addition, thermosensitive hydrogels are easily acceptable to patients because they exist in one state when the temperature is lower than the sol-gel transition temperature [13] (Fig. 15.2).

In order to treat peritoneal dissemination of gastric cancer, Bae et al. [14] prepared a thermo-responsive hydrogel based on poloxamer and linoleic acid-coupled Pluronic F127 (Plu-CLA). At room temperature, Plu-CLA exists in a liquid state, but is rapidly converted to a gelatin state at body temperature. Docetaxel was successfully encapsulated in the Plu-CLA and exhibited a controlled release profile. Intraperitoneal administration of docetaxel-Plu-CLA (Doc-Plu-CLA) showed better antitumor advantages than free drug administration, as evidenced through induction of apoptosis and a reduction in the number of peritoneal metastatic nodules. In addition, the Doc-Plu-CLA-treated peritoneal gastric cancer xenograft mice had the longest median survival time (Fig. 15.3). Taken together, these results show that IP Doc-Plu-CLA administration significantly inhibits peritoneal metastasis and prolongs survival in a xenograft mouse model of gastric cancer.

As a local treatment option, photodynamic therapy (PDT) consists of activating a photosensitizing agent using a specific laser wavelength [15]. Since photosensitizing agents allow for accumulation specifically at tumor sites, PDT

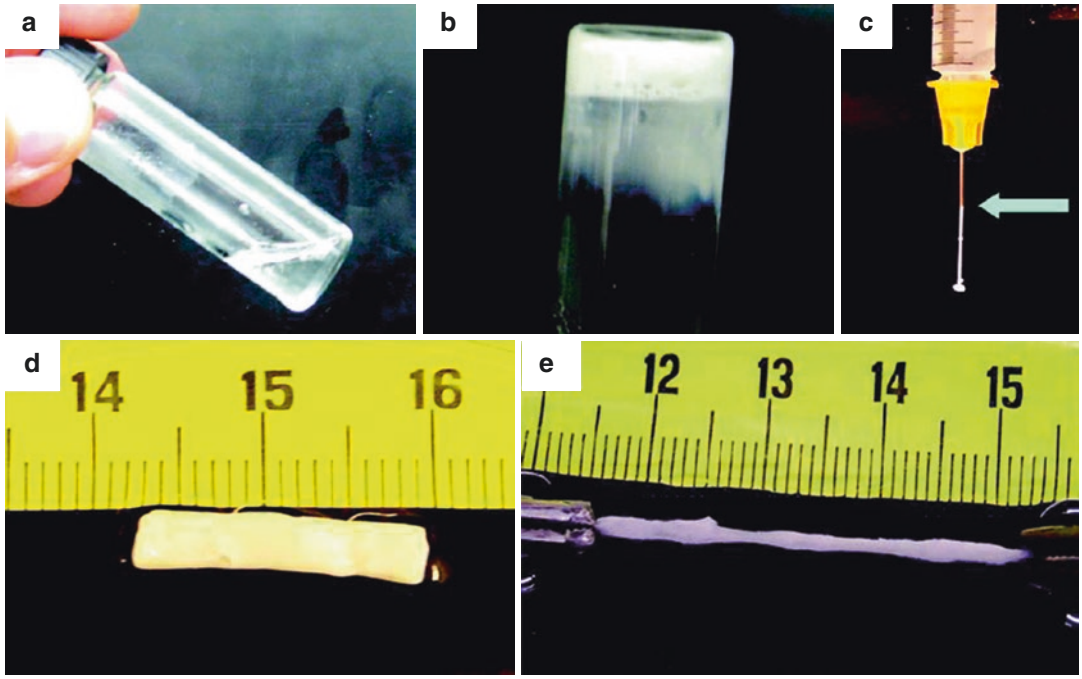

Fig. 15.2 (**a**) Thermosensitive gel is liquid at 4 °C. (**b**) Gelation at 37 °C. (**c**) Thermosensitive gel is easily injectable through a 26-gauge needle. (**d**–**e**) Thermosensitive gel is flexible at 37 °C. Reproduced with permission from Ref. [13]

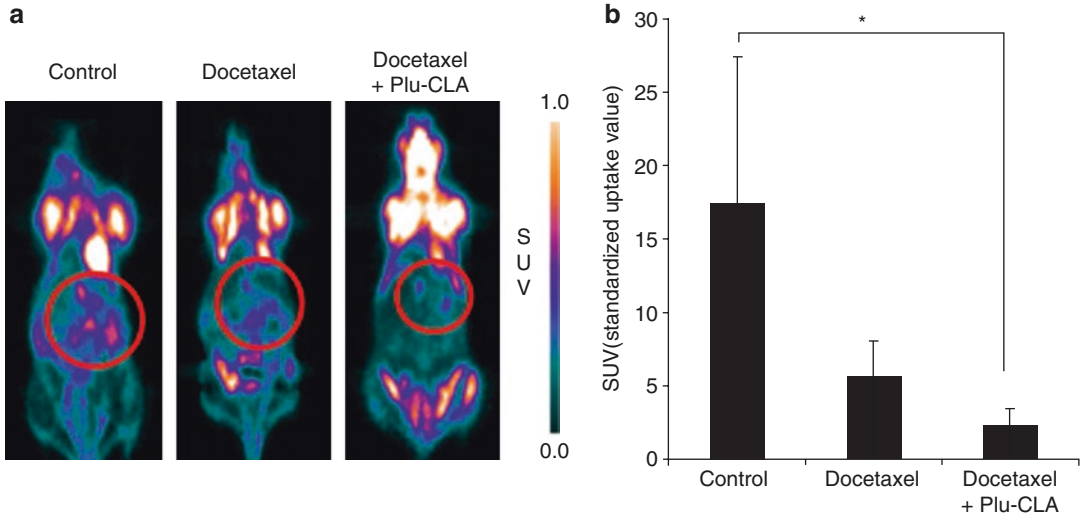

Fig. 15.3 ^{18}F-FDG PET image of mice with peritoneal metastases. (**a**) Tumoral ^{18}F-FDG uptake (*circle*) based on microPET images. (**b**) Comparison of ^{18}F-FDG SUV uptake in the control, docetaxel- and Doc-Plu-CLA-treated groups. *$p < 0.05$. Reproduced with permission from Ref. [14]

showed fewer side effects and reduced damage to normal tissue. When compared with either radiation or chemotherapy, PDT also rarely induced drug resistance. Due to the above advantages, PDT has been widely used to treat gastric, breast, and lung cancers, among other diseases. Tsujimoto et al. [16] prepared indocyanine green (ICG) derivatives-loaded nanoparticles and ICG-loaded lactosomes (ICGm) in order to investigate their PDT theranostic value in the mice model of experimental peritoneal dissemination of gastric cancer. After photodynamic therapy, the median survival time in ICGm- and ICG-treated mice was 32 days and 17 days, respectively. Moreover, body weight loss in ICG-treated group was significantly greater than that in ICGm-treated mice ($p < 0.05$). This result was taken as an indication of the safety of ICGm treatment.

15.3 Intratumoral Delivery of Therapeutic Agents

Local intratumoral delivery of chemotherapeutic agents is likely to provide better drug localization within the targeted tumor, thereby reducing systemic exposure to healthy organs. This would lead to increased efficacy and lower toxicity than treatment with aqueous, free drug solutions. To this end, Al-Abd et al. [17] prepared an injectable, thermosensitive hydrogel to deliver the anticancer drug doxorubicin (DOX). During their experiment, 0.6% of DOX was loaded into a 10% reversible thermal poly(organophosphazene) (PPZ) hydrogel that was capable of body temperature-dependent transformation. An in vitro release study showed that a initial burst drug release in the first few hours after administration. However, DOX was released in vivo in a controlled and sustained manner over a 5-week period. The hydrogel mass was not completely degraded over 7 weeks (Fig. 15.4). It should be noted that an initial burst effect is beneficial for fast control over tumor growth, with the subsequent sustained release ensuring long-lasting tumor control. The PPZ hydrogel was then given intratumorally in a human gastric tumor xenograft mice model. In this case, the tumor T1/T2 for locally and systemically administered DOX was 2.6 days to 4.6 days, respectively, showing successful increase in local drug retention. Moreover, the data suggest that the hydrogel decreased systemic exposure and cardiac toxicity. The longer tumor DOX exposure levels obtained in the hydrogel delivery system mean better antitumor

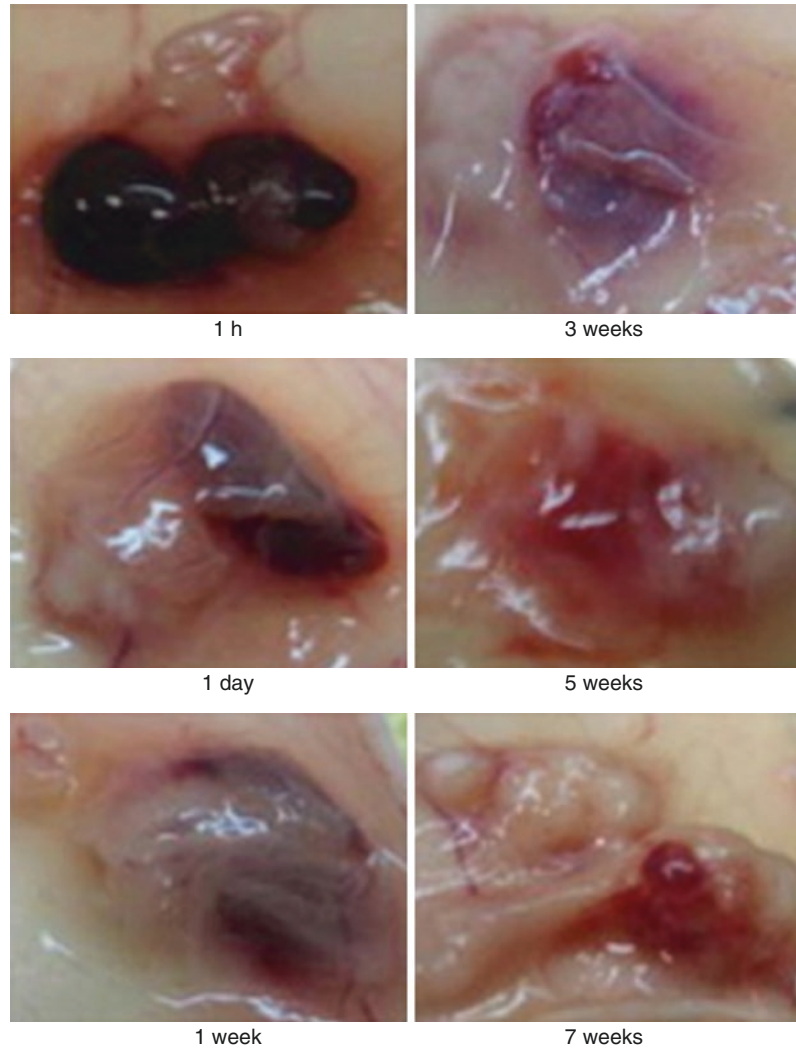

Fig. 15.4 DOX-loaded hydrogel contacted the tumor as a mass with a well-defined margin. Reproduced with permission from Ref. [17]

efficacy. After a single intratumoral administration, the DOX hydrogel formulation controlled gastric cancer size for up to 49 days without significant signs of toxicity.

Combination chemotherapy has become an important option for advanced gastric cancer treatment. Coadministration of DOX and PTX formulations using PPZ thermosensitive hydrogel has been assessed for the in vivo antitumor efficacy in local tumor management in human gastric cancer cell-xenografted mice [18]. Following intratumoral injection of PPZ into human SNU-601 gastric cancer cell-bearing mice, the combined DOX (15 mg/kg) and PTX (30 mg/kg) containing hydrogel resulted in the highest tumor inhibition in the tested experimental groups. The PTX-DOX hydrogel was injected intratumorally and gelated within the tumor site. PPZ hydrogel treatment exhibited no drug-related adverse effects and no mortality for 97 days. In comparison, the mortality rates in the PTX-DOX solution intratumoral and intravenous groups are 5/8 and 4/9, respectively. These results demonstrate that sustained release of a combined DOX and PTX treatment yielded a reduction in drug-induced toxicity.

Liposomes have been reported to successfully delivery a wide range of drugs. A large amount

of evidence has shown that drug-loaded liposomes are more advantageous than free drug in regard to cytotoxic and safety considerations. To this end, the antitumor effects of intratumoral docetaxel-loaded immuno-(trastuzumab)-liposomes (IDL) were evaluated in a local, clinical application of trastuzumab against NCI-N87 Her2/neu-overexpressing gastric cancer xenograft mouse model [19]. In this study, the liposome diameter was approximately 100 nm, as it has been reported that this size is more favorable for tumor uptake and retention time [20]. They also suggested that smaller liposomes may have greater surface-to-surface contact with the cell membrane. The NCI-N87 gastric cancer xenograft mice were treated with either IDL or docetaxel-loaded liposomes. When compared with docetaxel treatment alone, docetaxel-loaded liposomes, or the combined docetaxel/trastuzumab treatment, the intratumoral IDL-treated group exhibited higher drug concentration at the tumor site. Moreover, this treatment group also had far better antitumor efficacy in the N87 xenograft model. Intratumoral administration of either free trastuzumab or IDL significantly suppressed tumor cell growth without evidence of severe side effects. According to their study, intratumoral IDL administration resulted in a high docetaxel concentration in the tumor region and has great potential for use as a safe and effective local cancer therapy. It was also noted that the liposome delivery formations prolonged therapeutic retention time. Collectively, the docetaxel-loaded liposomes conjugated with trastuzumab exhibited several antitumor advantages, including [1] prolonged liposome-docetaxel retention time within tumor sites and [2] liposome promote trastuzumab to accumulation in tumors with no sign of decline. Furthermore nanoparticle formations could decrease the severe skin ulcerations resulting from docetaxel treatment. In this study, percutaneous injection of free docetaxel into the tumor sites resulted in severe skin ulceration in one-third (2/6) of mice. On the contrary, treatment with either DL or IDL did not result in any skin ulcerations. Thus, it is shown that docetaxel-loaded liposome formations may reduce the occurrence rate and severity of normal docetaxel side effects.

Nanoparticles have been explored to deliver their payloads at the local tumoral site and minimize systemic exposure. Previously, we prepared the paclitaxel (PTX) and berbamine (BA) co-deliver nanoparticles using methoxy poly (ethylene glycol)-polycaprolactone (mPEG-PCL) to [21]. This formulation allowed for both high encapsulation efficiency and controlled release at the tumor site. Intratumoral administration showed that when compared to free drug administration, PTX/BA-NP exhibited superior antitumor effects when delivered intratumorally in a human gastric cancer mouse model. This was evidenced by inhibition of tumor growth.

In addition to "passively" targeted nanocarriers, more and more "actively" targeted nanomedicines have been developed to improve therapeutic properties. Among them, stimulus-responsive drug delivery systems have significant benefits. These delivery systems are triggered upon exposure to a specific environmental condition, such as temperature, magnetic field, presence of tumor matrix metalloproteinases (MMPs), or low pH. Such stimulus-responsive nanomedicines accumulate within tumors via EPR effects, are transformed, and release their payloads under the influence of external impacts or conditions of the tumor microenvironment. Such a triggering mechanism might overcome transport barriers, decrease drug resistance, and allow for more controlled drug release. MMPs are highly expressed in various types of tumor tissues and play an important role in tumor invasion, metastasis, cancer stem cells, and drug resistance. The conjugation of polyethylene glycol (PEG) to nanoparticles, polymeric micelles, or liposomes can improve biocompatibility and prolong their time in blood circulation. However, it has been shown that PEGylation severely reduces their cellular uptake. To overcome this limitation, Park et al. developed a PEG-peptide-quantum dot (QD) that contained an MMP-2 cleavable peptide sequence. With this formulation, they showed that tumoral enzymatic dePEGylation effects improved intracellular drug delivery.

In a separate study, an antigen-binding fragment of an anti-MMP antibody was conjugated to doxorubicin-loaded liposomes via a PEG spacer. This approach showed enhanced tumor cell uptake and greater suppression of tumor growth in a cancer mouse model. In our previous studies, we have successfully synthesized PEG-PCL nanoparticles containing gelatinase-sensitive peptide. In the gelatinase (MMP2/9)-rich environment presented by gastric cancer tissue, nanoparticles have been shown to accumulate in both a targeted and effective manner. Moreover, nanoparticles provide a preferable platform for the co-delivery of different hydrophilic/hydrophobic agents including chemotherapeutics, nucleic acids, and small molecules of anti-gastric cancer activities, such as docetaxel [22], miR-200c [23], salinomycin, 5-aza-2'-deoxycytidine, and tetrandrine. Consequently, this kind of nanoparticles may also be used as a platform for local and regional delivery of therapeutic agents for the goal of tumor inhibition. We have also used this intelligent carrier to deliver a traditional medicine monomer evodiamine (EVO) [24]. These EVO-NPs were then intratumorally injected into tumor-bearing mice. Subsequent in vitro cellular uptake studies revealed gelatinase-stimuli nanoparticles could more easily enter the cytoplasm due to their hydrophobicity. Moreover, real-time in vivo nanoparticle biodistribution demonstrated that intelligent EVO-NPs could both efficiently accumulate and retain in the local tumor regions. Therefore, EVO-NPs showed higher tumor suppression and reduced side effects when compared to freely administered EVO ($p < 0.01$).

15.4 Peritumoral Delivery of Therapeutic Agents

Despite these advances, limitations still exist in achieving optimal intratumoral administration. For instance, it is difficult for drug-loaded nanoparticles to penetrate deep into the tumor mass and exert their growth inhibitory effects on cancer cells that are distant from the injection site. Tumor-induced lymphangiogenesis is directly correlated with tumor metastasis and progression. It has been found that peritumoral lymphatic vessel density (P-LVD) plays an important role in lymph node metastasis, while intratumoral lymphatic vessel density (I-LVD) is more associated with the depth of tumor invasion. Although P-LVD and I-LVD both contribute to gastric cancer progression and prognosis, peritumoral administration is superior to intratumoral injection [25]. This is because there is great improvement in the diffusion of the loaded drug throughout the tumor, resulting in improved tumor growth inhibition. Peritumoral administration is characterized by prolonged tumor exposure, enhanced drug concentration, and reduced systemic toxicity. Li et al. [26] developed a physically cross-linked gelatin hydrogel to encapsulate co-delivery of paclitaxel (PTX) and tetrandrine (TET) mPEG-PCL nanoparticles (P/T-NPs). This prepared nanoparticle/gelatin system (P/T-NPs-Gelatin) was locally implanted on the tumor site to allow for continuous drug release. Results showed that implanting P/T-NPs-Gelatin on the tumor surface led to a gradual melting at body temperature into a viscous sol. Gelatin has a phase shift that is below body temperature, but above its melting temperature. The phase of gelatin hydrogel shifts from solid to liquid as the temperature increases. Directly implanting the gel onto the tumor will greatly increase the contact area between the gel and the tumor, thereby accelerating the diffusion and penetration of the drug-loaded nanoparticles inside the tumor through tumor vessels. Their results showed the controlled release of drug-loaded nanoparticles from the gelatin during the melting process contributed most to the sustained loaded drug release and enabled continuous exposure of the tumor to the encapsulated drugs.

Previously, we reported a natural polymer novel silk fibroin (SF) nanoparticle for paclitaxel (PTX) delivery without adding any toxic organic solvents and surfactants [27]. The PTX-loaded silk fibroin nanoparticles (PTX-SF-NPs) had a 130-nm diameter and were efficiently taken up by human gastric cancer cells. An in vivo antitumor study showed that when compared to systemic administration, peritumoral delivery of PTX-SF-NPs [1] more effectively suppressed tumor growth and [2] decreased tumor weight in a gastric cancer

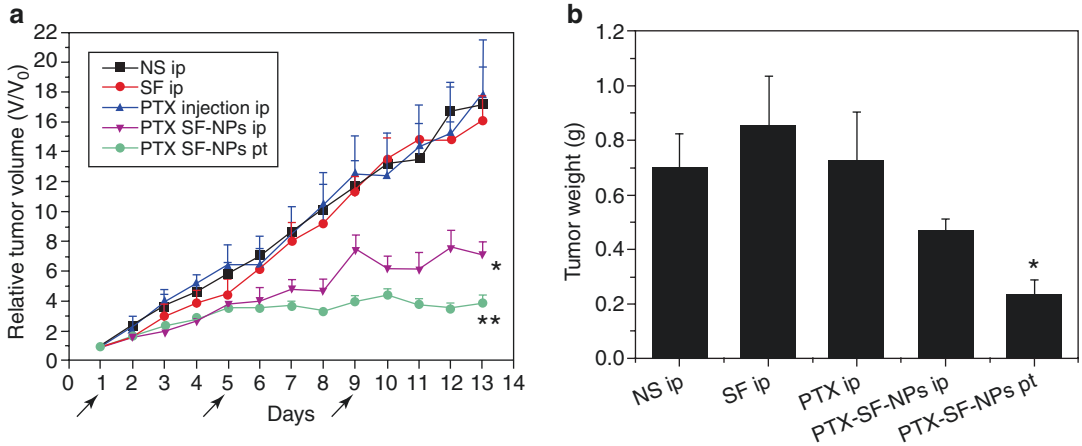

Fig. 15.5 (**a**) Relative tumor volumes for intraperitoneal (IP) PTX, intraperitoneal PTX-SF-NPs, and peritumoral (PT) injection of PTX-SF-NPs in a human gastric cancer xenograft mouse model (PTX concentration, 10 mg/kg). $*p < 0.05$, $**p < 0.01$. (**b**) Tumor weights in the group receiving IP PTX, IP PTX-SF-NPs, and PT on day 14 after administration of the first dose. $*p < 0.05$ when compared with PTX injection and PTX-SF-NPs IP groups. Reproduced with permission from Ref. [27]

nude mice xenograft model (Fig. 15.5). Furthermore, subsequent organ pathological examination clearly demonstrated that there were no obvious toxic side effects in the PTX-SF-NPs-treated groups, indicating the safety of in vivo nanoparticle use. Our results indicated that a peritumoral silk fibroin-based drug delivery system provides a promising strategy for reducing current treatment side effects and leading to overall improvements in future clinical cancer therapies.

15.5 Drug Penetration Concerns

Local administration of a nanoparticle-based delivery system results in high drug concentrations and retention times at the tumor site. The clinical benefits of intraperitoneal chemotherapy in advanced stage cancer patients were verified in work that showed local regional chemotherapy improved their clinical outcomes. However, chemotherapeutic efficacy also depends on the accessibility and retention of the delivered drug to tumor tissue. To this end, Saltzman et al. [28] studied the pharmacokinetic and tissue distribution of local polymer implants in the rat brain. They showed that at the end of the first day, therapeutic agent penetration was 5 mm from the site of implantation. From days 3 to 14, therapeutic penetration was reduced to 1 mm. According to rapid in vitro release kinetics, 84% of the drug was cumulatively released from this delivery system during the first 24 h. In the first few days after implantation, the penetration distance of the polymeric drug was reduced since the drug diffusion gradient was significantly diminished. It is possible that intraoperative administration could cause acute injury and enhance drug penetration via convection of interstitial fluid. This phenomenon might also be the reason for the rapid drug elimination seen after day 3. It should be noted that the authors did not take into account the effect of interstitial fluid convection to tissue penetration.

After reaching the target site, the cell membrane is an additional barrier to cross in order for efficient delivery of the loaded drug in nanodrug delivery systems (NDDSs) into specific organelles within the cytoplasm of cancer cells. Various strategies have been tried to stabilize lysosomal membrane and prevent lysosomes, such as targeting ligands, antibodies, as well as cell-penetrating peptides (CPPs). Suitable nanoparticle size also influences the penetration property of nanomedicines and affects their cellular uptake. It was found that 30-nm nanoparticles could more easily extravasate and penetrate into tumor tissue when compared with lager size nanoparticles. Moreover,

the penetration advantages of smaller nanoparticles exhibited distinct therapeutic effects.

Cell-penetrating peptides (CPPs) have been shown to help polymeric nanoparticles permeate cellular membranes and internalize into cancer cells. For instance, TATP, as a PEGylated CPPs, has been used to modify liposomes. The prepared micelles could be efficiently taken up by cancer cells and provided for high transfection productivity in cell nuclei. As a result, TATP improved cytoplasmic drug levels and overcame drug resistance in tumor-bearing mice.

Finally, iRGD is a tumor-specific penetrating peptide that can significantly enhance IP doxorubicin penetration into disseminated peritoneal tumor nodules in mice [29]. Intraperitoneally, coadministration of iRGD and doxorubicin specifically labeled suppressed peritoneal metastases in a mouse model. Importantly, iRGD improved intratumoral dextran and doxorubicin concentrations up to 3 and 2.5 times, respectively. When compared with administration of just intraperitoneal doxorubicin, a combination of iRGD and doxorubicin treatment significantly inhibited the growth of peritoneal metastatic tumors and reduced systemic drug toxicity. According to their study, intraperitoneal iRGD and nanodrugs were a simple and effective strategy to improve the IP therapeutic index and reduce systemic cytotoxicity for peritoneal carcinomatosis.

15.6 Future Prospects

Many cancer patients, particularly those suffering from gastric and lung cancers, die from locoregional recurrence. In order to enhance antitumor efficacy and reduce the severe side effects with systemic chemotherapy, localized delivery has been used to achieve high intratumoral drug distribution and cellular uptake in order to prevent such local recurrence. In most cases, localized chemotherapy is usually used as a supplement to surgery and/or radiotherapy and has been shown to play an important part in controlling disease progression, improving curative effects, and lowering patient morbidity due to disseminated metastatic disease. Compared with systemic chemotherapy, local delivery can sterilize the local, higher drug concentration to reduce the incidence of locoregional tumor recurrence.

However, there are also limitations with drug delivery systems that are based on local strategies. First, most studies are preclinical or in vitro, which currently restricts our understanding of their clinical applications. Second, the role of local chemotherapy in preventing locoregional or distal metastasis is still unclear. It is both desirable and difficult to eliminate all residual malignant tumor cells. Once a single residual cancer cell enters systemic circulation, distal metastasis forms and becomes an immediate life-threatening condition. This scenario has been reported in many gastric patients, and many of those at an advanced stage have died of distal metastasis. In this situation, local therapy is likely to be ineffective in prolonging a patient's life and at preventing the formation of secondary tumor. Therefore, more work is needed to explore the role of local treatment in preventing metastasis due to the suppression of primary tumors. Third, a large proportion of the studies were derived from similar studies about breast, lung, and colorectal cancers. Studies based on the clinical characteristics of gastric cancer are comparatively few.

A locoregional drug delivery system for gastric cancer treatment can reduce systemic drug exposure of normal organs and provide high drug concentration at the tumor site. To further promote the development of polymer-based delivery systems in the local treatment of gastric cancer, more in-depth studies and increased interdisciplinary collaboration will be required. It is believed that more intelligent local delivery systems will be extremely beneficial to extending patients' lives, improving the convenience of treatment, and reducing the systemic toxicity of treatment.

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