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REVIEW ARTICLE

Drug development for intraperitoneal chemotherapy against peritoneal carcinomatosis from gastrointestinal cancer

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Abstract Intraperitoneal (IP) chemotherapy for peritoneal carcinomatosis (PC) from gastrointestinal cancer has been investigated and applied clinically for several decades. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy have been considered to be the optimal treatment options for selected patients with colorectal and gastric cancers with PC. Accumulating evidence suggests that the administration of IP paclitaxel for patients with PC from gastric cancer may improve the patient survival. The pharmacokinetics of such treatment should be considered to optimize IP chemotherapy. In addition, newly emerging molecular-targeted therapies and research into new drug delivery systems, such as nanomedicine or controlled absorption/release methods, are essential to improve the effects of IP chemotherapy. This review summarizes the current status and future prospects of IP chemotherapy for the treatment of gastrointestinal cancer.

Keywords Colorectal cancer · Gastric cancer · Intraperitoneal chemotherapy · Peritoneal carcinomatosis · Pharmacokinetics

Introduction

Peritoneal carcinomatosis (PC) is the most serious metastatic pattern in gastrointestinal cancer, and is associated with an extremely poor prognosis [1, 2]. PC has long been considered to be a consequence of the systemic spread of cancer; therefore, systemic chemotherapy has usually been given as standard therapy. In spite of the consistent improvement in systemic chemotherapy regimens, the effects on PC are still limited, possibly because of the peritoneum-plasma barrier, which prevents effective drug delivery from the systemic circulation into the peritoneal cavity [3]. In contrast, intraperitoneal (IP) chemotherapy combined with cytoreductive surgery (CRS) as regional therapy for PC has demonstrated notable efficacy for the treatment of PC in various malignancies [4–7].

In 1978, Dedrick et al. [8] published the theoretical rationale that the IP administration of drugs would result in a higher drug concentration and longer half-life in the peritoneal cavity compared with intravenous (IV) administration. Since then, a number of basic studies on the pharmacokinetic and antitumor effects of IP administration and a number of clinical trials have proven the validity of IP chemotherapy. Three multicenter, randomized, phase III clinical trials have shown that IP chemotherapy is superior to standard IV systemic chemotherapy as the first-line chemotherapy against small volume, residual, advanced epithelial ovarian cancer [9–11]. Based on these results, the National Comprehensive Cancer Network guidelines now recommend IP chemotherapy for patients with stage III epithelial ovarian cancer after optimal debulking surgery [12]. Although evidence of the efficacy of CRS plus hyperthermic IP chemotherapy (HIPEC) has been established for gastrointestinal cancer, there is still controversy concerning whether IP chemotherapy, including HIPEC, is a standard treatment option or an experimental approach [13].

The peritoneum is not a simple membrane, but is a complicated organ. The route of peritoneal absorption and pharmacokinetics following IP administration vary a great deal between drugs. In addition, the formulation, solvent,

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concentration, administration rate and other factors critically affect the pharmacokinetics [14]. Ideally, the agents used for IP chemotherapy should slowly exit the peritoneal cavity to allow for optimal surface penetration of the tumors [14]. For some drugs, use under hyperthermic conditions can increase the cytotoxicity in the peritoneal cavity without an increase in systemic toxicity [15]. Investigations into drug delivery systems (DDS) are ongoing to develop new strategies that can be used in addition to IP administration of drugs to achieve better clinical results [16, 17]. Molecular-targeted therapy should be taken into account as one such option, and the development of drugs or solvents specific for IP chemotherapy may be a future issue that needs to be resolved in this field.

In this review, we summarize the current status of IP chemotherapy for PC from gastric cancer (GC) and colorectal cancer (CRC) and ongoing basic research on the DDS in IP chemotherapy.

Pharmacokinetics of IP chemotherapy

The aim of IP chemotherapy is to increase the dose and exposure time of anticancer drugs to the intraabdominal cancer cells, while inducing minimal systemic toxic effects. The pharmacokinetics after IP administration are affected by a variety of biophysical parameters, including the molecular weight and electric charge of the agent, as well as the temperature, pH and other conditions of the solution. Prolonged retention in the peritoneal cavity and clearance from systemic circulation are believed to be the key attributes for ideal drug candidates designed for IP chemotherapy [8, 14, 18]. Intraperitoneally administered materials are mainly absorbed by two anatomical routes. After IP administration, hydrophilic low-weight molecular materials, such as cisplatin (CDDP) or mitomycin C(MMC), are rapidly absorbed into the subperitoneal capillary vessels through the peritoneal mesothelial layer. In contrast, hydrophobic high-weight molecular materials, such as taxanes, are gradually drained, mainly from stomata or milky spots that are the direct openings of lymphatic vessels [19, 20]. Thus, the time–concentration curves of drugs in the peritoneum and plasma vary widely according to the drug type. The area under the curve (AUC) ratio of the peritoneal cavity to the plasma (AUC peritoneum/plasma) is approximately 1000 for paclitaxel (PTX) and approximately 10–21 for CDDP (Table 1) [14, 21–24]. In IP chemotherapy, the pharmacokinetic profile of each drug is as important as its cytotoxic activity.

Table 1 Drugs used for intraperitoneal chemotherapy against gastrointestinal cancer

Drug	M_w (Da)	AUC peritoneum/plasma	Penetration distance	Heat synergy
Mitomycin C	334	10–24	2 mm	+
Cisplatin	300	12–21	1–3 mm	+
Oxaliplatin	397	3.5	1–2 mm	+
5-Fluorouracil	130	360	0.2 mm	−
Irinotecan	677			−
Paclitaxel	854	1000	>80 cell layers	−
Docetaxel	862	207–552		+

M_w molecular weight, *AUC* area under the concentration–time curve

Currently used IP chemotherapy agents

HIPEC and agents with heat synergy

The aim of HIPEC is to achieve a high local concentration of chemotherapeutic agents in the peritoneal cavity and to promote good absorption of these agents from the surface of peritoneal tumors with minimal systemic toxic effects. Practically, multiple drainage tubes are placed in different areas of the abdomen after CRS. A roller pump with a heat exchanger is used, and the temperature is maintained at 42–43 °C throughout the perfusion duration of 30–120 min [25]. Heat has a synergistic effect with MMC, CDDP, oxaliplatin, and docetaxel (Table 1). MMC, CDDP, and oxaliplatin are generally used for HIPEC for CRC and GC. The previously reported clinical results of IP chemotherapy for CRC [26–40] and GC [39, 41–53] are shown in Tables 2 and 3, respectively. In these tables, most studies included only patients who underwent complete CRS, except for a few references [39, 46, 47, 49, 51–53].

A few studies have compared HIPEC with early postoperative intraperitoneal chemotherapy (EPIC) or non-hyperthermic sequential postoperative intraperitoneal chemotherapy (SPIC). Elias et al. [54] reported that HIPEC with oxaliplatin was better tolerated than EPIC with MMC, and that 5-fluorouracil (5-FU) was twice as efficient at curing residual PC from CRC with minimal residual disease after surgery. Cashin et al. [40, 55] reported that HIPEC was associated with an improved overall survival (OS) and disease-free survival compared with SPIC, with similar morbidity and mortality in patients with PC from CRC. They concluded that CRS and HIPEC might be the optimal treatment for patients with PC from CRC with minimal residual disease. However, in the SPIC and EPIC studies, the IP drug combination was MMC and 5-FU, whereas IP oxaliplatin was used in HIPEC studies,

Table 2 The clinical outcomes of intraperitoneal chemotherapy for colorectal cancer

References	*N*	Method	Intraperitoneally administered agents	MST (months)	1-year OS (%)	2-year OS (%)	3-year OS (%)	5-year OS (%)
Verwaal et al. [26]	54	HIPEC	MMC	22.4				
Mahteme et al. [27]	18	HIPEC	5-FU	32				
Glehen et al. [28]	377	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP EPIC: 5-FU (+MMC)	32				
Elias et al. [29]	16	EPIC	MMC + 5-FU			60		
Verwaal et al. [30]	117	HIPEC	MMC	21.8	75		28	19
Kianmanesh et al. [31]	30	HIPEC	MMC + CDDP	38.4				
Verwaal et al. [32]	54	HIPEC	MMC	22.2				
Shen et al. [33]	30	HIPEC		41				
Bijelic et al. [34]	49	HIPEC (+EPIC)	MMC + 5-FU	33				
Elias et al. [35]	48	HIPEC	L-OHP	62.7		81		51
Franko et al. [36]	67	HIPEC	MMC	34.7				
Elias et al. [37]	492	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP (+CPT-11) EPIC: MMC + 5-FU	30.1				27
Elias et al. [38]	341 (colon)	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP (+CPT-11) EPIC: MMC + 5-FU	32.4			46	30
	27 (rectum)	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP (+CPT-11) EPIC: MMC + 5-FU	34			45	38
Glehen et al. [39]	498	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP (+CPT-11) EPIC: MMC + 5-FU	30			41	26
Cashin et al. [40]	69	HIPEC	HIPEC: MMC (+CDDP) or L-OHP (+CPT-11)	34				40
	57	SPIC	MMC + 5-FU	25				18

MST median survival time, *OS* overall survival, *HIPEC* heated intraperitoneal chemotherapy, *MMC* mitomycin C, *5-FU* 5-fluorouracil, *L-OHP* oxaliplatin, *EPIC* early postoperative intraperitoneal chemotherapy, *CDDP* cisplatin, *CPT-11* irinotecan, *SPIC* sequential perioperative intraperitoneal chemotherapy

suggesting that further studies using oxaliplatin may be required in future EPIC and SPIC studies for a more reasonable comparison.

As for GC, Yonemura et al. [56] suggested that a combination of neoadjuvant IP/systemic chemotherapy (NIPS), such as CRS plus HIPEC, and EPIC/SPIC might be the best treatment strategy.

Mitomycin C

MMC is the most extensively used clinical IP chemotherapy agent that demonstrates favorable outcomes [28]. It is usually the first agent to be selected for HIPEC for CRC, and is used in combination with other drugs for GC. MMC can be co-administered with other agents such as oxaliplatin, CDDP and 5-FU due to its favorable compatibility profile. HIPEC achieves high peritoneal concentrations of MMC with limited systemic absorption [57].

Cisplatin

CDDP is one of the most widely used drugs for various cancers, including GC [58]. It is used for IP chemotherapy with or without hyperthermia. The AUC for the peritoneum/plasma is approximately 12–20 [14], which is not as high as that of many other drugs. However, significant antitumor activity during systemic chemotherapy has led physicians to evaluate IP CDDP, which led to improved survival compared with IV administration in patients with ovarian cancer [9]. Heat synergy of CDDP has been reported [59]. To prolong the retention of CDDP in the peritoneal cavity, continuous IP infusion was attempted with tolerable toxicity [60].

Oxaliplatin

Oxaliplatin is the main agent used during systemic chemotherapy for CRC. Elias et al. [35, 61–64] reported on the

Table 3 Clinical outcomes of intraperitoneal chemotherapy for gastric cancer

References	*N*	Method	Intraperitoneally administered agents	MST (months)	1-year OS (%)	2-year OS (%)	3-year OS (%)	5-year OS (%)
Fujimoto et al. [41]	48	HIPEC	MMC		54		42	31
Beaujard et al. [42]	28	HIPEC	MMC		48	33		
Hall et al. [43]	34	HIPEC	MMC	11.2	45	45		21
Glehen et al. [44]	25	HIPEC	MMC	21.3	75	37		29
Yonemura et al. [45]	47	HIPEC	MMC + CDDP + VP-16	15.5				13
Yonemura et al. [46]	61[a]	NIPS	DOC + CBDCA	14.4				
Cheong et al. [47]	154[a]	EPIC	5-FU + CDDP	11.4				12.2
Yonemura et al. [48]	41	NIPS	DOC + CDDP	20.4	67	40	30	
Yang et al. [49]	28[a]	HIPEC	MMC + HCPT, MMC + CDDP	12	50	43		
Glehen et al. [50]	85	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP (+CPT-11) EPIC: MMC + 5-FU	15	61		31	23
Glehen et al. [39]	152[a]	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP (+CPT-11) EPIC: MMC + 5-FU	9			18	13
Ishigami et al. [51]	40[a]	SPIC	PTX		78			
Yang et al. [52]	34[a]	HIPEC	MMC + CDDP	11				
Fushida et al. [53]	27[a]	SPIC	DOC	16.2	70	33.4		

MST median survival time, *OS* overall survival, *HIPEC* heated intraperitoneal chemotherapy, *MMC* mitomycin C, *CDDP* cisplatin, *VP-16* etoposide, *DOC* docetaxel, *CBDCA* carboplatin, *5-FU* 5-fluorouracil, *HCPT* hydroxycamptothecin, *EPIC* early postoperative intraperitoneal chemotherapy, *L-OHP* oxaliplatin, *CPT-11* irinotecan, *SPIC* sequential perioperative intraperitoneal chemotherapy, *PTX* paclitaxel

[a] Including data for R2 surgery or without surgery

pharmacokinetics and significant efficacy of IP oxaliplatin for patients with PC from CRC. They demonstrated the effectiveness of bidirectional chemotherapy, that is, a combination of HIPEC with oxaliplatin and intraoperative IV chemotherapy [61, 62]. Then, they retrospectively compared patients with resectable PC treated with complete CRS and HIPEC ($n = 48$) to those treated with standard systemic chemotherapy ($n = 48$). The median OS was 63 months in the HIPEC group versus 24 months in the systemic chemotherapy group [35].

Agents without heat synergy

Paclitaxel and docetaxel

PTX is water insoluble, and for clinical use, it is conventionally solubilized in a polyoxyethylated castor oil called Cremophor EL and ethanol (i.e., Taxol®) [65, 66]. Taxol® is considered to be suitable for IP chemotherapy due to its large particle size (10–12 nm in diameter), which can result in prolonged retention of the drug in the peritoneal cavity [14, 67, 68], although Cremophor EL can cause severe hypersensitivity reactions, which occur in 2–4 % of patients [65, 66].

In patients with GC, IP PTX was demonstrated to be clinically safe and effective in phase I and II trials [51, 69–72]. The bidirectional administration of IV and IP PTX maintained effective concentrations of PTX in the peritoneal cavity for over 72 h [70] (Fig. 1). In a phase II trial of combination chemotherapy with oral S-1 and IV and IP PTX for patients with PC from GC, the one-year OS rate was 78 % and the overall response rate (ORR) was 22 %, even though most of the patients had highly advanced PC [51]. The advantage of this regimen was the administration of IP chemotherapy both before and after CRS, whereas in the previous studies, IP therapy was limited to a short postoperative period. A randomized, multicenter, phase III trial (PHOENIX-GC trial, UMIN Trial ID: UMIN000005930) comparing S-1 in combination with IV and IP PTX versus S-1 with IV CDDP, as a standard regimen for Japanese patients with advanced or recurrent GC [58], began in November 2011 (Fig. 2).

IP docetaxel for patients with PC from GC was also evaluated; the one-year OS rate was 70 % and the ORR was 22 % [53, 73].

Taxanes are not commonly used for systemic chemotherapy for patients with CRC since phase II trials yielded negative results [74–76]. However, clinical evaluation of IP PTX could also be considered for patients with PC from CRC, because the pharmacokinetics of PTX after IP administration are very different from those after IV administration, and preclinical investigations of IP PTX for CRC showed desirable efficacy [77, 78].

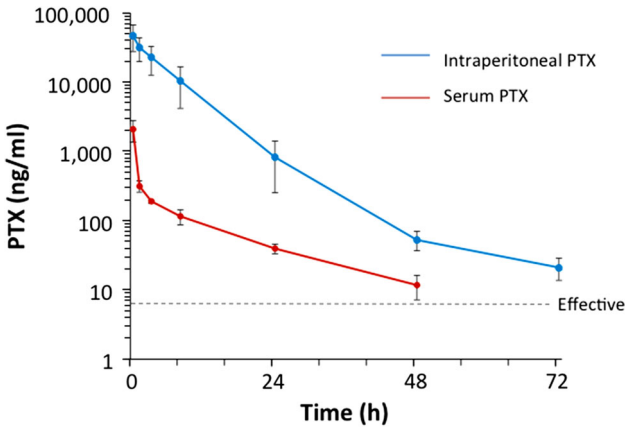

Fig. 1 The concentration-versus-time curves of intraperitoneal and serum PTX. After the administration of PTX (50 mg/m^2 intravenously, 20 mg/m^2 intraperitoneally), serum and intraperitoneal fluid was periodically collected. The PTX concentrations were measured by a reverse-phase high-performance liquid chromatography assay. *PTX* paclitaxel (adapted from Ref. [70])

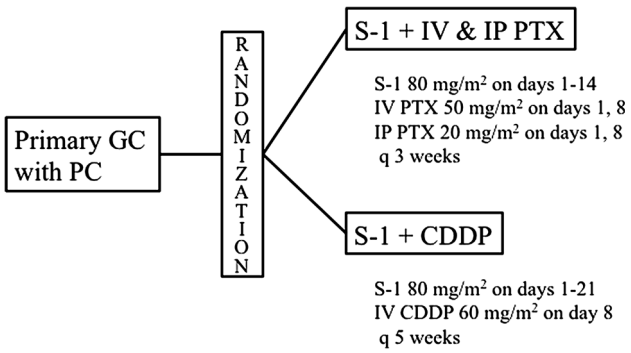

Fig. 2 The design of the PHOENIX-GC trial. *GC* gastric cancer, *PC* peritoneal carcinomatosis, *IP* intraperitoneal, *IV* intravenous, *PTX* paclitaxel, *CDDP* cisplatin

Irinotecan

Irinotecan is one of the key drugs used for the treatment of CRC and GC. It is a pro-drug that exerts its anticancer activity after transformation into SN-38 by carboxylesterases in the liver. SN-38 is 100- to 1000-fold more cytotoxic than irinotecan. Carboxylesterases are reported to be minimally present in the peritoneum [79], and Elias et al. [80] performed an IP administration of irinotecan and reported that SN-38 was detected in the peritoneal cavity just after the IP administration of irinotecan. However, their clinical trial comparing CRS plus HIPEC using oxaliplatin with or without irinotecan showed that the addition of irinotecan did not confer a survival benefit, and instead increased morbidity [81]. These results were unexpected, but might be explained by the local inefficiency of irinotecan from the viewpoint of its metabolism. In addition, it was speculated that the efficiency of HIPEC might be less dependent on the drug used, unlike the case for systemic chemotherapy.

5-Fluorouracil

5-FU is a widely used IP agent for the treatment of patients with gastrointestinal cancer. Because it has no heat synergy, 5-FU is currently used in EPIC and SPIC for CRC and GC. Since IP administration of 5-FU results in absorption from the peritoneum and direct first-pass metabolism in the liver, IP administration requires a 1.5-fold higher dose than that used for systemic administration [82]. Cashin et al. [40] reported a retrospective cohort study of SPIC treatment consisting of IP 5-FU at 500–600 mg/m^2 and IV leucovorin at 60 mg/m^2 once a day for 6 days. Eight cycles of SPIC with at 4- to 6-week intervals over a six-month period were planned as an adjuvant chemotherapy regimen. The OS of 57 patients who underwent CRS and received SPIC was 25 months, with a five-year survival rate of 18 %. Glehen et al. [28] reported that the OS of 235 patients with CRC who received EPIC with 5-FU and/or MMC was 19.2 months.

Molecular-targeted therapy in patients with malignant ascites

Catumaxomab

Epithelial cell adhesion molecule (EpCAM, CD326) is a surface antigen present on various kinds of epithelial cancer and normal epithelial cells [83]. Catumaxomab is a trifunctional monoclonal antibody with two different antigen-binding sites and a functional Fc domain [84]. It binds to human EpCAM-positive cancer cells and redirects CD3-positive T lymphocytes and Fcγ-receptor-positive accessory cells to the cancer cells, thereby activating a complex antitumor immune reaction through various effector functions, such as antibody-dependent cellular cytotoxicity, phagocytosis and T cell-mediated cytotoxicity [85–89] (Fig. 3).

A randomized phase II/III trial of catumaxomab in patients with malignant ascites due to epithelial cancer, including ovarian, gastric, breast, pancreatic, colorectal and endometrial cancers was conducted. Patients with malignant ascites ($n = 258$) were randomized to receive paracentesis plus catumaxomab or paracentesis alone and stratified by cancer type. The puncture-free survival was significantly longer in the catumaxomab group than in the control group (46 vs. 11 days, hazard ratio = 0.254, $P < 0.0001$) as was the median time to the next

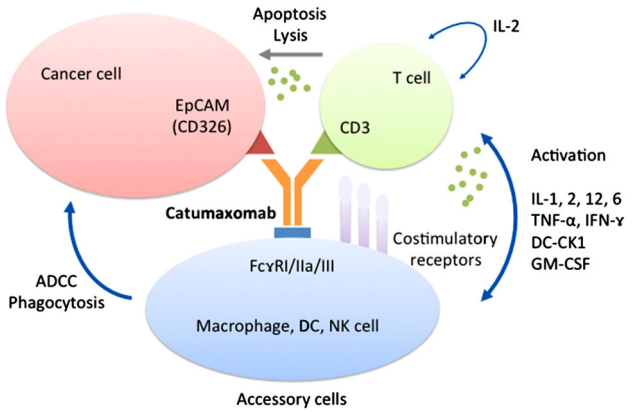

Fig. 3 The mechanism(s) of action of catumaxomab. *ADCC* antibody-dependent cellular cytotoxicity, *DC* dendritic cell, *DC-CK1* dendritic cell cytokine 1, *EpCAM* epithelial cell adhesion molecule (adapted from Ref. [89])

paracentesis (77 vs. 13 days, $P < 0.0001$). The OS showed a positive trend in the catumaxomab group and was significantly prolonged in patients with GC (71 vs. 44 days, $P = 0.0313$) [90]. Moreover, treatment with catumaxomab significantly delayed the deterioration of the patient quality of life (QoL) in the same trial [91].

Bevacizumab

Vascular endothelial growth factor A (VEGF-A) is a key mediator of angiogenesis [92, 93]. The activities of VEGF-A are mediated by two tyrosine kinase receptors, vascular endothelial growth factor receptors 1 and 2. In patients with CRC, bevacizumab, a humanized variant of an anti-VEGF antibody, has shown significant efficacy in combination with chemotherapy, and is now widely used in the clinical setting [94]. Although, the primary endpoint of OS was not reached in the AVAGAST trial, the addition of bevacizumab to chemotherapy was associated with significant increases in progression-free survival and the ORR in the first-line treatment of patients with advanced GC [95].

Malignant ascites caused by PC not only leads to the deterioration of the patients' QoL, but also results in a poor prognosis [96, 97]. VEGF is markedly elevated in malignant ascites, where it worsens the condition by increasing the endothelial cell permeability [98]. VEGF inhibition in the peritoneal cavity is therefore considered to be beneficial not only as an inhibitor of tumorigenesis, but also as an inhibitor of the formation of malignant ascites [99]. In surgically resected specimen from patients with GC, the VEGF expression was indicated to be an independent predictor of peritoneal recurrence [100].

With regard to the route of administration, bevacizumab should be administered systemically, because it is rapidly absorbed from the peritoneum and enters the systemic circulation when administered by IP injection [101, 102].

There have been so far no clinical trials addressing the use of bevacizumab with IP chemotherapy, although the effects of bevacizumab on murine PC models of GC were promising [103, 104].

Utilization of new DDS in IP chemotherapy

Nanodrugs

Nanodrugs are a new type of drug formulation, comprising particles of 20–100 nm in molecular diameter, smaller than conventional drugs. Since the discovery of selective accumulation by passive targeting, known as the enhanced permeability and retention (EPR) effect [105], various kinds of nanodrugs have been developed for cancer treatment (Table 4) [106–108]. One of the barriers to systemic chemotherapy is the high interstitial pressure of solid tumors, which prevents drugs from leaking from vessels and penetrating into tumor tissue [109–112]. Nanodrugs accumulate in tumor tissue by the EPR effect, which results in enhanced antitumor effects and less toxicity in normal tissues. The EPR effect is based on the special characteristics of solid tumor tissues, such as incomplete vascular architecture, hyperpermeability of tumor vessel walls and immature lymphatic drainage [105] (Fig. 4). Nanodrugs of the polymeric micellar type are retained for a long period in the systemic blood stream [113, 114], where they are easily extravasated from tumor vessels into the interstitium of tumor tissue, resulting in greater intratumoral exposure compared with conventional small-molecule agents [105, 115].

Various types of Cremophor-free, nanoparticulate PTX have recently been investigated to reduce the risk of allergic reactions and to take advantage of the EPR effect [116–120]. Abraxane®, an albumin-bound PTX, is currently in clinical use for breast, lung and gastric cancers [121, 122]. NK105 is a PTX-incorporating "core–shell-type" polymeric micellar nanoparticle formulation [123, 124] (Fig. 5). A phase II trial of NK105 as second-line chemotherapy in patients with advanced GC reported an

Table 4 Nanocarrier-based drugs licensed for gastrointestinal cancer

Drug	Platform	Compound	Mean diameter (nm)	Clinical stage
Abraxane	Albumin conjugate	Paclitaxel	120	Approved
NK105	Micelles	Paclitaxel	85	P3
NK012	Micelles	SN-38	20	P2
NC-6004	Micelles	Cisplatin	20	P1/2
NC-4016	Micelles	Dachplatin	40	P1

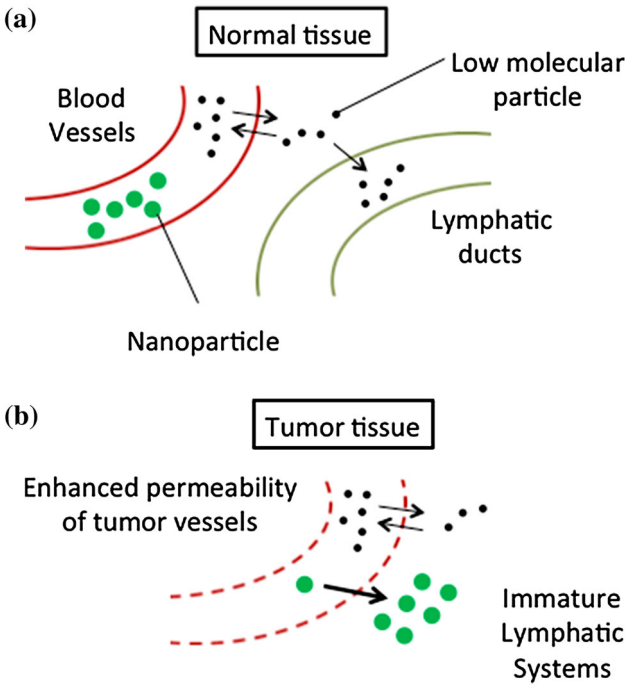

Fig. 4 The enhanced permeability and retention (EPR) effect. **a** Small molecules easily leak from normal capillary vessels and are drained via lymphatic vessels in normal tissue, whereas nanoparticle macromolecules do not pass through the normal vessel walls. Nanoparticles do not harm the normal tissue. **b** In contrast, nanoparticles leak from vessels and persist for a long time in the tumor tissue, where the vascular permeability is elevated and the lymphatic system is immature. As a result, nanoparticles accumulate in the tumor tissue

ORR of 25 % and a median OS of 14.4 months [125]. A phase III trial to verify the non-inferiority of NK105 to Taxol® in terms of the progression-free survival in patients with metastatic or recurrent breast cancer is ongoing (NCT01644890).

The IV administration of NK012, an SN-38-releasing polymeric nanomicellar agent, showed a significantly enhanced antitumor effect against PC in a mouse GC xenograft model compared with irinotecan [126]. However, the IP administration of nanoparticulate anticancer agents for PC has received little attention despite the existence of data indicating the potency of this type of treatment [127].

PMB-30W is a water-soluble, amphiphilic polymer composed of 2-methacryloxyethyl phosphorylcholine and n-butyl methacrylate. As is the case for NK105, this co-polymer is biocompatible, forms micelles when dissolved in aqueous media, and provides hydrophobic domains in such media. As a solvent, PMB-30W is 1000-fold better than water, and enables the construction of PTX-containing nanoparticles approximately 50 nm in diameter [119]. The IP administration of nanoparticulate PTX resulted in deeper penetration into peritoneal nodules and exhibited enhanced antitumor effects compared to conventional Cremophor-conjugated PTX (Fig. 6) [128, 129], although the reason why nanomicellar particles can penetrate deeply into peritoneal nodules is unclear.

Higher and longer retention in the systemic circulation after IP administration of NK105 was also shown in a mouse model [130]. IP NK105 showed significantly enhanced antitumor effects against both subcutaneous and peritoneal xenografts of human GC compared with IP Taxol®. IP chemotherapy with nanoparticulate agents could be a promising strategy for the treatment of PC.

Controlled absorption and drug release

Water-soluble low molecular weight agents such as CDDP are rapidly absorbed via the capillary blood vessels of the peritoneum after IP administration [14]. Therefore, the ratio of the AUC for the peritoneum to that for plasma of these agents is low [15, 18, 131]. To keep this ratio high, frequent or continuous IP administration of these agents has been attempted, which sometimes caused stress for patients because of catheter-related complications [4, 17]. The IP administration of CDDP in a hypotonic solution resulted in a high AUC in the plasma, a high intratumoral uptake and prolonged survival in animal models; however,

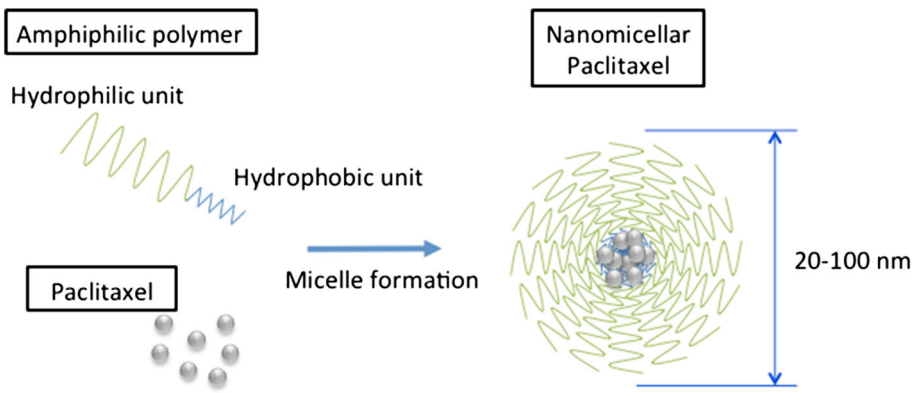

Fig. 5 A core–shell-type polymeric nanomicellar paclitaxel. Hydrophilic paclitaxel was made water soluble by its incorporation into micelles of amphiphilic polymers

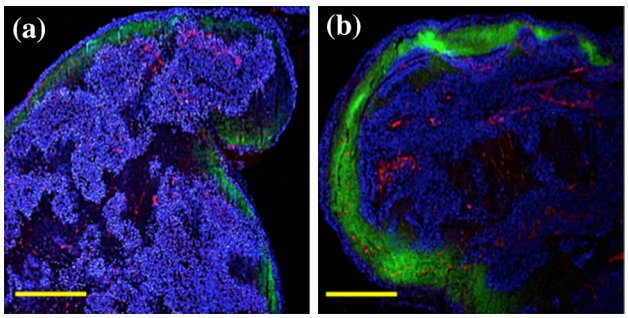

Fig. 6 The spatial distribution of Cremophor-conjugated paclitaxel (PTX) or nanomicellar PTX (PTX-30W) in disseminated tumors after IP injection. Peritoneal xenografts in nude mice were excised 24 h after IP injection of Cremophor-conjugated PTX (**a**) or PTX-30W (**b**). PTX was labeled by Oregon green fluorescence. The infiltration of PTX into nodules was significantly deeper following PTX-30W (**b**) compared with Cremophor-conjugated PTX (**a**) treatment. *Scale bars* indicate 1 mm (adapted from Ref. [128])

the AUC in the IP fluid was low, and this strategy caused an increase in the renal toxicity [132, 133].

However, IP administration of water-soluble agents is still widely performed without any special artifice in DDS in clinical practice, but further research is needed to prolong the retention of drugs in the peritoneal cavity [14, 17, 134].

Hydrogels are formed by cross-linking hydrophilic macromolecules. They have been reported to prolong drug retention in the peritoneal cavity and to enhance the antitumor effects for PC [135–138]. The hyaluronic acid (HA)-based hydrogel is a biocompatible material that prevents peritoneal adhesion after surgical processes [139–141]. Hydrogels that are sensitive to stimuli such as temperature [136, 137, 142, 143] or pH [144] have considerable potential in biomedical and pharmaceutical applications, especially in site-specific and controlled DDS [145].

The IP administration of CDDP via a HA-based hydrogel resulted in the sustained release of CDDP in the peritoneal cavity and enhanced antitumor activity against PC in a mouse model [146], revealing a novel DDS for the treatment of PC. A combination of controlled release and target-specific delivery by HA-based hydrogel through interactions between CD44 and HA also seems promising [147–149].

Conclusion

This review has attempted to highlight the current status and future prospects of IP chemotherapy for patients with PC from GC and CRC, with a focus mainly on the pharmacokinetics. Since the infusion of anticancer agents into the abdominal cavity enables direct exposure of a high concentration of drugs to each tumor cell, it seems to be a reasonable drug delivery method. The results suggest that multimodal treatment including IP chemotherapy may be the best approach for PC, with the potential to improve the survival of the patients with this dismal disease.

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