hepatocyte growth factor (HGF) antagonist, NK4, suppresses peritoneal metastases of gastric cancer in nude mice. Eur J Cancer 40(14):2135–2142. doi:10.1016/j.ejca.2004.05.006

27. Yu HK, Ahn JH, Lee HJ, Lee SK, Hong SW, Yoon Y, Kim JS (2005) Expression of human apolipoprotein(a) kringles in colon cancer cells suppresses angiogenesis-dependent tumor growth and peritoneal dissemination. J Gene Med 7(1):39–49. doi:10.1002/jgm.638
28. Machida S, Saga Y, Takei Y, Mizuno I, Takayama T, Kohno T, Konno R, Ohwada M, Suzuki M (2005) Inhibition of peritoneal dissemination of ovarian cancer by tyrosine kinase receptor inhibitor SU6668 (TSU-68). Int J Cancer 114(2):224–229. doi:10.1002/ijc.20751

Surgical Oncology 23 (2014) 99–106

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Review

Intraperitoneal chemotherapy against peritoneal carcinomatosis Current status and future perspective

Joji Kitayama*

Department of Surgical Oncology, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

ARTICLE INFO

Article history:
Accepted 18 March 2014

Keywords:
Gastric cancer
Colorectal cancer
Intraperitoneal chemotherapy
Peritoneal carcinomatosis
Pharmacokinetics

ABSTRACT

Peritoneal carcinomatosis (PC), caused by advanced abdominal malignancies, such as those of the ovarian and gastrointestinal tracts, has an extremely poor prognosis. Intraperitoneal (IP) chemotherapy has been clinically applied for several decades, but its clinical efficacy has not been fully determined. An accumulating body of evidence suggests that cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is the optimal treatment for selected patients with ovarian and colorectal cancers with PC. Recent studies suggest that IP administration of taxane with systemic chemotherapy in a neoadjuvant setting improves patient survival in gastric cancer with PC. The pharmacokinetics of IP-administered drugs should be primarily considered in order to optimize IP chemotherapy. Therefore, the development of specific IP drugs using newly emerging molecular targeted reagents or new drug delivery systems, such as nanomedicine or controlled absorption/release methods, is essential to improve the efficacy of IP chemotherapy.

Contents

* Tel.: +81 3 3815 5411; fax: +81 3 3811 6822.
E-mail address: kitayama-1SU@h.u-tokyo.ac.jp.

http://dx.doi.org/10.1016/j.suronc.2014.03.004
0960-7404/

Table 1
Clinical outcomes of intraperitoneal chemotherapy for ovarian cancer.

Author, year	*N*	Method	Intraperitoneally administered agents	MST (months)	2 yr-OS (%)	3 yr-OS (%)	5 yr-OS (%)
Zanon 2004 [21]	30	HIPEC	CDDP 100–150 mg/m^2	28.1 (37.8)	60		
Ryu, 2004 [22]	35	**HIPEC**	**CBDCA 350 mg/m^2 + IFN-α 5,000,000 IU/m^2**	**40.6 (60.9)**			**53.8 (65.6)**
Armstrong, 2006 [18]	**205**	**EPIC**	**CDDP 100 mg/m^2 + PTX 60 mg/m^2**	**(65.6)**			
Raspagliesi 2006 [23]	40	HIPEC	CDDP 25 mg/m^2/l + MMC 3.3 mg/m^2/l CDDP 43 mg/l + DOX 15.25 mg/l	31.5 (41.4)			(15)
Rufian, 2006 [30]	33	HIPEC	PTX 60 mg/m^2	38		46	37 (60)
Cotte, 2007 [24]	81	HIPEC	CDDP 20 mg/ml	28.4 (54.9)			
Bae, 2007 [31]	**44**	**HIPEC**	**CBDCA 350 mg/m^2 (n = 30)** **PTX 175 mg/m^2 (n = 14)**				**63 (CBDCA) 84.6 (PTX)**
Di Giorgio, 2008 [25]	47	HIPEC	CDDP 75 mg/m^2	24 (26)			16.7 (25.9)
Pavlov, 2009 [27]	56	HIPEC	DOX 0.1 mg/kg, CDDP 15 mg/m^2	38.1			67
Tentes, 2012 [28]	39	HIPEC	CDDP 50 mg/m^2 + DOX 15 mg/m^2 GEM 1000 mg/m^2	37			54 (62.5)
Bakrin, 2012 [29]	246	HIPEC	CDDP, CDDP + DOX, CDDP + MMC	48.9		60	35

Abbreviations: MST: median survival time, OS: overall survival, HIPEC: heated intraperitoneal chemotherapy, EPIC: early post-operative intraperitoneal chemotherapy, CDDP: cisplatin, MMC: mitomycin C, GEM: gemcitabine, DOX: doxorubicin, CBDCA: carboplatin, L-OHP: oxaliplatin, PTX: paclitaxel.
Quoted values are those in patients who received complete cytoreductive surgery for PC.
Studies written in bold letters are prospective controlled studies.

Introduction

Peritoneal metastasis frequently occurs in recurrent abdominal malignancy, such as gastrointestinal [1] and ovarian cancer [2]. The most serious condition that can develop in peritoneal metastasis is peritoneal carcinomatosis (PC), which has an extremely poor prognosis [3–5]. PC has long been considered 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 effect of systemic chemotherapy on PC is still limited, possibly because of the peritoneum-plasma barrier, which prevents effective drug delivery from the systemic circulation into the peritoneal cavity [6].

In contrast, intraperitoneal (IP) chemotherapy combined with cytoreductive surgery (CRS) has demonstrated notable efficacy for the treatment of PC in various malignancies, such as ovarian cancer [7], colorectal cancer [8], pseudomyxoma peritonei [9] and mesothelioma [10]. The theoretical rationale of IP chemotherapy was first described in 1978 by Dedrick et al., who showed that IP administration of drugs would result in a higher drug concentration and longer half-life in the peritoneal cavity, as compared with intravenous (IV) administration [11]. Since then, many basic studies on the pharmacokinetic and antitumor effects of IP chemotherapy have been performed, which have shown variable results. The peritoneum is not a simple membrane, but rather a complicated organ. The route of peritoneal absorption and pharmacokinetics following IP administration vary a great deal according to the biophysical characteristics of each drug. In addition, the formulation, solvent, concentration, administration rate, and other factors critically affect the pharmacokinetics. Ideally, an anti-cancer agent used for IP chemotherapy would slowly exit the peritoneal cavity, which would allow optimal penetration of the tumor surface [12]. For some drugs, use under hyperthermic conditions may increase cytotoxicity in the peritoneal cavity, without an increase in systemic toxicity [13].

This review attempts to highlight the current status and future prospects of IP chemotherapy for patients with PC, especially focusing on the pharmacokinetics of IP-administered drugs. We first summarize the current status of IP chemotherapy for PC in ovarian, colorectal and gastric cancer based on the literature published over the last ten years, and then investigate drug delivery systems (DDS) that are suitable for IP chemotherapy, which may achieve better clinical results against PC.

Clinical results of IP chemotherapy

Ovarian cancer

Ovarian cancer is the most lethal malignancy in the field of gynecology. Peritoneal seeding is the most frequent type of metastasis of advanced ovarian cancer, which results in a poor prognosis, with 5-year survival of around <25% [14]. IP chemotherapy has been performed for PC of ovarian cancer since the 1980s, and has suggested promising clinical effects [15]. Multicenter randomized phase III trials of IP chemotherapy have been performed and clearly demonstrated that regimens containing IP chemotherapy are superior to standard IV protocols in primary chemotherapy management for PC of advanced ovarian cancer with no residual mass greater than 1.0 cm [16–18]. Based on these results, the National Comprehensive Cancer Network guidelines now recommend IP chemotherapy for patients with stage III epithelial ovarian cancer after optimal cytoreductive surgery (CRS) [19].

On the other hand, numerous studies of the treatment of PC of ovarian cancer by CRS intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) have been published, although most of them were non-randomized and had a small sample size (Table 1). These results have been summarized in previous reviews [4,20]. In short, platinum drugs, such as cisplatin, carboplatin or oxaliplatin, were mainly used and median survival (MST) for all of the patients was 24–48.9 months with 5-year survival (5 y-OS) of 12–67% [21–29]. Paclitaxel was also used at 60 mg/m^2 [30] or 175 mg/m^2 [31], which produced excellent survival.

However, the variable outcome is thought to be related to the different stages of peritoneal carcinomatosis (peritoneal carcinomatosis index; PCI) as well as the completeness of CRS, and these retrospective results should be interpreted with care. Moreover, the morbidity of HIPEC and CRS was still high (0–40%) and mortality was not negligible (0–10%), as reported in previous reviews [4]. Therefore, the real efficacy of these drugs in HIPEC after invasive surgical procedures must be investigated in prospective randomized trials in selected centers. In this sense, three randomized control trials are currently on-going [20]. Results from those studies will bring an adequate answer to the question of whether the addition of HIPEC actually brings clinical benefit in patients with PC of primary and recurrent ovarian cancer.

Colorectal cancer (CRC)

Although evidence of the efficacy of IP chemotherapy has been well established for ovarian cancer, there is still controversy concerning the use of IP chemotherapy, including CRS plus HIPEC, for PC of colorectal cancer (CRC) [32]. The clinical outcomes of IP chemotherapy for PC in CRC are summarized in Table 2.

In contrast to ovarian cancer, MMC and 5-Fu have been often used as IP treatment in HIPEC, presumably because these two drugs are the first agents to be clinically introduced for systemic chemotherapy for CRC. Verwaal et al. performed a comparative study between HIPEC using MMC and conventional chemotherapy, and reported MST of around 22 months in the HIPEC group, which was better than that in the conventional chemotherapy group (12 months), although the number of cases was not sufficient [33–35]. On the other hand, Glehen et al. summarized multi-institutional registry data and reported MST of 19.2 months in total patients and 32.4 months in patients who received complete cytoreduction [36]. More recently, they reported better survival, with MST of more than 30 months in other series [37–39]. Similar results have been reported by other groups [40–44]. Kianmanesh et al. have proposed that the presence of resectable hepatic metastasis associated with PC is not a contraindication for HIPEC [43].

Recently, Elias et al. have reported significant efficacy of HIPEC using oxaliplatin, another key drug for metastatic CRC [45]. According to their analysis, median OS of patients who were treated with complete CRS and HIPEC was 63 months, which surpassed that of the systemic chemotherapy group (24 months). Although PCI score and the extent of CRS in these patients were not clearly described in this series, the excellent outcome suggests that HIPEC with oxaliplatin may be a promising strategy for PC of CRS.

As described in ovarian cancer, HIPEC was associated with a high complication rate [5,36]. Moreover, 5-Fu has little heat synergy and thus it is currently used in early postoperative intraperitoneal chemotherapy (EPIC) or non-hyperthermic sequential post-operative intraperitoneal chemotherapy (SPIC) for CRC. Cashin et al. performed a retrospective cohort study [46] and a comparative study [47], in which SPIC treatment consisted of IP 5-FU 500–600 mg/m^2 and IV leucovorin 60 mg/m^2 once a day for 6 days. According to their results, however, the outcome of patients with SPIC did not exceed that of patients with HIPEC. However, in these studies, the drug combinations were different between HIPEC and EPIC/SPIC, and a further controlled study is necessary to evaluate the real benefit of HIPEC.

In summary, MST of patients who received IP chemotherapy was mostly 19.2–38.4 months with 5-year survival of 19–51%, which were almost the same as those of patients with ovarian cancer. Again, cautious interpretation is necessary for these retrospective data. However, taking into account that survival of CRC patients with peritoneal metastasis was relatively shorter than that of patients with metastasis at other sites [48], this trend suggests the clinical usefulness of HIPEC for, at least, selected patients with PC of CRC.

Gastric cancer (GC)

The clinical results of IP chemotherapy for PC of gastric cancer (GC) are summarized in Table 3. As in ovarian and colorectal cancer, CRS and HIPEC using MMC, 5-Fu, CDDP or L-OHP were performed for PC of GC [49–54], but MST was 9–12 months and 5-year survival was 6.7–16%, and MST of patients who received optimal cytoreduction was 15–23.3 months, which were significantly worse than those of patients with ovarian cancer or CRC. This is presumably due to the higher malignant potential of seeded GC cells, as compared with ovarian or colorectal cancer cells.

Recently, IP chemotherapy has been used in a neoadjuvant setting combined with systemic chemotherapy (NIPS) for PC of GC in Japan [55–59]. In particular, IP administration of paclitaxel (PTX) or docetaxel (DOC) without heating during the perioperative period has been used and produced MST of more than 20 months and 1-year survival of more than 70% [56–58].

PTX is water insoluble and, for clinical use, is conventionally solubilized in polyoxyethylated castor oil named Cremophor EL and ethanol (i.e., Taxol®) [60,61]. Taxol® is considered suitable for IP chemotherapy, due to its large particle size (10–12 nm diameter),

Table 2
Clinical outcomes of intraperitoneal chemotherapy for colorectal cancer.

Author, year	*N*	Method	Intraperitoneally administered agents	MST (months)	1 yr-OS (%)	2 yr-OS (%)	3 yr-OS (%)	5 yr-OS (%)
Glehen, 2004[36]	377	HIPEC and/or EPIC	HIPEC: MMC (+CDDP) or L-OHP EPIC: 5-FU (+MMC)	19.2 (32.4)	72 (87)		39 (47)	19 (31)
Verwaal, 2005[33]	**117**	**HIPEC**	**MMC (35 mg/m^2)**	**21.8 (42.9)**	**75 (94)**		**28 (56)**	**19 (43)**
Da Silva[41]	156	HIPEC and/or EPIC	MMC (10–12.5 mg/m^2), 5-FU (650 mg/m^2)	(33)	(88)		(44)	(32)
Kianmanesh, 2007[43]	43	HIPEC	MMC (120 mg/m^2) + CDDP (200 mg/m^2)	38.4		72		
Verwaal, 2008[35]	**54**	**HIPEC**	**MMC (35 mg/m^2)**	**22.2**				
Shen, 2008[40]	55	HIPEC	Variable	34	91		48	26
Elias, 2009[45]	48	HIPEC	L-OHP (460 mg/m^2)	62.7		81		51
Franko, 2010[42]	67	HIPEC	MMC (30 mg/m^2)	34.7				
Elias, 2010[39]	341 colon	HIPEC and/or EPIC	HIPEC: MMC (30–50 mg/m^2) (+CDDP 50–100 mg/m^2) EPIC: MMC (30 mg/m^2) + 5-FU (600 mg/m^2)	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
Cashin, 2012[46]	69	HIPEC	HIPEC: MMC (30 mg/m^2) + L-OHP (460 mg/m^2)	34				40
	57	SPIC	SPIC:5-FU (500–600 mg/m^2)	25				18
Cashin, 2012[47]	**16**	**HIPEC SPIC**	**HIPEC: MMC (30 mg/m2) + L-OHP**	**36.5**				
	16		**(460 mg/m^2)** **SPIC:5-FU (500–600 mg/m^2)**	**23.9**				
Yonemura, 2013[44]	142	HIPEC	MMC (20 mg/m^2) + CDDP (100 mg/m^2)	24.4				23.4

Abbreviations: MST: median survival time, OS: overall survival, HIPEC: heated intraperitoneal chemotherapy, EPIC: early post-operative intraperitoneal chemotherapy, SPIC: sequential perioperative intraperitoneal chemotherapy, MMC: mitomycin C, 5-FU: 5-fluorouracil, L-OHP: oxaliplatin, EPIC: early postoperative intraperitoneal chemotherapy, CDDP: cisplatin, CPT-11: irinotecan.
Quoted values are those in patients who received complete cytoreductive surgery for PC.
Studies written in bold letters are prospective controlled studies.

Table 3
Clinical outcomes of intraperitoneal chemotherapy for gastric cancer.

Author, year	N	Method	Intraperitoneally administered agents	MST (months)	1 yr-OS (%)	2 yr-OS (%)	3 yr-OS (%)	5 yr-OS (%)
Hall, 2004 [49]	34	HIPEC	MMC (30 mg + 10 mg)	11.2 (23.3)	45	16		
Glehen, 2004 [50]	49	HIPEC	MMC (40–60 mg)	10.3 (21.3)	48.1 (74.8)	19.9 (36.8)		16 (29.4)
Yonemura, 2005 [51]	47	HIPEC	MMC (30 mg) + CDDP (300 mg) + VP-16 (150 mg)	11.5 (15.5)				6.7 (13)
Yonemura, 2006 [55]	61	NIPS	DOC (40 mg/m^2) + CBDCA (150 mg/m^2)	14.4 (20.4)	67			
Cheong, 2007 [52]	154	EPIC	5-FU (500 mg/m^2) + CDDP (40 mg/m^2)	11.4 (25.5)				12.2 (31.7)
Yang, 2010 [53]	28	HIPEC	MMC (30 mg) + HCPT (20 mg) or CDDP (120 mg)	12	50	43		
Glehen, 2010 [54]	85	HIPEC and/or EPIC	HIPEC: MMC (30–50 mg/m^2) + CDDP (50–100 mg/m^2) or L-OHP (360–460 mg/m^2)+ CPT-11 (100–200 mg/m^2) EPIC: MMC (10 mg/m^2)+ 5-FU (600 mg/m^2)	9.2 (15)	48 (61)		18 (31)	13 (23)
Ishigami, 2010 [56]	40	NIPS	PTX (20 mg/m^2)	22.6	78			
Fujiwara, 2012 [57]	18	NIPS	DOC (40–60 mg/m^2)	24.6	76	54		
Fushida, 2013 [58]	27*	NIPS	DOC (60 mg/m^2)	16.2	70.4	33.4		

Abbreviations: MST: median survival time, OS: overall survival, HIPEC: heated intraperitoneal chemotherapy, NIPS; Neoadjuvant intraperitoneal and systemic chemotherapy, MMC: mitomycin C, CDDP: cisplatin, VP-16: etoposide, DOC: docetaxel, CBDCA: carboplatin, 5-FU: 5-fluorouracil, HCPT: hydroxycamptothecin, L-OHP: oxaliplatin, CPT-11: irinotecan, SPIC: sequential perioperative intraperitoneal chemotherapy, PTX: paclitaxel.
Quoted values are those in patients who received complete cytoreductive surgery for PC.

which results in prolonged retention of the drug in the peritoneal cavity [12,62], suggesting a pharmacokinetic advantage for IP chemotherapy. In fact, bidirectional administration of IV and IP PTX maintained an effective concentration of PTX in the peritoneal cavity for over 72 h [63]. Another advantage of this regimen is that PTX can be repeatedly administered many times, both before and after CRS, whereas in previous studies, IP therapy was limited to a short postoperative period. In fact, salvage gastrectomy after a good response to this combination chemotherapy prolonged the survival of patients with severe PC with malignant ascites [64].

More importantly, the toxicity of the NIPS regimen and complications of subsequent CRS are relatively mild [57,58,64]. Although the real efficacy should be evaluated in a comparative study, these results strongly suggest the advantage of NIPS using taxanes. 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 [65], began in November 2011.

Present issues of IP chemotherapy

The aim of IP chemotherapy is to increase the dose and exposure time of intra-abdominal cancer cells to anticancer drugs, with minimal systemic toxic effects. Prolonged retention in the peritoneal cavity and clearance from the systemic circulation are believed to be key attributes for ideal drug candidates designed for IP chemotherapy [11,12]. Pharmacokinetics after IP administration are affected by a variety of biophysical parameters, including molecular weight and electric charge of drugs, as well as temperature, pH, and other conditions of the solution. Thus, the time–concentration curves of drugs in the peritoneum and plasma vary widely according to drug type. After IP administration, hydrophilic low-weight molecular materials, such as cisplatin, 5-FU, and MMC, are rapidly absorbed into the subperitoneal capillary vessels through the peritoneal mesothelial layer. In contrast, hydrophobic high-weight molecular materials, such as taxanes, gradually drain, mainly from stomata or milky spots that are the direct openings of lymphatic vessels [66,67]. 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 [12,68,69]. In IP chemotherapy, therefore, the pharmacokinetic profile of each drug is considered to critically affect the clinical efficacy against PC.

In fact, IP administration of PTX showed excellent clinical results for PC of ovarian cancer [30,70], as well as GC [56,64]. Docetaxel was reported to be effective against PC of GC [58,71]. Taxanes are not commonly used for systemic chemotherapy for patients with CRC, since phase II trials yielded negative results [72–74]. However, clinical evaluation of IP PTX should also be considered for patients with PC from CRC, since preclinical investigations of IP PTX for CRC showed efficacy [75,76].

Another important issue in IP chemotherapy is whether or not a hyperthermic condition is necessary. Historically, IP chemotherapy was often performed with hyperthermia, designated as HIPEC. The aim of HIPEC is to achieve a high local concentration of chemotherapeutic agents in the peritoneal cavity and to promote good absorption of agents from the surface of peritoneal tumors, with minimal systemic toxic effects. In fact, heat has been shown to elicit a synergistic antitumor effect with MMC, CDDP, and oxaliplatin [77,78]. In general, however, HIPEC is considered to be associated with high morbidity and mortality, which has hampered the widespread use of this treatment strategy.

Few studies have compared HIPEC with early postoperative intraperitoneal chemotherapy (EPIC) or non-hyperthermic sequential postoperative intraperitoneal chemotherapy (SPIC). Elias et al. reported that HIPEC with oxaliplatin was better tolerated than was EPIC with MMC and 5-FU, and was twice as efficient at curing residual PC from CRC with minimal residual disease after surgery [79]. Cashin et al. reported that HIPEC was associated with improved outcome compared with SPIC, with similar morbidity and mortality in patients with PC from CRC [46]. They concluded that CRS with HIPEC might be the optimal treatment of choice for patients with PC from CRC with minimal residual disease. However, in these studies, drug combinations were different between HIPEC and EPIC/SPIC, and thus further studies are required for a more valid comparison.

New approach in IP chemotherapy

Catumaxomab

Catumaxomab is a trifunctional monoclonal antibody with two different antigen-binding sites and a functional Fc domain [80]. 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 [81–84]. Heiss et al. reported the results of 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. In this study, 258 patients with malignant ascites were randomized to receive paracentesis plus catumaxomab or paracentesis alone, and improved puncture-free survival and a better survival trend were reported. Moreover, treatment with catumaxomab significantly delayed deterioration in patient quality of life [85].

Bevacizumab

Vascular endothelial growth factor A (VEGF-A) is a key mediator of angiogenesis, and bevacizumab, a humanized variant of an anti-VEGF antibody, has shown significant efficacy in combination with chemotherapy and is now widely used for metastatic CRC [86]. VEGF is markedly elevated in malignant ascites, where it worsens the condition by increasing endothelial cell permeability [87]. Therefore, VEGF inhibition in the peritoneal cavity is considered beneficial, not only as an inhibitor of tumorigenesis but also as an inhibitor of malignant ascites formation [88], although no clinical trials addressing the use of bevacizumab with IP chemotherapy have been reported. However, bevacizumab might be administered systemically, because it is rapidly absorbed from the peritoneum and enters the systemic circulation when administered by IP injection [89,90].

Nanodrugs

Nanodrugs are a new type of drug formulation, 20–100 nm in molecular diameter, significantly smaller than conventional drugs. Nanodrugs effectively accumulate in tumor tissue due to enhanced permeability and retention (EPR) [91], which results in enhanced antitumor effects and less toxicity in normal tissues. The EPR effect is based on the particular characteristics of solid tumor tissues, such as incomplete vascular architecture, hyperpermeability of tumor vessel walls, and immature lymphatic drainage. Based on this concept, various kinds of nanodrugs have been developed for cancer treatment [92–95]. For example, Abraxane®, an albumin-bound PTX, is currently in clinical use for breast, lung, and gastric cancer [96,97]. NK105 is a PTX-incorporating "core-shell-type" polymeric micellar nanoparticle formulation [98,99]. PMB-30W is a water-soluble, amphiphilic polymer composed of 2-methacryloxyethyl phosphorylcholine and n-butyl methacrylate enables the construction of PTX-containing nanoparticles of approximately 50 nm diameter [100]. IP administration of PTX formulated with PMB-30W resulted in deeper penetration into peritoneal nodules and exhibited enhanced anti-tumor effects against peritoneal xenografts of human GC as compared to conventional cremophor-conjugated PTX in a murine model [101,102]. In the same model, IP administration of NK105 was also shown to enhance antitumor effects, compared with IP Taxol® [103]. These results suggest that IP chemotherapy with nanoparticulate drugs might be a promising strategy for the treatment of PC. Although these drugs have all been examined with systemic administration, IP administration of these drugs for PC should be evaluated in a clinical study.

Controlled absorption and drug release

Water-soluble, low molecular-weight agents are rapidly absorbed from the peritoneum after IP administration, and the ratio of AUC for the peritoneum to that for plasma is low [12,104,105]. Although IP administration of such agents is still widely performed without any special artifice in DDS in clinical practice, development of new techniques to prolong the retention of drugs in the peritoneal cavity is necessary. Several studies have suggested that the addition of high molecular weight agents such as 4% icodextrin [106], 6% hydroxyethyl starch (hetastarch) [107], or non-animal stabilized hyaluronic acid [108] can prolong the retention time in the abdominal cavity. Since hyaluronic acid (HA) exists in the peritoneal cavity to make the peritoneal membrane a non-adhesive surface and prevent abrasion, it might be quite useful for IP chemotherapy. Hydrogels are formed by cross-linking hydrophilic macromolecules, which is another useful material for IP chemotherapy. HA-based hydrogel is a biocompatible material that prevents peritoneal adhesion after surgical procedures [109,110]. Since hydrogels are sensitive to stimuli such as temperature [111,112] or pH [113], they have considerable potential in biomedical and pharmaceutical applications, especially in site-specific and controlled DDS [114]. In fact, the addition of hydrogels has been reported to prolong drug retention in the peritoneal cavity and to enhance the antitumor effects against PC [115–119]. In particular, a combination of controlled release and target-specific delivery by HA-based hydrogel through interactions between CD44 and HA also seems promising [120,121].

Conclusion

For many years, PC has been considered to be a terminal disease, and treatment has typically been palliative. In some institutes, aggressive treatment such as peritonectomy and HIPEC has somehow prolonged the survival of these patients. However, because of high morbidity and mortality, such treatment strategies have not been performed worldwide. IP chemotherapy enables direct exposure of each tumor cell to a high concentration of drugs, and thus seems to be a reasonable drug delivery method. However, the effectiveness of IP chemotherapy critically depends on how long the anticancer agents are retained in the abdominal cavity, and thus taxanes are considered to be the most suitable drug for IP chemotherapy, thus far. Another important concern is how deeply the drug can directly infiltrate into peritoneal tumors. However, many factors are related to the distance of drug penetration in solid tumors, and the mechanisms are still largely unknown [122]. Drug modification, to prolong drug retention in the peritoneal cavity and to enhance permeability in solid tumors, should improve the survival of patients with this dismal disease.

Disclosure statement

The author has no financial or personal relationship with other people or organizations that could inappropriately influence the work.

Role of funding source

This study was financially supported by the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest statement

The authors have no conflict of interest to declare.

Authorship statement

Guarantor of the integrity of the study: Joji Kitayama.
Study concepts: Joji Kitayama.

Study design: Joji Kitayama.
Definition of intellectual content: Joji Kitayama.
Literature research: Joji Kitayama.
Clinical studies: Joji Kitayama.
Experimental studies: Joji Kitayama.
Data acquisition: Joji Kitayama.
Data analysis: Joji Kitayama.
Statistical analysis: Joji Kitayama.
Manuscript preparation: Joji Kitayama.
Manuscript editing: Joji Kitayama.
Manuscript review: Joji Kitayama.

Acknowledgments

This study was funded by the Ministry of Education, Culture, Sports, Science, and Technology (24659599) and the Ministry of Health, Labor and Welfare of Japan (Iryougijutsu-ippann-003).

References

[1] Yonemura Y, Endou Y, Sasaki T, Hirano M, Mizumoto A, Matsuda T, et al. Surgical treatment for peritoneal carcinomatosis from gastric cancer. Eur J Surg Oncol – J Eur Soc Surg Oncol Br Assoc Surg Oncol 2010;36:1131–8.
[2] Colombo N, Van Gorp T, Parma G, Amant F, Gatta G, Sessa C, et al. Ovarian cancer. Crit Rev Oncol Hematol 2006;60:159–79.
[3] Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358–63.
[4] Chua TC, Robertson G, Liauw W, Farrell R, Yan TD, Morris DL. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery in ovarian cancer peritoneal carcinomatosis: systematic review of current results. J Cancer Res Clin Oncol 2009;135:1637–45.
[5] Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol – Off J Am Soc Clin Oncol 2006;24:4011–9.
[6] Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. Cancer Treat Res 1996;82:53–63.
[7] Markman M, Walker JL. Intraperitoneal chemotherapy of ovarian cancer: a review, with a focus on practical aspects of treatment. J Clin Oncol – Off J Am Soc Clin Oncol 2006;24:988–94.
[8] Piso P, Arnold D. Multimodal treatment approaches for peritoneal carcinosis in colorectal cancer. Dtsch Arztebl Int 2011;108:802–8.
[9] Chua TC, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, Gilly FN, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol – Off J Am Soc Clin Oncol 2012;30:2449–56.
[10] Chua TC, Chong CH, Morris DL. Peritoneal mesothelioma: current status and future directions. Surg Oncol Clin N Am 2012;21:635–43.
[11] Dedrick RL, Myers CE, Bungay PM, DeVita Jr VT. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 1978;62:1–11.
[12] Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. Lancet Oncol 2003;4:277–83.
[13] Sugarbaker PH, Mora JT, Carmignani P, Stuart OA, Yoo D. Update on chemotherapeutic agents utilized for perioperative intraperitoneal chemotherapy. Oncologist 2005;10:112–22.
[14] Ozols RF. Treatment goals in ovarian cancer. Int J Gynecol Cancer 2005;15(Suppl. 1):3–11.
[15] Markman M. Intraperitoneal antineoplastic agents for tumors principally confined to the peritoneal cavity. Cancer Treat Rev 1986;13:219–42.
[16] Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996;335:1950–5.
[17] Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol – Off J Am Soc Clin Oncol 2001;19:1001–7.
[18] Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34–43.
[19] Morgan Jr RJ, Alvarez RD, Armstrong DK, Boston B, Burger RA, Chen LM, et al. Epithelial ovarian cancer. J Natl Compr Canc Netw 2011;9:82–113.
[20] Deraco M, Baratti D, Laterza B, Balestra MR, Mingrone E, Macri A, et al. Advanced cytoreduction as surgical standard of care and hyperthermic intraperitoneal chemotherapy as promising treatment in epithelial ovarian cancer. Eur J Surg Oncol – J Eur Soc Surg Oncol Br Assoc Surg Oncol 2011;37:4–9.
[21] Zanon C, Clara R, Chiappino I, Bortolini M, Cornaglia S, Simone P, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. World J Surg 2004;28:1040–5.
[22] Ryu KS, Kim JH, Ko HS, Kim JW, Ahn WS, Park YG, et al. Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer. Gynecol Oncol 2004;94:325–32.
[23] Raspagliesi F, Kusamura S, Campos Torres JC, de Souza GA, Ditto A, Zanaboni F, et al. Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: the experience of National Cancer Institute of Milan. Eur J Surg Oncol – J Eur Soc Surg Oncol Br Assoc Surg Oncol 2006;32:671–5.
[24] Cotte E, Glehen O, Mohamed F, Lamy F, Falandry C, Golfier F, et al. Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemoresistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. World J Surg 2007;31:1813–20.
[25] Di Giorgio A, Naticchioni E, Biacchi D, Sibio S, Accarpio F, Rocco M, et al. Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer 2008;113:315–25.
[26] Guardiola E, Delroeux D, Heyd B, Combe M, Lorgis V, Demarchi M, et al. Intraoperative intra-peritoneal chemotherapy with cisplatin in patients with peritoneal carcinomatosis of ovarian cancer. World J Surg Oncol 2009;7:14.
[27] Pavlov MJ, Kovacevic PA, Ceranic MS, Stamenkovic AB, Ivanovic AM, Kecmanovic DM. Cytoreductive surgery and modified heated intraoperative intraperitoneal chemotherapy (HIPEC) for advanced and recurrent ovarian cancer – 12-year single center experience. Eur J Surg Oncol – J Eur Soc Surg Oncol Br Assoc Surg Oncol 2009;35:1186–91.
[28] Tentes AA, Kakolyris S, Kyziridis D, Karamveri C. Cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy in the treatment of advanced epithelial ovarian cancer. J Oncol 2012;2012:358341.
[29] Bakrin N, Cotte E, Golfier F, Gilly FN, Freyer G, Helm W, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. Ann Surg Oncol 2012;19:4052–8.
[30] Rufian S, Munoz-Casares FC, Briceno J, Diaz CJ, Rubio MJ, Ortega R, et al. Radical surgery-peritonectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer. J Surg Oncol 2006;94:316–24.
[31] Bae JH, Lee JM, Ryu KS, Lee YS, Park YG, Hur SY, et al. Treatment of ovarian cancer with paclitaxel- or carboplatin-based intraperitoneal hyperthermic chemotherapy during secondary surgery. Gynecol Oncol 2007;106:193–200.
[32] Sugarbaker PH, Ryan DP. Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: standard of care or an experimental approach? Lancet Oncol 2012;13:e362–9.
[33] Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol 2005;12:65–71.
[34] Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol – Off J Am Soc Clin Oncol 2003;21:3737–43.
[35] Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426–32.
[36] Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol – Off J Am Soc Clin Oncol 2004;22:3284–92.
[37] Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol – Off J Am Soc Clin Oncol 2010;28:63–8.
[38] Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010;116:5608–18.
[39] Elias D, Glehen O, Pocard M, Quenet F, Goere D, Arvieux C, et al. A comparative study of complete cytoreductive surgery plus intraperitoneal chemotherapy to treat peritoneal dissemination from colon, rectum, small bowel, and nonpseudomyxoma appendix. Ann Surg 2010;251:896–901.
[40] Shen P, Thai K, Stewart JH, Howerton R, Loggie BW, Russell GB, et al. Peritoneal surface disease from colorectal cancer: comparison with the hepatic metastases surgical paradigm in optimally resected patients. Ann Surg Oncol 2008;15:3422–32.
[41] da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal

chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg 2006;203:878–86.
[42] Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh 3rd HJ. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer 2010;116:3756–62.
[43] Kianmanesh R, Scaringi S, Sabate JM, Castel B, Pons-Kerjean N, Coffin B, et al. Iterative cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. Ann Surg 2007;245:597–603.
[44] Yonemura Y, Canbay E, Ishibashi H. Prognostic factors of peritoneal metastases from colorectal cancer following cytoreductive surgery and perioperative chemotherapy. Sci World J 2013;2013:978394.
[45] Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol – Off J Am Soc Clin Oncol 2009;27:681–5.
[46] Cashin PH, Graf W, Nygren P, Mahteme H. Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: prognosis and treatment of recurrences in a cohort study. Eur J Surg Oncol – J Eur Soc Surg Oncol Br Assoc Surg Oncol 2012;38:509–15.
[47] Cashin PH, Graf W, Nygren P, Mahteme H. Intraoperative hyperthermic versus postoperative normothermic intraperitoneal chemotherapy for colonic peritoneal carcinomatosis: a case-control study. Ann Oncol – Off J Eur Soc Med Oncol/ESMO 2012;23:647–52.
[48] Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol – Off J Am Soc Clin Oncol 2012;30:263–7.
[49] Hall JJ, Loggie BW, Shen P, Beamer S, Douglas Case L, McQuellon R, et al. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for advanced gastric cancer. J Gastrointest Surg 2004;8:454–63.
[50] Glehen O, Schreiber V, Cotte E, Sayag-Beaujard AC, Osinsky D, Freyer G, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. Arch Surg 2004;139:20–6.
[51] Yonemura Y, Kawamura T, Bandou E, Takahashi S, Sawa T, Matsuki N. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Br J Surg 2005;92:370–5.
[52] Cheong JH, Shen JY, Song CS, Hyung WJ, Shen JG, Choi SH, et al. Early postoperative intraperitoneal chemotherapy following cytoreductive surgery in patients with very advanced gastric cancer. Ann Surg Oncol 2007;14:61–8.
[53] Yang XJ, Li Y, Yonemura Y. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat gastric cancer with ascites and/or peritoneal carcinomatosis: results from a Chinese center. J Surg Oncol 2010;101:457–64.
[54] Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010;17:2370–7.
[55] Yonemura Y, Bandou E, Sawa T, Yoshimitsu Y, Endou Y, Sasaki T, et al. Neoadjuvant treatment of gastric cancer with peritoneal dissemination. Eur J Surg Oncol – J Eur Soc Surg Oncol Br Assoc Surg Oncol 2006;32:661–5.
[56] Ishigami H, Kitayama J, Kaisaki S, Hidemura A, Kato M, Otani K, et al. Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. Ann Oncol – Off J Eur Soc Med Oncol/ESMO 2010;21:67–70.
[57] Fujiwara Y, Takiguchi S, Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, et al. Intraperitoneal docetaxel combined with S-1 for advanced gastric cancer with peritoneal dissemination. J Surg Oncol 2012;105:38–42.
[58] Fushida S, Kinoshita J, Kaji M, Hirono Y, Goda F, Yagi Y, et al. Phase I/II study of intraperitoneal docetaxel plus S-1 for the gastric cancer patients with peritoneal carcinomatosis. Cancer Chemother Pharmacol 2013;71:1265–72.
[59] Yamaguchi H, Kitayama J, Ishigami H, Emoto S, Yamashita H, Watanabe T. A phase 2 trial of intravenous and intraperitoneal paclitaxel combined with S-1 for treatment of gastric cancer with macroscopic peritoneal metastasis. Cancer 2013;119:3354–8.
[60] Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med 1995;332:1004–14.
[61] Singla AK, Garg A, Aggarwal D. Paclitaxel and its formulations. Int J Pharm 2002;235:179–92.
[62] Soma D, Kitayama J, Ishigami H, Kaisaki S, Nagawa H. Different tissue distribution of paclitaxel with intravenous and intraperitoneal administration. J Surg Res 2009;155:142–6.
[63] Ishigami H, Kitayama J, Otani K, Kamei T, Soma D, Miyato H, et al. Phase I pharmacokinetic study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer. Oncology 2009;76:311–4.
[64] Kitayama J, Ishigami H, Yamaguchi H, Yamashita H, Emoto S, Kaisaki S, et al. Salvage gastrectomy after intravenous and intraperitoneal paclitaxel (PTX) administration with oral S-1 for peritoneal dissemination of advanced gastric cancer with malignant ascites. Ann Surg Oncol 2014 Feb;21(2):539–46.
[65] Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008;9:215–21.
[66] Flessner MF, Fenstermacher JD, Blasberg RG, Dedrick RL. Peritoneal absorption of macromolecules studied by quantitative autoradiography. Am J Physiol 1985;248:H26–32.
[67] Wang ZB, Li M, Li JC. Recent advances in the research of lymphatic stomata. Anat Rec (Hoboken) 2010;293:754–61.
[68] Ceelen WP, Flessner MF. Intraperitoneal therapy for peritoneal tumors: biophysics and clinical evidence. Nat Rev Clin Oncol 2010;7:108–15.
[69] Yan TD, Cao CQ, Munkholm-Larsen S. A pharmacological review on intraperitoneal chemotherapy for peritoneal malignancy. World J Gastrointest Oncol 2010;2:109–16.
[70] Armstrong DK, Fleming GF, Markman M, Bailey HH. A phase I trial of intraperitoneal sustained-release paclitaxel microspheres (Paclimer) in recurrent ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2006;103:391–6.
[71] Fujiwara Y, Takiguchi S, Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, et al. Neoadjuvant intraperitoneal and systemic chemotherapy for gastric cancer patients with peritoneal dissemination. Ann Surg Oncol 2011;18:3726–31.
[72] Pazdur R, Lassere Y, Soh LT, Ajani JA, Bready B, Soo E, et al. Phase II trial of docetaxel (Taxotere) in metastatic colorectal carcinoma. Ann Oncol – Off J Eur Soc Med Oncol/ESMO 1994;5:468–70.
[73] Sternberg CN, ten Bokkel Huinink WW, Smyth JF, Bruntsch V, Dirix LY, Pavlidis NA, et al. Docetaxel (Taxotere), a novel taxoid, in the treatment of advanced colorectal carcinoma: an EORTC Early Clinical Trials Group Study. Br J Cancer 1994;70:376–9.
[74] Einzig AI, Neuberg D, Wiernik PH, Grochow LB, Ramirez G, O'Dwyer PJ, et al. Phase II trial of paclitaxel in patients with advanced Colon Cancer previously Untreated with cytotoxic chemotherapy: an Eastern Cooperative Oncology group trial (PA286). Am J Ther 1996;3:750–4.
[75] Hribaschek A, Ridwelski K, Pross M, Meyer F, Kuhn R, Halangk W, et al. Intraperitoneal treatment using taxol is effective for experimental peritoneal carcinomatosis in a rat model. Oncol Rep 2003;10:1793–8.
[76] Hribaschek A, Meyer F, Schneider-Stock R, Pross M, Ridwelski K, Lippert H. Comparison of intraperitoneal with intravenous administration of taxol in experimental peritoneal carcinomatosis. Chemotherapy 2007;53:410–7.
[77] Gonzalez-Moreno S, Gonzalez-Bayon LA, Ortega-Perez G. Hyperthermic intraperitoneal chemotherapy: rationale and technique. World J Gastrointest Oncol 2010;2:68–75.
[78] Detroz B, Laurent S, Honore P, Blaffart F, Limet R, Meurisse M. Rationale for hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment or prevention of peritoneal carcinomatosis. Acta Chir Belg 2004;104:377–83.
[79] Elias D, Benizri E, Di Pietrantonio D, Menegon P, Malka D, Raynard B. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. Ann Surg Oncol 2007;14:509–14.
[80] Bokemeyer C. Catumaxomab–trifunctional anti-EpCAM antibody used to treat malignant ascites. Expert Opin Biol Ther 2010;10:1259–69.
[81] Riesenberg R, Buchner A, Pohla H, Lindhofer H. Lysis of prostate carcinoma cells by trifunctional bispecific antibodies (alpha EpCAM x alpha CD3). J Histochem Cytochem 2001;49:911–7.
[82] Schmitt M, Schmitt A, Reinhardt P, Thess B, Manfras B, Lindhofer H, et al. Opsonization with a trifunctional bispecific (alphaCD3 x alphaEpCAM) antibody results in efficient lysis in vitro and in vivo of EpCAM positive tumor cells by cytotoxic T lymphocytes. Int J Oncol 2004;25:841–8.
[83] Ruf P, Gires O, Jager M, Fellinger K, Atz J, Lindhofer H. Characterisation of the new EpCAM-specific antibody HO-3: implications for trifunctional antibody immunotherapy of cancer. Br J Cancer 2007;97:315–21.
[84] Strohlein MA, Heiss MM. The trifunctional antibody catumaxomab in treatment of malignant ascites and peritoneal carcinomatosis. Future Oncol 2010;6:1387–94.
[85] Wimberger P, Gilet H, Gonschior AK, Heiss MM, Moehler M, Oskay-Oezcelik G, et al. Deterioration in quality of life (QoL) in patients with malignant ascites: results from a phase II/III study comparing paracentesis plus catumaxomab with paracentesis alone. Ann Oncol – Off J Eur Soc Med Oncol/ESMO 2012;23:1979–85.
[86] Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.
[87] Zebrowski BK, Liu W, Ramirez K, Akagi Y, Mills GB, Ellis LM. Markedly elevated levels of vascular endothelial growth factor in malignant ascites. Ann Surg Oncol 1999;6:373–8.
[88] Kobold S, Hegewisch-Becker S, Oechsle K, Jordan K, Bokemeyer C, Atanackovic D. Intraperitoneal VEGF inhibition using bevacizumab: a potential approach for the symptomatic treatment of malignant ascites? Oncologist 2009;14:1242–51.
[89] Yagi Y, Fushida S, Harada S, Tsukada T, Kinoshita J, Oyama K, et al. Biodistribution of humanized anti-VEGF monoclonal antibody/bevacizumab on peritoneal metastatic models with subcutaneous xenograft of gastric cancer in mice. Cancer Chemother Pharmacol 2010;66:745–53.
[90] Shah DK, Veith J, Bernacki RJ, Balthasar JP. Evaluation of combined bevacizumab and intraperitoneal carboplatin or paclitaxel therapy in a mouse model of ovarian cancer. Cancer Chemother Pharmacol 2011;68:951–8.
[91] Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res 1986;46:6387–92.

[92] Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release 2000;65:271–84.
[93] Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol 2007;2:751–60.
[94] Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nat Rev Drug Discov 2008;7:771–82.
[95] Matsumura Y, Kataoka K. Preclinical and clinical studies of anticancer agent-incorporating polymer micelles. Cancer Sci 2009;100:572–9.
[96] Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol – Off J Am Soc Clin Oncol 2005;23:7794–803.
[97] Petrelli F, Borgonovo K, Barni S. Targeted delivery for breast cancer therapy: the history of nanoparticle-albumin-bound paclitaxel. Expert Opin Pharmacother 2010;11:1413–32.
[98] Hamaguchi T, Matsumura Y, Suzuki M, Shimizu K, Goda R, Nakamura I, et al. NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumour activity and reduce the neurotoxicity of paclitaxel. Br J Cancer 2005;92:1240–6.
[99] Kato K, Tahara M, Hironaka S, Muro K, Takiuchi H, Hamamoto Y, et al. A phase II study of paclitaxel by weekly 1-h infusion for advanced or recurrent esophageal cancer in patients who had previously received platinum-based chemotherapy. Cancer Chemother Pharmacol 2011;67:1265–72.
[100] Konno T, Watanabe J, Ishihara K. Enhanced solubility of paclitaxel using water-soluble and biocompatible 2-methacryloyloxyethyl phosphorylcholine polymers. J Biomed Mater Res A 2003;65:209–14.
[101] Soma D, Kitayama J, Konno T, Ishihara K, Yamada J, Kamei T, et al. Intraperitoneal administration of paclitaxel solubilized with poly(2-methacryloxyethyl phosphorylcholine-co n-butyl methacrylate) for peritoneal dissemination of gastric cancer. Cancer Sci 2009;100:1979–85.
[102] Kamei T, Kitayama J, Yamaguchi H, Soma D, Emoto S, Konno T, et al. Spatial distribution of intraperitoneally administrated paclitaxel nanoparticles solubilized with poly (2-methacryloxyethyl phosphorylcholine-co n-butyl methacrylate) in peritoneal metastatic nodules. Cancer Sci 2011;102:200–5.
[103] Emoto S, Yamaguchi H, Kishikawa J, Yamashita H, Ishigami H, Kitayama J. Antitumor effect and pharmacokinetics of intraperitoneal NK105, a nanomicellar paclitaxel formulation for peritoneal dissemination. Cancer Sci 2012;103:1304–10.
[104] Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst 1997;89:480–7.
[105] Echarri Gonzalez MJ, Green R, Muggia FM. Intraperitoneal drug delivery for ovarian cancer: why, how, who, what, and when? Oncol (Williston Park) 2011;25:156–65. 70.
[106] Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM. Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% icodextrin. Drug Deliv 2001;8:9–12.
[107] Mohamed F, Marchettini P, Stuart OA, Sugarbaker PH. Pharmacokinetics and tissue distribution of intraperitoneal paclitaxel with different carrier solutions. Cancer Chemother Pharmacol 2003;52:405–10.
[108] Yamada J, Kitayama J, Tsuno NH, Yamashita H, Miyato H, Soma D, et al. Intraperitoneal administration of paclitaxel with non-animal stabilized hyaluronic acid as a vehicle–a new strategy against peritoneal dissemination of gastric cancer. Cancer Lett 2008;272:307–15.
[109] Yeo Y, Highley CB, Bellas E, Ito T, Marini R, Langer R, et al. In situ cross-linkable hyaluronic acid hydrogels prevent post-operative abdominal adhesions in a rabbit model. Biomaterials 2006;27:4698–705.
[110] Ito T, Yeo Y, Highley CB, Bellas E, Benitez CA, Kohane DS. The prevention of peritoneal adhesions by in situ cross-linking hydrogels of hyaluronic acid and cellulose derivatives. Biomaterials 2007;28:975–83.
[111] Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev 2001;53:321–39.
[112] Kwak MK, Hur K, Yu JE, Han TS, Yanagihara K, Kim WH, et al. Suppression of in vivo tumor growth by using a biodegradable thermosensitive hydrogel polymer containing chemotherapeutic agent. Invest New Drugs 2010;28:284–90.
[113] Wu W, Liu J, Cao S, Tan H, Li J, Xu F, et al. Drug release behaviors of a pH sensitive semi-interpenetrating polymer network hydrogel composed of poly(vinyl alcohol) and star poly[2-(dimethylamino)ethyl methacrylate]. Int J Pharm 2011;416:104–9.
[114] He C, Kim SW, Lee DS. In situ gelling stimuli-sensitive block copolymer hydrogels for drug delivery. J Control Release 2008;127:189–207.
[115] Luo Y, Kirker KR, Prestwich GD. Cross-linked hyaluronic acid hydrogel films: new biomaterials for drug delivery. J Control Release 2000;69:169–84.
[116] Wang Y, Gong C, Yang L, Wu Q, Shi S, Shi H, et al. 5-FU-hydrogel inhibits colorectal peritoneal carcinomatosis and tumor growth in mice. BMC Cancer 2010;10:402.
[117] Yu J, Lee HJ, Hur K, Kwak MK, Han TS, Kim WH, et al. The antitumor effect of a thermosensitive polymeric hydrogel containing paclitaxel in a peritoneal carcinomatosis model. Invest New Drugs 2012;30:1–7.
[118] Bajaj G, Kim MR, Mohammed SI, Yeo Y. Hyaluronic acid-based hydrogel for regional delivery of paclitaxel to intraperitoneal tumors. J Control Release 2012;158:386–92.
[119] Emoto S, Yamaguchi H, Kamei T, Ishigami H, Suhara T, Suzuki Y, et al. Intraperitoneal administration of cisplatin via an in situ cross-linkable hyaluronic acid-based hydrogel for peritoneal dissemination of gastric cancer. Surg Today; 2013 Jul 26 [in press].
[120] Luo Y, Ziebell MR, Prestwich GD. A hyaluronic acid-taxol antitumor bioconjugate targeted to cancer cells. Biomacromolecules 2000;1:208–18.
[121] Auzenne E, Ghosh SC, Khodadadian M, Rivera B, Farquhar D, Price RE, et al. Hyaluronic acid-paclitaxel: antitumor efficacy against CD44(+) human ovarian carcinoma xenografts. Neoplasia 2007;9:479–86.
[122] Minchinton AI, Tannock IF. Drug penetration in solid tumours. Nat Rev Cancer 2006;6:583–92.

Case Reports in Oncology

Case Rep Oncol 2014;7:58–64

DOI: 10.1159/000358379
Published online: January 24, 2014

1662–6575/14/0071–58–64$39.50/0
www.karger.com/cro

Karger Open access

Intraperitoneal Paclitaxel Is Useful as Adjuvant Chemotherapy for Advanced Gastric Cancer with Serosal Exposure

Joji Kitayama Hironori Ishigami Hironori Yamaguchi
Shigenobu Emoto Toshiaki Watanabe

Department of Surgical Oncology, University of Tokyo, Tokyo, Japan

Key Words

Peritoneal recurrence · Nodal recurrence · Gastric cancer · Serosal invasion · Intraperitoneal chemotherapy · Paclitaxel

Abstract

Background: Intraperitoneal administration of paclitaxel (PTX) can elicit a marked clinical response in peritoneal metastases of gastric cancer. ***Methods:*** In this study, we retrospectively analyzed the clinical outcome of 17 patients who underwent R0 resection with D2 dissection for advanced gastric cancer with macroscopic serosal exposure and received intraperitoneal PTX as adjuvant therapy. ***Results:*** A pathological study revealed that the depth of invasion of the primary tumor was pT4a or pT4b in 10 cases, and that the pN stage was more than pN2 in 8 cases. Genetic analysis of peritoneal lavage fluid was performed in 14 cases, all of which were positive for carcinoembryonic antigen mRNA. In these patients, PTX was intraperitoneally administered at 20–60 mg/m^2 with oral S-1 for 3–36 months after surgery. In a median follow-up period of 66 months, recurrence occurred in the liver and peritoneum in 2 (11.7%) and 1 (5.9%) patients, respectively, and no nodal recurrence was observed. Five-year overall survival and disease-free survival were 88.2 and 82.3%, respectively. ***Conclusion:*** Since these patients are considered to be a high-risk group for peritoneal recurrence, this result strongly suggests that adjuvant chemotherapy including intraperitoneal PTX is a promising protocol to improve the outcome of patients with advanced gastric cancer with serosal exposure.

Joji Kitayama, MD
Department of Surgical Oncology
University of Tokyo
7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655 (Japan)
E-Mail kitayama-1SU@h.u-tokyo.ac.jp

KARGER

Introduction

Gastric cancer is the fourth leading cause of cancer-related deaths worldwide, and peritoneal dissemination is the most life-threatening form of metastasis and recurrence in patients with advanced gastric cancer [1]. In spite of the recent improvement in chemotherapeutic treatment for solid cancers, the effect of systemic chemotherapy on peritoneal metastases is still limited, possibly because of the peritoneum-plasma barrier which prevents effective drug delivery from the systemic circulation into the peritoneal cavity [2].

In contrast, intraperitoneal administration of paclitaxel (PTX) was developed to enhance antitumor activity against peritoneal metastases by maintaining a high concentration of the drug in the peritoneal cavity over a long period, and its clinical effects have been verified by a number of convincing clinical trials on ovarian cancer with peritoneal metastases [3, 4]. These results inspired us to use intraperitoneal PTX for peritoneal metastases of gastric cancer, and we therefore designed a study involving intraperitoneal and intravenous PTX combined with oral S-1 chemotherapy. A phase I study determined the optimum dose of intraperitoneal PTX to be 20 mg/m^2 [5]. We then conducted a phase II study in 40 patients with gastric cancer who had peritoneal metastases, showing a 1-year overall survival rate of 78% and a median survival time of 23.6 months [6]. In fact, we found that many metastatic nodules had macroscopically disappeared after several courses of the regimen even in cases with malignant ascites [7].

These results suggest that intraperitoneal PTX can be used as an adjuvant therapy to suppress peritoneal recurrence in advanced gastric cancer. According to the results of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) [8], postoperative administration of S-1 for 1 year is now considered to be the standard adjuvant treatment for curatively resected stage II/III gastric cancer in Japan. However, 5-year survival data indicate that the benefit of S-1 is less significant in stage III cancer, especially in patients with T4 tumor (serosal exposure) [9]. More recently, the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial has been performed in Korea, which demonstrates significant benefit in 3-year disease-free survival in stage III gastric cancer [10]. However, even in this study, the effect on peritoneal recurrence was not as marked as that on recurrence at other sites. Therefore, the development of a highly effective adjuvant method to suppress peritoneal recurrence is considered to be the key factor to improve the survival of patients with stage III gastric cancer. In this study, we, therefore, retrospectively examined the clinical course of patients who received intraperitoneal PTX after curative gastrectomy with D2 dissection in our Department, and discussed the possibility of usage of intraperitoneal PTX in an adjuvant setting.

Patients and Methods

This retrospective study included 17 patients with advanced gastric cancer who received curative gastrectomy with D2 nodal dissection and subsequent adjuvant therapy including intraperitoneal administration of PTX using a subcutaneously placed peritoneal access port from December 2005 to November 2011 in the Department of Surgical Oncology, University of Tokyo, Japan. In all cases, the primary tumor was macroscopically exposed to the serosal surface, and no tumor cells were detected on peritoneal cytological examination (CY0). Surgical specimens were pathologically examined, and all cases were confirmed to be R0 resection. The pathological stage was determined according to the 14th edition of the general rules for gastric cancer published by the Japanese Gastric Cancer Association [11]. In

14 cases, carcinoembryonic antigen (CEA) mRNA in peritoneal lavage fluid was additionally examined by RT-PCR as described previously [12].

In the initial 11 patients, 20–60 mg/m^2 PTX was administered only through the intraperitoneal route for 6–36 months after surgery. Ten of these patients received oral S-1 (40–80 mg/day) for 2–14 months. In the other 6 cases, patients received a fixed protocol of intraperitoneal (20 mg/m^2) and intravenous (50 mg/m^2) PTX and S-1 (80 mg/day), as used for the phase II study for patients with peritoneal metastases [6], for 4–24 months. All the patients were basically treated in the outpatient clinic and followed up for more than 5 years, except the last patient with a 2-year follow-up. Tumor marker levels of CEA, CA19–9, CA125 and CA72–4 were periodically examined every 3–6 months. The patients also received CT examination every 6 months for 2 years after surgery, and every year thereafter until 5 years after surgery, and the images were checked for the presence of recurrence by both radiologists and surgeons.

Disease-free survival was defined as the period between surgery and first recurrence, regardless of where it appeared. Data for patients without events were censored as the date of the final observation, and overall survival and disease-free survival curves were calculated using the Kaplan-Meier method (fig. 1).

Results

The characteristics of the 17 patients are summarized in table 1. The primary tumor was restricted to the lower and upper stomach in 7 and 1 cases, respectively, while it was located in more than 2 regions in the other 9 cases, and was macroscopically defined as type 2, 3 and 4 in 1, 9 and 7 cases, respectively. Histologically, undifferentiated carcinoma was predominant in 13 cases, and was partially observed at the invasive front in other 2 cases. The depth of invasion was pathologically defined as pT2 and pT3 in 1 and 6 cases and as pT4a or pT4b in the other 10 cases. Nodal metastases were observed in 14 cases and determined as pN1, pN2, pN3a, and pN3b in 4, 2, 3 and 5 cases, respectively. Thus, 7 and 10 cases were classified as p stage II and III, respectively. It is notable that CEA mRNA was positive in all 14 cases examined, suggesting that the patients were in the high-risk group for peritoneal recurrence.

The detailed treatment methods and outcome are summarized in table 2. Most of the patients received S-1 as standard adjuvant treatment, except 1 patient because of gastrointestinal toxicity. In addition, PTX was given through a peritoneal access port at a dose of 20–60 mg/m^2 for 3–36 months after surgery. PTX was administered only by the intraperitoneal route in 11 patients, and together with the intravenous route in the other 6 patients. Recurrence was observed in the liver in 2 patients (11.7%) at 11 and 24 months, and they died 14 and 34 months after surgery, respectively. Both patients were classified as p stage III, and histological examination of the primary tumor showed predominantly differentiated carcinoma. Peritoneal recurrence was observed only in 1 patient (5.9%), just before the 5-year examination after surgery, who is currently under treatment with a second-line regimen. More impressively, nodal recurrence was observed in none of the patients. In the median follow-up period of 66 months, 5-year overall survival and disease-free survival were calculated as 88.2 and 82.3%, respectively.

Discussion

PTX is water insoluble and, for clinical use, conventionally solubilized in a polyoxyethylated castor oil named Cremophor EL and ethanol (i.e., Taxol®). Due to its large particle size (10–12 nm diameter) and hydrophobicity, intraperitoneally administered PTX is slowly absorbed from the peritoneal cavity, which results in prolonged retention in the peritoneal cavity and allows direct penetration of PTX into peritoneal tumors [13]. From its pharmacokinetic characteristics, PTX is considered to be an ideal drug for intraperitoneal chemotherapy. In fact, we have established combination chemotherapy using intraperitoneal PTX together with intravenous PTX and oral S-1, and reported marked clinical effects in gastric cancer with macroscopic peritoneal metastases [6, 7]. Moreover, Imano et al. [14] have demonstrated that cancer cells were totally eradicated from intra-abdominal fluid at 24 h after intraperitoneal PTX.

From these clinical results, it is expected that regimens including intraperitoneal PTX could be a powerful method to suppress peritoneal recurrence in selected patients with advanced gastric cancer who have undergone surgical resection of the primary tumor. With this concept, we used intraperitoneal PTX in an adjuvant setting for 17 patients with gastric cancer with macroscopic serosal exposure, and found that peritoneal recurrence was observed in only 1 case (5.8%) during the median follow-up period of more than 5 years. According to the 5-year ACTS-GC results, peritoneal recurrence was reported to occur in 18.9 and 14.6% in the surgery alone and S-1 group, respectively [9]. In the 3-year results of the CLASSIC trial, peritoneal recurrence was observed in 56 of 515 patients (10.8%) with surgery alone and 47 of 520 patients (9.0%) who received XELOX therapy [10]. Since the patients in our series had a primary tumor with macroscopic serosal exposure and were thus associated with much higher risk for peritoneal recurrence as compared with patients in these two adjuvant studies, this result, although the number of the cases is not sufficient, suggests great potential for intraperitoneal PTX to suppress recurrence in the peritoneum.

Two patients with a p stage III tumor, however, developed recurrence in the liver. Both patients had a primary tumor consisting mainly of a differentiated type carcinoma with a relatively high potential to metastasize to the liver. Since PTX in the abdominal cavity is not easily transferred to the systemic circulation, it may be reasonable that intraperitoneal PTX is less effective in distant organs and thus stronger regimens may be necessary to reduce hematogenous recurrence in those cases.

However, another interesting finding is that nodal recurrence was never detected in these 17 patients, although most of the patients showed a highly advanced pN stage. Since none of the patients received extended nodal lymphadenectomy, this result is totally dependent on the pharmacological effects. Previous studies have shown that PTX retained in the abdominal cavity is mostly absorbed through the lymphatic system [13]. In fact, we confirmed in an animal study that the concentration of PTX in mesenteric lymph nodes was maintained at a higher level after intraperitoneal than after intravenous administration [15]. Thus, in our patients, it is speculated that a large amount of PTX was delivered to regional lymph nodes after intraperitoneal administration, where PTX might effectively suppress the growth of micrometastases or isolated tumor cells.

In recent clinical trials, the efficacy of intravenous PTX as an adjuvant drug has been evaluated for advanced gastric cancer. However, our data suggest that intraperitoneal PTX can produce more marked effects to suppress peritoneal as well as nodal recurrence in advanced gastric cancer with a high risk of recurrence in those sites. The result appears to be reasonable from the pharmacokinetic point of view. In adjuvant treatment, it is critically important to deliver the drugs preferentially to sites that are most liable to develop

recurrence. Although the retrospective result with a small sample size has its limitation and a clinical study is essential to see the real feasibility, it raises the possibility that adjuvant chemotherapy including intraperitoneal PTX could be a promising strategy to improve the outcome of patients with advanced gastric cancer, especially those with serosal exposure.

Acknowledgements

We thank Ms. Ikuko Nieda for her clerical work. This study was funded by the Ministry of Health, Labor and Welfare of Japan.

References

1 Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
2 Jacquet P, Sugarbaker PH: Peritoneal-plasma barrier. Cancer Treat Res 1996;82:53–63.
3 Markman M, Brady MF, Spirtos NM, et al: Phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube, and peritoneum: a Gynecologic Oncology Group Study. J Clin Oncol 1998;16:2620–2624.
4 Armstrong DK, Bundy B, Wenzel L, et al: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34–43.
5 Ishigami H, Kitayama J, Otani K, et al: Phase I pharmacokinetic study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer. Oncology 2009;76:311–314.
6 Ishigami H, Kitayama J, Kaisaki S, et al: Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. Ann Oncol 2010;21:67–70.
7 Kitayama J, Ishigami H, Yamaguchi H, et al: Salvage gastrectomy after intravenous and intraperitoneal paclitaxel (PTX) administration with oral S-1 for peritoneal dissemination of advanced gastric cancer with malignant ascites. Ann Surg Oncol 2013, Epub ahead of print.
8 Sakuramoto S, Sasako M, Yamaguchi T, et al: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810–1820.
9 Sasako M, Sakuramoto S, Katai H, et al: Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011;29:4387–4393.
10 Bang YJ, Kim YW, Yang HK, et al: Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315–321.
11 Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma – 2nd English edition. Gastric Cancer 1998;1:10–24.
12 Kodera Y, Nakanishi H, Ito S, et al: Quantitative detection of disseminated free cancer cells in peritoneal washes with real-time reverse transcriptase-polymerase chain reaction: a sensitive predictor of outcome for patients with gastric carcinoma. Ann Surg 2002;235:499–506.
13 Markman M: Intraperitoneal antineoplastic drug delivery: rationale and results. Lancet Oncol 2003;4:277–283.
14 Imano M, Imamoto H, Itoh T, et al: Impact of intraperitoneal chemotherapy after gastrectomy with positive cytological findings in peritoneal washings. Eur Surg Res 2011;47:254–259.
15 Soma D, Kitayama J, Ishigami H, et al: Different tissue distribution of paclitaxel with intravenous and intraperitoneal administration. J Surg Res 2009;155:142–146.

Table 1. Clinicopathological findings of the 17 patients who received intraperitoneal PTX in an adjuvant setting

Patient No.	Age, gender	Surgery	Locus	Macroscopic appearance	Histology	pT	pN	mLN	p stage	CEA mRNA
1	77, F	DG	L	3	muc>tub	T4a	N2	5/49	IIIB	+
2	63, F	TG + S	MU	3	muc>pap	T4a	N3b	38/56	IIIC	+
3	47, F	DG	L	4	sig	T2	N1	1/49	IIA	ND
4	60, M	DG	L	3	tub	T3	N1	1/70	IIB	ND
5	28, F	TG + S	UM	4	por2>sig	T3	N3b	16/81	IIIB	+
6	76, M	DG	LM	3	por2>tub	T3	N0	0/41	IIA	+
7	57, M	TG + S	MUL	4	tub>por1	T4a	N3b	26/32	IIIC	+
8	69, M	TG + TC	UE	3	por	T4b	N3b	18/62	IIIC	+
9	69, M	DG	LM	3	muc>>sig	T3	N1	1/45	IIB	+
10	70, M	DG	L	3	tub>por1	T4a	N0	0/25	IIB	+
11	73, M	DG	L	2	por	T4a	N2	4/36	IIIB	+
12	57, M	DG	LD	3	pap/tub	T3	N3a	8/67	IIIB	+
13	57, M	DG	L	3	por	T3	N1	2/19	IIB	+
14	48, M	DG	L	4	muc>sig	T4a	N0	0/61	IIB	+
15	63, M	TG + S	MUL	4	por	T4a	N3a	8/67	IIIC	+
16	55, M	TG	LUM	4	por	T4a	N3a	7/26	IIIC	+
17	43, M	TG + S	LUM	4	por	T4a	N3b	8/35	IIIC	ND

DG = Distal gastrectomy; TG = total gastrectomy; S = splenectomy; TC = total colectomy; U = upper; M = middle; L = lower; UE = upper extremity; mLN = number of metastatic lymph nodes of total lymph nodes resected; ND = not determined. pT, pN, and p stage was determined in 17 patients. CEA mRNA in peritoneal lavages was determined by RT-PCR.

Table 2. Treatment method and outcome of the 17 patients who received intraperitoneal PTX in an adjuvant setting

Patient No.	PTX IP, mg/m²	PTX IV, mg/m²	Cycle of PTX, n/weeks	Period of PTX, months	S-1, mg/day	Period of S-1, months	Outcome	Recurrence site
1	20	–	1/2	6	40	6	7-year survival	–
2	20	–	2/3	10	50	2	7-year survival	–
3	20	–	1/2	5	50	6	7-year survival	–
4	60	–	1/2	6	–	6	7-year survival	–
5	60	–	1/2	36	40	36	7-year survival	–
6	20	–	2/3	4	80	12	7-year survival	–
7	60	–	2/3	14	80	14	34 months dead	liver
8	50	–	1/2	3	40	12	7-year survival	–
9	60	–	1/2	6	40	2	6-year survival	–
10	20	–	2/3	6	80	6	6-year survival	–
11	20	–	1/2	9	40	12	6-year survival	–
12	20	50	2/3	4	80	6	14 months dead	liver
13	20	50	2/3	6	80	12	5-year survival	–
14	20	50	2/3	4	80	12	5-year survival	peritoneum
15	20	50	2/3	24	80	24	5-year survival	–
16	20	50	2/3	4	80	12	5-year survival	–
17	20	50	2/3	4	80	6	2-year survival	–

IP = Intraperitoneal; IV = intravenous.

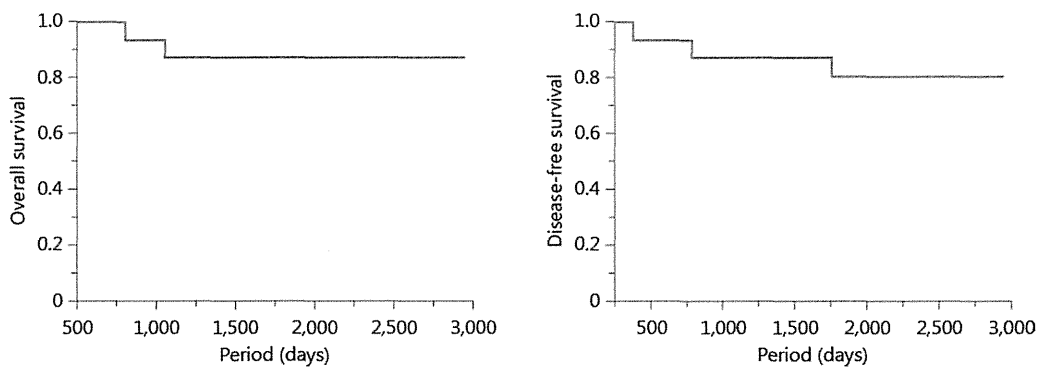

Fig. 1. Overall survival (left) and disease-free survival (right) in 17 patients.

J Gastrointest Canc (2014) 45:307–311
DOI 10.1007/s12029-014-9603-1

ORIGINAL RESEARCH

Intravenous and Intraperitoneal Paclitaxel with S-1 for Refractory Pancreatic Cancer with Malignant Ascites: an Interim Analysis

Naminatsu Takahara · Hiroyuki Isayama · Yousuke Nakai · Takashi Sasaki · Hironori Ishigami · Hiroharu Yamashita · Hironori Yamaguchi · Tsuyoshi Hamada · Rie Uchino · Suguru Mizuno · Koji Miyabayashi · Dai Mohri · Kazumichi Kawakubo · Hirofumi Kogure · Natsuyo Yamamoto · Naoki Sasahira · Kenji Hirano · Hideaki Ijichi · Keisuke Tateishi · Minoru Tada · Joji Kitayama · Toshiaki Watanabe · Kazuhiko Koike

Published online: 28 March 2014

Abstract
Objectives Here, we reported an interim analysis of feasibility and safety in the first 10 cases of 30 cases in a phase II trial of intravenous and intraperitoneal paclitaxel combined with S-1 for gemcitabine-refractory pancreatic cancer with malignant ascites.
Methods Paclitaxel was administered intravenously at 50 mg/m^2 and intraperitoneally at 20 mg/m^2 on days 1 and 8 every 3 weeks, and S-1 was administered at 80 mg/m^2/day for 14 consecutive days, followed by 7-day rest.
Results Between April 2011 and February 2012, ten patients were enrolled. A partial response was achieved in two patients (20 %) and a disease control rate of 50 %. The median time to progression and overall survival were 2.1 and 3.4 months, respectively. Malignant ascites was completely resolved in two patients (20 %). Major grade 3/4 adverse events were myelosuppression including neutropenia (50 %) and catheter-related infection (10 %).
Conclusions This novel combination chemotherapy was feasible and showed promising results in pancreatic cancer patients with malignant ascites (clinical trial registration number: UMIN000005306).

Keywords Pancreatic cancer · Malignant ascites · S-1 · Paclitaxel · Intraperitoneal chemotherapy

N. Takahara · H. Isayama (✉) · Y. Nakai · T. Sasaki · T. Hamada · R. Uchino · S. Mizuno · K. Miyabayashi · D. Mohri · K. Kawakubo · H. Kogure · N. Yamamoto · N. Sasahira · K. Hirano · H. Ijichi · K. Tateishi · M. Tada · K. Koike
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku Tokyo 113-8655, Japan
e-mail: isayama-2im@h.u-tokyo.ac.jp

H. Ishigami
Department of Outpatient Chemotherapy, The University of Tokyo, Tokyo, Japan

H. Ishigami · H. Yamashita · H. Yamaguchi · J. Kitayama · T. Watanabe
Department of Surgical Oncology, The University of Tokyo, Tokyo, Japan

Introduction

The prognosis of pancreatic cancer patients with peritoneal metastasis remains dismal [1]. Peritoneal metastasis is one of the most life-threatening factors in patients with pancreatic cancer [2]. Moreover, peritoneal metastasis causes several complications such as massive ascites, intestinal obstruction, and hydronephrosis, which seriously impair patients' quality of life.

Recently, a new multiagent chemotherapy, FOLFIRINOX, is shown to be superior to gemcitabine monotherapy in metastatic pancreatic cancer [3]. However, gemcitabine is still recognized as a standard chemotherapy, especially in patients with a poor performance status (PS) such as those with peritoneal metastasis [4]. Treatment for gemcitabine-refractory pancreatic cancer has been extensively investigated, and the CONKO-003 study has proven survival benefit over best supportive care alone in the second-line setting [5]. However, optimal second-line chemotherapy remains to be defined.

Intraperitoneal (i.p) chemotherapy has been developed to enhance antitumor activity against peritoneal metastasis by maintaining a high concentration of a drug in the peritoneal cavity over a long period while sparing the systemic host

tissues from drug toxicity. Paclitaxel (PTX) has a high transition rate into the peritoneal cavity and low clearance rate from the peritoneal cavity which is favorable for the treatment of peritoneal metastasis [6]. The clinical effects of i.p chemotherapy with PTX have been verified by convincing clinical trials in ovarian cancer [7, 8]. We previously reported efficacy of combination of intravenous and i.p PTX and oral S-1 in gastric cancer patients with peritoneal metastasis [9]. Intravenous, not i.p, PTX was shown to be active in patients with gemcitabine-refractory pancreatic cancer, with median overall survival (OS) of 4.0–7.6 months [10, 11]. On the other hand, S-1, which is widely used as one of the key drugs for pancreatic cancer in Japan, has been reported to be effective in patients with chemotherapy-naïve or chemotherapy-refractory pancreatic cancer [12, 13].

Therefore, we conducted a prospective phase II trial of this novel regimen of intravenous and i.p PTX in addition to oral S-1 in pancreatic cancer with peritoneal metastasis. Given the lack of clinical data of this regimen in pancreatic cancer patients, an interim analysis was planned, and here, we reported promising results in this study population who are refractory to chemotherapy, which may potentially lead to a paradigm shift in the treatment of pancreatic cancer with malignant ascites.

Patients and Methods

This prospective, single-arm phase II study was conducted at the University of Tokyo Hospital, Japan. The protocol was approved by the institutional review board, and informed consent was obtained from each participant. Though phase I and II trials of this regimen have been reported in gastric cancer patients, no clinical data was available in pancreatic cancer patients [9, 14]. Therefore, an interim analysis was planned to assess the feasibility and safety of this study after the first ten patients' enrollment.

Patients

The eligibility criteria were as follows: (1) histologically or cytologically proven pancreatic adenocarcinoma, (2) malignant ascites with cytological diagnosis, (3) refractory to gemcitabine defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15], (4) age >20 years, (5) Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2, and (6) adequate bone marrow function (white blood count $\geq 3{,}000/mm^3$, hemoglobin ≥ 9.0 g/dl, and platelet count $\geq 100{,}000/mm^3$), liver function (total bilirubin less than or equal to three times the upper limit of normal (ULN) and aspartate/alanine transaminases less than or equal to five times ULN), and renal function (serum creatinine ≤ 1.5 times ULN). The exclusion criteria were as follows: (1) active concomitant malignancies, (2) a history of drug hypersensitivity to PTX or S-1, (3) pregnant or lactating, and (4) concurrent severe medical conditions, such as active infection and cardiac or renal disease.

Treatment

Patients received PTX intravenously at 50 mg/m^2 and i.p at 20 mg/m^2 on days 1 and 8, and S-1 orally at 80 mg/m^2/day for 14 days followed by 7-day rest between each 21-day cycle. PTX was administered i.p through a peritoneal access port which was implanted in the subcutaneous space of the lower abdomen, with a catheter placed in the pelvic cavity through laparoscopy. PTX was diluted in 500 ml of normal saline and administered i.p over 1 h concurrently with intravenous infusion after standard premedication. The treatment was given until disease progression, unacceptable toxicity, or withdrawal of consent.

Dose Modification

Treatment was temporarily suspended in the case of grade 3/4 hematological toxicity or grade 2 or higher non-hematological toxicity. After recovery to grade 1 toxicity or lower, treatment was restarted at the following reduced doses. As this combination chemotherapy consisted of two drugs administered via three routes, doses were modified for each, if a distinction in toxicity could be made. That is, in case of severe digestive toxicity, S-1 was discontinued and then resumed at a dose reduced by 20 mg/m^2. In case of grade 3/4 hematological toxicity, intravenous PTX administration was suspended and then reduced by 5 mg/m^2. I.p PTX was reduced by 5 mg/m^2 if abdominal pain was observed after i.p infusion. If both drugs were suspected of causing the toxicities, the doses of both drugs were reduced as described above. No dose escalation was allowed following dose reduction.

Evaluation of Efficacy and Safety

Pretreatment evaluations included medical history and physical examination, laboratory studies (complete blood cell count, serum biochemical tests, electrolytes, and urinalysis), electrocardiogram, chest X-ray, and computed tomography (CT). The ECOG PS and laboratory tests, including complete blood counts and serum biochemical tests, were checked on days 1, 8, and 15. Serum and ascitic carcinoembryonic antigen (CEA) and cytology of ascites were evaluated at the beginning of each course.

The primary end point was OS. Secondary end points were clinical outcomes, including time to progression (TTP), efficacy against malignant ascites, and safety. OS was defined as

the time from initiation of therapy to final follow-up or until death from any cause. TTP was calculated from the start of the treatment to the first day of documented disease progression. Objective tumor responses were evaluated every two courses using RECIST (ver. 1.1) [15]. To evaluate the antitumor effects of the treatment on peritoneal metastasis, the amount and cytology of ascites and CEA level in ascites (aCEA) were also taken into account. According to the Japanese Classification of Gastric Carcinoma [16], the amount of ascites was assessed by radiologists using CT. Toxicity was monitored weekly and graded according to the National Cancer Institute Common Toxicity Criteria (ver. 3.0).

Statistical Methods

The required number of patients was calculated according to the Southwest Oncology Group One Arm Survival program. Assuming a null hypothesis of 3.0 months and an alternative hypothesis of 5.0 months with two-sided type I error of 0.05 and power of 0.8, with an accrual time of 27 months and follow-up of 9 months after closure of recruitment, it was necessary to enroll 30 fully assessable patients.

TTP and OS were calculated using the Kaplan–Meier method. This analysis was based on follow-up information, which was received until March 2013. JMP 9.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Table 1 Baseline patient characteristics (n=10)

	Number (range/percentage)
Age	67 (54–76)
Sex, male/female	8 (80)/2 (20)
ECOG performance status, 0/1/2	0 (0)/7 (70)/3 (30)
Location of primary disease, head/body/tail	3 (30)/5 (50)/2 (20)
Sites of metastasis	
Liver	5 (50)
Lung	5 (50)
Lymph node	8 (80)
Line of treatment	
Second line	5 (50)
Third line	5 (50)
Prior first-line chemotherapy	
Gemcitabine	7 (70)
Gemcitabine + S-1	3 (30)
Prior second-line chemotherapy	
S-1	5 (50)

All values are expressed as n (%) or median (range)

ECOG Eastern Cooperative Oncology Group, *RECIST* Response Evaluation Criteria in Solid Tumors

Results

From April 2011 to February 2012, ten patients were enrolled in this study. All patients had measurable target lesions and were fully evaluated for tumor response and toxicity. Eight patients were previously treated with S-1-containing regimen. Patient characteristics are shown in Table 1.

Safety

Seven patients completed the first 2 cycles of this chemotherapy. Treatment was early terminated within 2 cycles due to the deterioration of PS (n=2) or hemobilia caused by portobiliary fistula (n=1). None of the patients discontinued this regimen due to toxicity.

Hematological and non-hematological toxicities were listed in Table 2. Major grade 3/4 adverse events included neutropenia (50 %), anemia (40 %), and thrombocytopenia (30 %). Infection related to the peritoneal access device was observed in two patients (20 %), and removal and replacement of a peritoneal port device was required in one patient. There were no treatment-related deaths.

Efficacy

The median TTP and OS were 2.1 months (95 % confidence interval (CI), 0.7–3.2) and 3.4 months (95 % CI, 0.9–5.9), respectively (Fig. 1). A median of three courses were administered with a range from 1 to 14. Complete response was not observed. Partial response and stable disease were observed in two and three patients, respectively, with a response rate (RR)

Table 2 Toxicities

	Grades 1–4	Grades 3–4
Hematological		
Leukopenia	9 (90)	5 (50)
Neutropenia	8 (80)	5 (50)
Anemia	8 (80)	4 (40)
Thrombocytopenia	4 (40)	3 (30)
Non-hematological		
Anorexia	9 (90)	1 (10)
Nausea	4 (40)	2 (20)
Vomiting	2 (20)	0 (0)
Diarrhea	1 (10)	2 (20)
Constipation	1 (10)	0 (0)
Fatigue	7 (70)	0 (0)
Alopecia	6 (60)	- (-)
Catheter-related infection	2 (20)	1 (10)

All values are expressed as n (%)

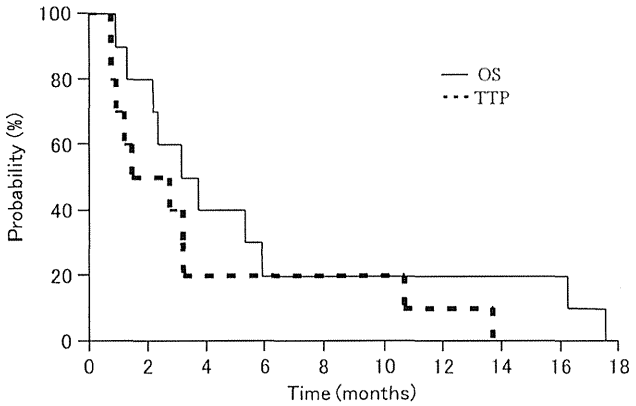

Fig. 1 Kaplan–Meier curves for overall survival and time to progression. *TTP* time to progression, *OS* overall survival

of 20 % and a disease control rate (DCR) of 50 %. Malignant ascites completely disappeared in two patients (20 %) and was stable in five patients (50 %). Cancer cells ceased to be detected by peritoneal cytology in six patients (60 %). aCEA was measured before and after 2 cycles of the treatment in seven cases, and aCEA decreased in all seven cases. The median aCEA was 94.5 mg/dl before treatment and 26.7 mg/dl after 2 cycles of treatment.

In one patient who underwent peritoneal port replacement, a second-look laparoscopy demonstrated a remarkable response of peritoneal metastases (Fig. 2).

Discussion

This is the first report that investigated intravenous and i.p PTX combined with S-1 for gemcitabine-refractory pancreatic cancer with malignant ascites. This interim analysis demonstrated the feasibility of this regimen in pancreatic cancer and promising results with complete disappearance of ascites in 20 %, DCR of 50 %, and median OS of 3.4 months.

The prognosis of newly diagnosed pancreatic cancer patients with malignant ascites was extremely poor with a reported median survival of 64 days [1]. In a retrospective study in 23 patients with malignant ascites who were refractory to gemcitabine, systemic PTX achieved the median OS of 101 days and ascites decrease rate of 30 % [17]. Our preliminary results of i.p in addition to systemic PTX demonstrated 20 % ascites disappearance rate, suggesting the efficacy of additional i.p PTX.

I.p chemotherapy has been established in patients with ovarian and gastric cancer, but there were few studies in pancreatic cancer [7–9]. The rationale of i.p chemotherapy is to achieve high concentrations of antitumor agents in the peritoneal cavity with low systemic exposure. Previously, the pharmacokinetics of i.p gemcitabine in patients with pancreatic cancer showed that peritoneal gemcitabine concentrations declined rapidly after administration, and therefore, it was well tolerated [18]. However, this finding of gemcitabine may be disadvantageous, given the abovementioned rationale of i.p therapy. PTX was expected as a better candidate agent because of its low clearance rate from the peritoneal cavity [6].

Of note, catheter-related infection was observed in two patients (20 %). Though the rate was comparable to the previous study with i.p chemotherapy for ovarian cancer [7], this complication is specific to i.p chemotherapy and should be addressed in the future.

In conclusion, combination chemotherapy of intravenous and i.p PTX with S-1 was feasible and showed promising results. The final results of this phase II study is awaited, but the preliminary results of i.p chemotherapy will open up a novel therapeutic option for pancreatic cancer patients with malignant ascites.

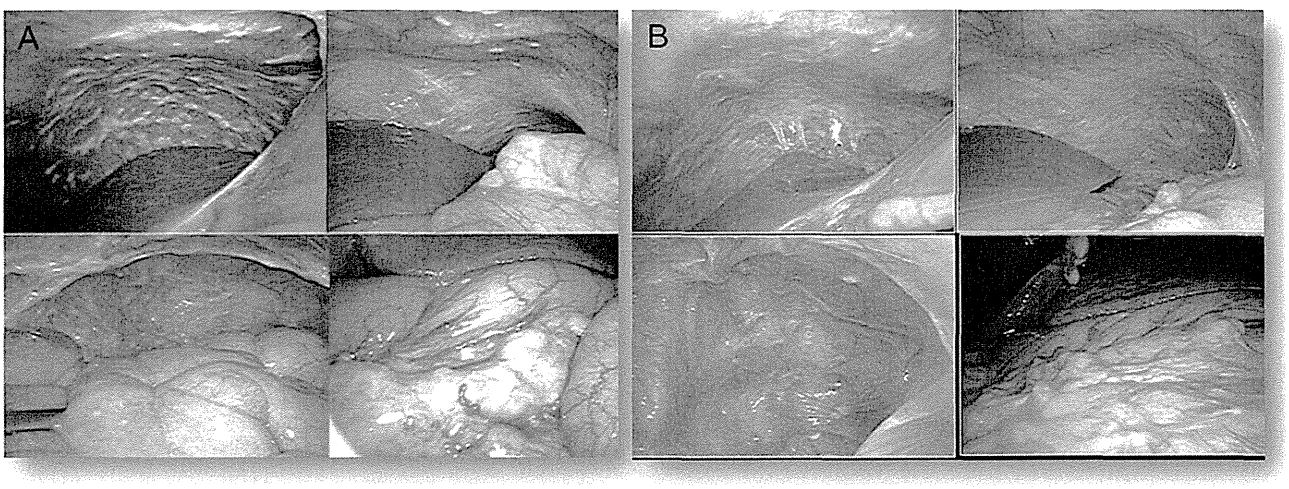

Fig. 2 Laparoscopy prior to (**a**) and after 12 courses of (**b**) treatment. Second-look laparoscopy demonstrated remarkable improvement of peritoneal dissemination