

Recent advances in the treatment of peritoneal dissemination of gastrointestinal cancers by nucleoside antimetabolites

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Peritoneal dissemination is the most common cause of metastasis from malignancies in the abdominal cavity. There are no standard treatments for peritoneal dissemination and the results are poor. The reasons for this are as follows: (1) no effective chemotherapeutic agents have been identified or developed; (2) surgical cytoreduction has little effect on survival improvement; and (3) the molecular mechanisms of peritoneal dissemination have not been clarified and no therapy against the target molecules has been developed. However, studies on the molecular mechanisms of peritoneal dissemination have elucidated some of the target molecules and the development of new multimodal therapies has also improved survival. Early postoperative intraperitoneal chemotherapy, hyperthermic intraperitoneal perfusion chemotherapy and neoadjuvant intraperitoneal-systemic chemotherapy have been newly developed, and a novel surgical therapy named peritonectomy has been proposed to perform complete cytoreduction of peritoneal dissemination. At present, these approaches appear to be effective therapeutic modalities for peritoneal dissemination. However, TS-1 and capecitabine have shown worthwhile results in recent clinical trials for patients with advanced gastric cancer. We recently found that newly developed antitumor cytosine nucleoside analogs show a survival advantage in peritoneal dissemination models using human cancer cells. These non-fluoropyrimidine nucleosides may potentially help to improve the poor prognosis observed in patients with advanced cancers involving peritoneal dissemination. (*Cancer Sci* 2007; 98: 11–18)

Peritoneal dissemination remains the most difficult type of metastasis to treat, and almost all surgeons believe that an operation is not indicated for such metastasis.^(1–3) Systemic chemotherapy tends to have little effect on the treatment of peritoneal dissemination, because the peritoneal–blood barrier existing between mesothelial cells and the submesothelial capillary hinders drug distribution throughout the peritoneal cavity. Recent advances in the studies of new drugs and multimodal therapies have proposed the therapeutic potency for advanced cancer with peritoneal dissemination. Neoadjuvant chemotherapy is also known to reduce the tumor burden, thus resulting in a stage reduction. As a result, the incidence of complete cytoreduction may increase after neoadjuvant chemotherapy. A new type of neoadjuvant intraperitoneal–systemic chemotherapy (NIPS) has been developed to increase the rate of complete cytoreduction.⁽⁴⁾ The complete removal of peritoneal dissemination is an independent prognostic factor. A peritonectomy is a novel surgical procedure by which complete cytoreduction for peritoneal dissemination is performed.^(5–8) These approaches are now being carried out as treatment modalities for peritoneal dissemination from appendiceal, colon and gastric cancer. Furthermore, several recent phase II

studies that evaluated the efficacy of new anticancer drugs including taxanes, TS-1 and capecitabine have shown promising results for patients with peritoneal dissemination of gastric cancer.^(9,10) In addition, potent therapeutic effects of non-fluoropyrimidine antimetabolites have been demonstrated in clinical and preclinical studies. We recently found that newly developed antitumor cytosine nucleoside analogs such as 1-(2-deoxy-2-fluoro-4-thio- β -D-arabino-pentofuranosyl) cytosine (4'-thio-FAC), 1-(2-C-cyano-2-deoxy-1- β -D-arabino-pentofuranosyl) cytosine (CNDAC) and 1-(3-C-ethynyl- β -D-ribo-pentofuranosyl) cytosine (ECyd) show a survival advantage in peritoneal dissemination models using human cancer cells.⁽¹¹⁾ This review outlines the recent advances of the basic preclinical research and clinical trial results in the treatment of peritoneal dissemination from gastric cancer, including our recent findings. Furthermore, we also propose the possibility of non-fluoropyrimidine nucleosides as an agent for patients with peritoneal dissemination of gastric cancer.

Molecular mechanisms of peritoneal dissemination

Peritoneal dissemination is established through a multistep process. Many metastasis-related factors, including adhesion molecules, matrix proteases, motility factors and angiogenic factors, are involved in the formation of peritoneal dissemination. The first step is the detachment of cancer cells from the serosal surface of the primary tumor; such detached cancer cells are called peritoneal free cancer cells (Fig. 1, step 1). E-cadherin is the key molecule for detachment.⁽¹²⁾ In addition, during an operation, blood or lymphatic fluid contaminated with cancer cells may spill into the peritoneal cavity from torn blood and lymphatic vessels.

Two different processes have so far been proposed for the attachment of peritoneal free cancer cells on the peritoneum, designated as *trans*-mesothelial (Fig. 1, process A, steps 1–6) and *trans*-lymphatic metastasis (Fig. 1, process B, steps 1–3' or 3''). The *trans*-mesothelial process is the direct attachment of peritoneal free cancer cells on the peritoneal surface (step 2). CD44 is considered to be important for adhesion and interaction between gastric cancer cells and mesothelial cells.^(13,14) Using a high-density cDNA microarray analysis, Sakakura *et al.* demonstrated that CD44 expression is upregulated in gastric cancer cell lines established through metastasis to the peritoneal cavity.⁽¹⁵⁾ The tissue that exists between mesothelial cells and the submesothelial capillary is named the peritoneal–blood barrier, which hinders the penetration of oxygen, nutrients and drugs from the submesothelial

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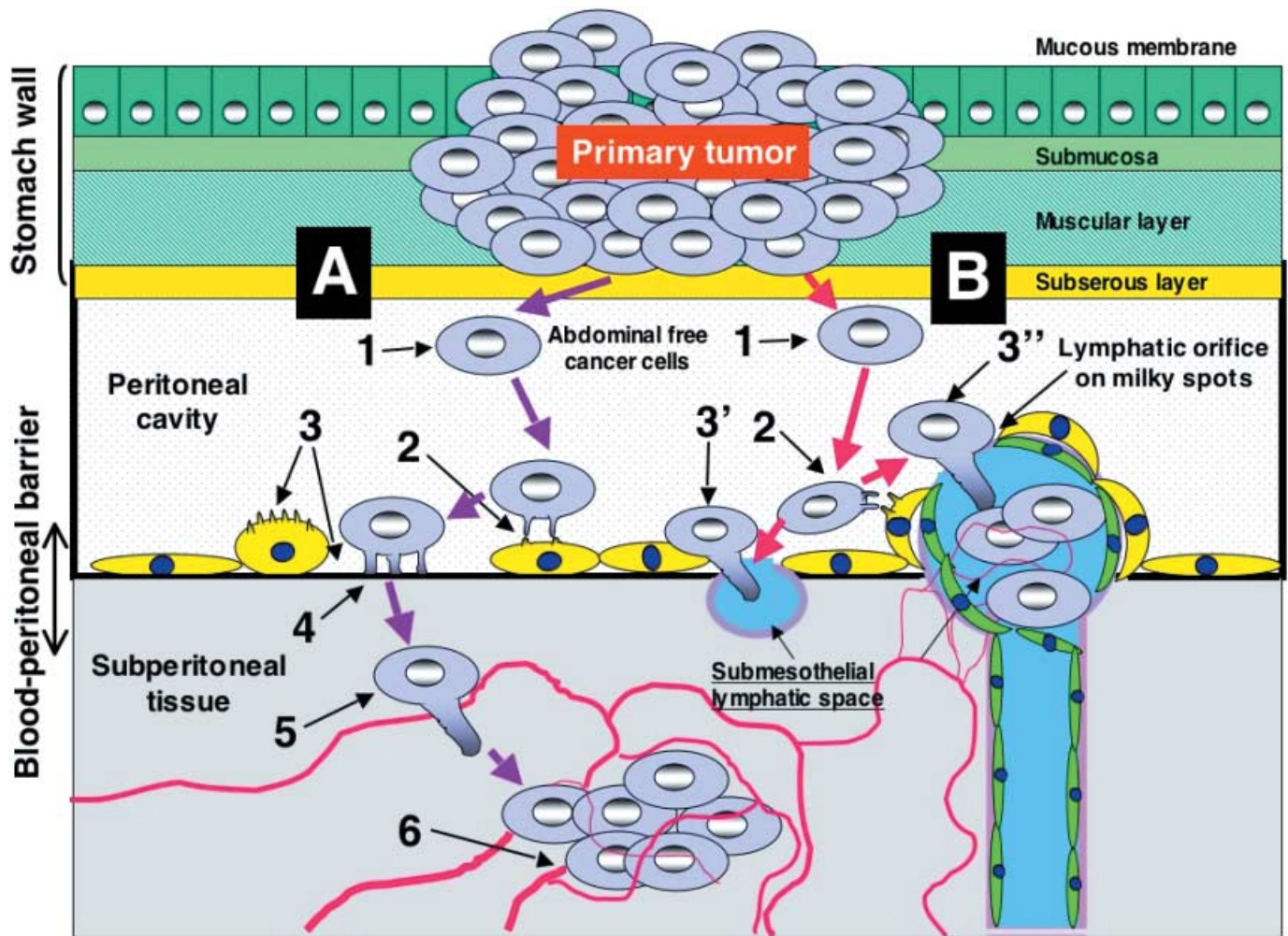


Fig. 1. Peritoneal dissemination is established through a multistep process. There are two different processes for the attachment of peritoneal free cancer cells on the peritoneum. (A) Trans-mesothelial process (steps 1–6): step 1, detachment from serosa; step 2, adhesion to mesothelial cells; step 3, contraction of mesothelial cells and submesothelial basement membrane; step 4, adhesion to submesothelial basement membrane; step 5, invasion of cancer cells into submesothelial tissue; step 6, vascular neogenesis, lymphangiogenesis and lymphatic dilatation. (B) Trans-lymphatic metastasis process (steps 1–3' or 3''): step 3', exposure of lymphatic stomata or lymphatic orifices; step 3'', invasion through lymphatic stomata.

capillary to the peritoneal cavity.⁽¹⁶⁾ After the attachment of peritoneal free cancer cells on the peritoneum, most free cancer cells die off due to the existence of the peritoneal–blood barrier.⁽¹⁷⁾ However, some populations of free cancer cells can penetrate into the submesothelial space through gaps between the mesothelial cells (step 3).⁽¹⁸⁾ Cytokines such as tumor necrosis factor- α and interleukin-8 appear to be involved in the contraction of mesothelial cells and gap formation.⁽¹⁹⁾ Cancer cells attach themselves to the exposed submesothelial basement membrane through integrins expressed on the membrane (step 4)⁽²⁰⁾ and thereafter invade the peritoneal–blood barrier (step 5).

According to our findings, patients with matrix metalloproteinase (MMP)-7-positive gastric cancer have significantly poorer survival and die more frequently of peritoneal recurrence than those with MMP-7-negative tumors.⁽²¹⁾ Furthermore, treatment by antisense oligonucleotides specific for MMP-7 effectively suppresses the peritoneal dissemination of MKN-45-P cells without influencing proliferation in a nude mouse model.⁽²²⁾ The concerted expression of motility factors (hepatocyte growth factor receptor/c-met, autocrine motility factor) and matrix-digesting enzymes (urokinase-type plasminogen activator and MMP-7) plays an important role in invasion. We have reported that the simultaneous overexpression of c-met, autocrine motility factor

receptor and urokinase-type plasminogen activator receptor are also closely associated with lymph node metastasis and peritoneal dissemination.⁽²³⁾ Cancer cells invade near the subperitoneal blood vessels, proliferate by inducing vascular neogenesis and then evolve into the established peritoneal dissemination (step 6). Angiogenic factors such as vascular endothelial growth factor (VEGF)-A and VEGF-C secreted from peritoneal free cancer cells induce vascular neogenesis in the peritoneal–blood barrier.^(24,25) As a result, the distance of the peritoneal–blood barrier shortens and an environment with a rich vasculature is established. VEGF is a well-known angiogenic factor that induces a mitogenic signal for endothelial cells by binding to endothelial cell receptors VEGFR-1 (Flt-1) and VEGFR-2 (KDR). A soluble form of FLT-1 binds VEGF specifically and inhibits its activity. Recently, it has been demonstrated that transduction of the soluble *Flt-1* gene to peritoneal mesothelial cells using adenoviral vector effectively suppresses the peritoneal metastasis of gastric cancer.⁽²⁶⁾ From these findings, it is proposed that the development of antiangiogenic therapy targeted to peritoneal mesothelial cells may become a useful approach for regulating the peritoneal dissemination of gastric cancer.

The second metastatic process is *trans*-lymphatic metastasis (Fig. 1, process B). Peritoneal free cancer cells migrate to the

subperitoneal lymphatic sinus through the lymphatic orifices (stomata), and then progress to the peritoneal surface (step 3'). There are many lymphatic orifices on the greater omentum: appendices epiploicae of the colon, the inferior surface of diaphragm, the falciform ligament, Douglas' pouch and the small bowel mesentery. These peritoneal parts have many milky spots, including the lymphatic apparatus, which is composed of peritoneal macrophages and lymphocytes in the lymphatic sinus. The lymphatic orifices are found on the milky spots. The peritoneal free cancer cells migrate to the lymphatic sinus in the milky spot, and undergo proliferation accompanied by neovascularization (step 3''). In the diaphragm, a large number of lymphatic orifices designated as stomata are found, and the stomata connect with the submesothelial lymphatic vessel. Peritoneal free cancer cells migrate into the submesothelial lymphatic space and then proliferate. In contrast, there are no lymphatic stomata and milky spots on the liver capsule, the peritoneum covering the abdominal wall, the serosal surface of the small bowel or the splenic capsule. These peritoneal parts are not affected until the late stages of peritoneal dissemination.

Recent advances in the multimodal therapy of peritoneal dissemination

The prognosis of patients with peritoneal dissemination from gastrointestinal cancer is very poor, with a median survival time (MST) of approximately 3 months.^(2,3) No standard treatments for peritoneal dissemination have been reported. Recent advances in the study of new drugs and multimodal therapies are summarized in Table 1. Wilke *et al.* reported that preoperative chemotherapy with etoposide, doxorubicin and cisplatin (EAP) could improve the prognosis of patients with locally advanced and non-resectable gastric cancer, but a considerable number of patients could not be treated with EAP partly because of its severe toxicity (myelosuppression, nausea and vomiting).^(27,28) At present, intravenous 5-fluorouracil (5-FU) has been used either alone or in combination with other anticancer drugs such as FAM (5-FU, doxorubicin, and mitomycin C) or FAMTX (5-FU, doxorubicin, and methotrexate) as chemotherapy against advanced gastric cancer.^(29,30) However, systemic chemotherapy does not improve the survival of patients with peritoneal dissemination^(7,31) because the existence of the peritoneal–blood barrier hinders the distribution of drug throughout the peritoneal cavity. In contrast, intraperitoneal chemotherapy offers potential therapeutic advantages over systemic chemotherapy by generating high local concentrations of drugs.^(32,33) After intraperitoneal chemotherapy, drugs are absorbed from the lymphatic orifices, and cancer cells that are growing in the submesothelial lymphatic sinus are exposed to drugs at high concentrations. In intraperitoneal chemotherapy, the instillation time and kinds of drugs are the important factors. According to pharmacokinetic studies, 4 h intraperitoneal instillation of cisplatin shows a significantly higher area under the curve (AUC) than 2 h instillation.⁽³⁴⁾ However, after intraperitoneal docetaxel administration in patients, higher drug concentration can be achieved for over 12 h, with very low plasma levels.^(35,36) In the experimental peritoneal dissemination model of gastric cancer cell line of MKN-45-P, the survival time of mice treated with intraperitoneal administration of docetaxel was markedly prolonged in comparison to that in the intravenous injection group.⁽³⁷⁾ We monitored the intraperitoneal carcinoembryonic antigen (CEA) level of mice during docetaxel treatment. The CEA level was well correlated with the therapeutic efficacy of docetaxel. When docetaxel was injected into the mice either intravenously or intraperitoneally, the drug concentrations in the peritoneal cavity, peritoneal solid cancer tissue and ascites cancer cells were significantly higher for a longer time in the intraperitoneal injection group compared with the intravenous injection group.⁽³⁸⁾ These results indicate that the intraperitoneal administration of docetaxel for peritoneal

dissemination is likely to be an effective treatment method, without causing any increase in systemic toxicity. Currently, the therapeutic efficacy of docetaxel as a single agent and in combination with modalities using other agents in patients with advanced gastric cancer is being evaluated in clinical studies in many countries.

Early postoperative intraperitoneal chemotherapy (EPIC) is a new method designated as early postoperative intraperitoneal chemotherapy. In this treatment, the abdominal cavity is instilled with 500 mL saline with anticancer agents from postoperative day 1 for several postoperative days. The aim of EPIC is to kill the residual intraperitoneal cancer cells by intraperitoneal chemotherapy as early as possible before the cancer cells adhere to the peritoneal surface and are buried with fibrin materials. Jeung *et al.* reported the feasibility of EPIC in treating gastric cancer with peritoneal dissemination.⁽³⁹⁾ When EPIC started on the day of operation with 5-FU 500 mg/m² and cisplatin 40 mg/m² (days 1–3) over a 4-week interval, the overall survival was 12 months. EPIC is thus considered to be a simple and useful method for the treatment of peritoneal dissemination.

Hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) is a method used to treat the whole peritoneal cavity by circulating heated saline containing a high dose of anticancer drug.^(40,41) We have previously reported the efficacy of HIPEC in 83 patients with peritoneal dissemination of gastric cancer.⁽⁴⁰⁾ Among the 43 evaluable patients, 17 (40%) exhibited a response. The overall 1- and 5-year survival rates were 43 and 11%, respectively. However, HIPEC is indicated for tumors less than 2–3 mm in diameter because it is limited to a penetration depth of 1–2 mm from the peritoneal surface.⁽⁴²⁾ Fujimoto *et al.* reported that the intraperitoneal hyperthermic perfusion (IPHP) treatment did not kill all of the gastric cancer cells that had penetrated deeply into subperitoneal layers, whereas gastric cancer cells in the abdominal effusion or lavage vanished.⁽⁴³⁾ Verwaal *et al.* carried out a randomized controlled study in 105 patients with peritoneal dissemination from colorectal cancer.⁽⁴¹⁾ Patients were assigned to receive either a standard treatment consisting of systemic chemotherapy (5-FU–leucovorin) with or without palliative surgery, or experimental therapy consisting of aggressive cytoreduction with HIPEC, followed by the same systemic chemotherapy regime. The survival in the standard therapy arm was significantly poorer than that in the experimental therapy arm. If the cytoreduction was macroscopically complete, the median survival was significantly better than in patients with residual disease.⁽⁴¹⁾ Therefore, a cytoreduction followed by HIPEC is important to improve survival in patients with peritoneal dissemination of gastric and colorectal origin.

According to the recent studies, complete removal of peritoneal dissemination is the independent prognostic factor.⁽⁴⁴⁾ In 1995, peritonectomy was first described as a surgical procedure used to carry out complete cytoreduction for peritoneal dissemination.⁽⁸⁾ At present, this approach is being used as a treatment modality in combination with intraperitoneal chemotherapy including HIPEC.^(45,46)

Neoadjuvant chemotherapy is known to reduce the tumor burden, thus resulting in a stage reduction. NIPS as a new type of neoadjuvant chemotherapy was developed to increase the rate of complete cytoreduction.⁽⁴⁵⁾ The nutrition of peritoneal nodules can be derived from both the peritoneal surface and the blood supply.⁽⁴⁷⁾ In NIPS, peritoneal dissemination is attacked both intraperitoneally and intravenously. Accordingly, two-route chemotherapy may be the best method for preoperative chemotherapy. Carboplatin, docetaxel and 5-FU are used for NIPS because these agents show high cytotoxicity against clinically obtained gastric cancer samples in *in vitro* chemosensitivity tests.⁽⁴⁸⁾ Docetaxel and carboplatin are administered from a peritoneal port system. On the same day, methotrexate and 5-FU are injected via the peripheral vein. This regimen is repeated weekly. After several cycles of NIPS, a complete cytoreduction is attempted by peritonectomy.

Table 1. Clinical studies in advanced gastric cancer

Regimen	Reference	Patient	Case no.	Target metastasis	Effect	Survival	Side-effect (grade 3 or 4)
FAM	MacDonald <i>et al.</i> ⁽²⁹⁾	Patients with measurable cancer	62	AM, H, N, bone	PR:42%	MST: 5.5 months responder: 12.5 months non-responder: 3.5 months	Bone marrow: 7/62
FAMTX	Wils <i>et al.</i> ⁽³⁰⁾	Advanced gastric cancer with or without measurable disease Randomized clinical trial: FAMTX versus FAM	105	PT, H, N, P	PR:41% (FAM 9%)	1-year survival: 41% 2 years survival 9% Survival was significantly better than FAM	Nausea: 63% Mucositis: 51% Diarrhea: 20% Alopecia: 24%
EAP	Wilke <i>et al.</i> ⁽²⁷⁾	Advanced gastric cancer with or without measurable disease	34	PT, H, N, P	PR + CR:64%	MST 18 months 2 years survival 26%	Bone marrow: 48%
XELOX	Park <i>et al.</i> ⁽⁶¹⁾	Advanced gastric cancer with or without measurable disease	20	PT, H, N, P	PR(11) + CR(2): 65%	Median progression free survival: 7.5 months	No grade 3 and 4
Gemcitabine + FOLFOX-4	Correale <i>et al.</i> ⁽⁶⁷⁾	Metastatic gastric cancer	36	H, N, P, ovary, lung	PR(15) + CR(4): 53%	Survival: 11 months	Neutropenia: 3/36 Mucositis: 4/36 Bone marrow: 6.7%
Docetaxel + capecitabine	Kim <i>et al.</i> ⁽⁶²⁾	Untreated metastatic or recurrent gastric cancer	32	PT, H, N, P	PR ¹³ + CR(1): 44%	MST: 8.4 month 1 years survival 0%	
TS-1	Osugi <i>et al.</i> ⁽⁶⁴⁾	Advanced gastric cancer with peritoneal dissemination	18	P	Non-evaluable	MST: 211 days Control MST: 118 days	Bone marrow: 1/18
TS-1	Yonemura <i>et al.</i> ⁽⁵⁸⁾	Advanced gastric cancer with positive cytology	35	Cy1/P0	Non-evaluable	2 years survival 53% Control 2-year survival 9%	Grade 3 and 4: 0%
Paclitaxel + TS-1	Kobayashi <i>et al.</i> ⁽⁷⁸⁾	Advanced gastric cancer Standard gastrectomy of more than a D2 dissection	50 and CY0-1	T3-4, N0-2, P0, H0 M0,	Safe and feasible	Non-evaluable	PTX: Neuropathy 1/50, leucopenia 1/50, neutropenia 4/50 S-1: Diarrhea 1/50, neutropenia 3/50, anemia 1/50 Bone marrow: 58% Anorexia: 15%
Docetaxel + TS-1	Yoshida <i>et al.</i> ⁽⁵⁷⁾	Advanced, recurrent gastric cancer	48	H, N, P, remnant, stomach	PR:56%	MST: 14.3 months Median time tumor progression: 7.3 months	Bone marrow: 58% Anorexia: 15%
HIPEC	Yonemura <i>et al.</i> ⁽⁴⁰⁾	Advanced, recurrent gastric cancer	83	P	PR:39% (17/43)	Complete resection1 and 5 years survival: 61%, 17% Incomplete resection: 1 and 5 years survival: 30%, 2%	Bowel perforation: 3/83 Bone marrow: 2/83
EPIC	Jeung <i>et al.</i> ⁽³⁹⁾	Advanced gastric cancer with peritoneal dissemination Palliative gastrectomy	49	P	Better than control group	MST: 12 months Median progression free survival: 7 months	Bone marrow: 17/49 Nause vomiting: 10/49
Peritonectomy + hyperthermic i.p. chemotherapy (cisplatin + mitomycin C)	Yonemura <i>et al.</i> ⁽⁴⁵⁾	Advanced gastric cancer with peritoneal dissemination Aggressive cytoreduction	107	P	Non-evaluable	MST: 11.5 months 5 years survival: 6.7%	Not described
NIPS	Yonemura <i>et al.</i> ⁽⁵⁾	Advanced gastric cancer Preoperative chemotherapy Clinical phase I	51	P	Cytology 75%, PR:45%	MST: 18 months, Peritonectomy: 18 months Complete cytoreduction: 20.4 months	Bone marrow: 16% Operative mortality: 4.5%

5-FU, 5-fluorouracil; AM, abdominal mass; CR, complete response; EAP, etoposide + doxorubicin + cisplatin; EPIC, early postoperative intraperitoneal chemotherapy (5-FU + cisplatin); FAM, 5-FU + doxorubicin + mitomycin C; FAMTX, 5-FU + doxorubicin + methotrexate; FOLFOX-4, oxaliplatin + folinic acid + infusional 5-FU; H, liver metastasis; HIPEC, hyperthermic intraperitoneal perfusion chemotherapy mitomycin C + etoposide + cisplatin; MST, median survival time; N, lymph node metastasis; NIPS, neoadjuvant intraperitoneal-systemic chemotherapy (methotrexate+ 5-FU, i.v./docetaxel +carboplatin, i.p.); P, peritoneal dissemination; PR, partial response; PT, primary tumor; XELOX, oxaliplatin + capecitabine.

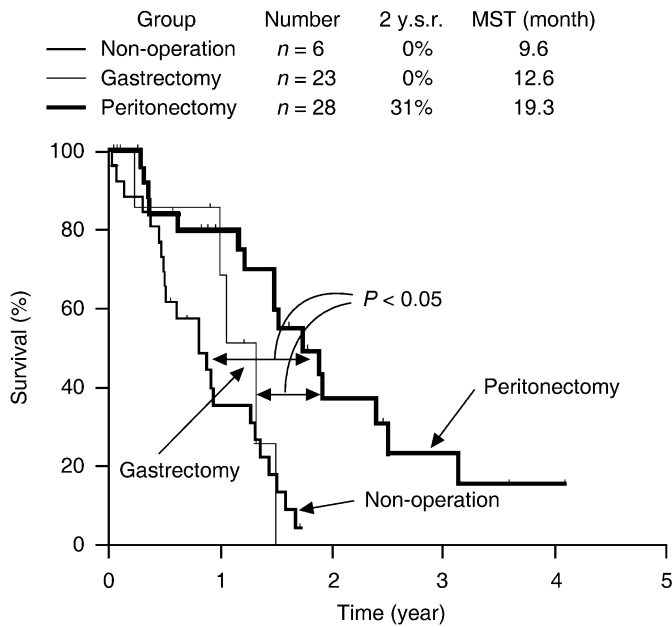


Fig. 2. Survival curves of patients with clinically detectable peritoneal dissemination, treated by neoadjuvant intraperitoneal or systemic chemotherapy. All patients had P2 or P3 peritoneal dissemination. Fifty-seven patients were treated with neoadjuvant intraperitoneal–systemic chemotherapy, using intraperitoneal administration of 30 mg/m² docetaxel and 100 mg/m² carboplatin with 1000 mL saline from a peritoneal port system, and intravenous infusion of 100 mg/m² methotrexate and 600 mg/m² 5-fluorouracil via a peripheral vein. Surgical exploration was done in 51 patients, and 28 patients received peritonectomy. Gastrectomy alone was done in 23 patients. Survival of patients who underwent peritonectomy showed the best prognosis. 2 y.s.r., 2-year survival rate; MST, median survival time.

A peritonectomy consists of two procedures, including a parietal and visceral peritonectomy. For the complete removal of visceral peritoneum bearing cancer, a total gastrectomy, combined with resection of the organs involved, is carried out. The final goal of a peritonectomy is complete removal of the primary tumor, lymph node metastasis and all of the peritoneal nodules. In our study, the MST of patients who received a peritonectomy after NIPS was 19.3 months, whereas that of patients who did not undergo an operation was 9.6 months (Fig. 2. $P < 0.05$).⁽⁴⁾ The patients who received a complete resection showed a significantly better prognosis than those who received an incomplete cytoreduction (Fig. 3). After NIPS, positive cytology changed to negative cytology in 24 (67%) of 35 patients. NIPS, therefore, can eradicate intraperitoneal free cancer cells prior to a peritonectomy.

Although the aggressive combination treatment of a surgical cytoreduction and intraperitoneal chemotherapy to improve the prognosis of patients with peritoneal dissemination is an advance, the efficacy of this treatment is still limited. Major problems are not associated with the surgical techniques but rather in the regimens or efficacy of the anticancer agents themselves. To successfully control the peritoneal dissemination of gastric cancer, the monitoring of intraperitoneal free cancer cells is extremely important. In addition, both the intraperitoneal protein levels and the mRNA levels of tumor markers (e.g. CEA and CA19-9) and metastasis- or angiogenesis-related factors such as MMP-7 and VEGF may be useful markers together with a cytological test.^(37,49–53) As the development of new drugs overcomes many intractable diseases, new regimens and drugs are needed to improve the poor prognosis of patients with peritoneal dissemination. We will introduce and propose agents that may be applicable for the treatment of peritoneal dissemination in the next section.

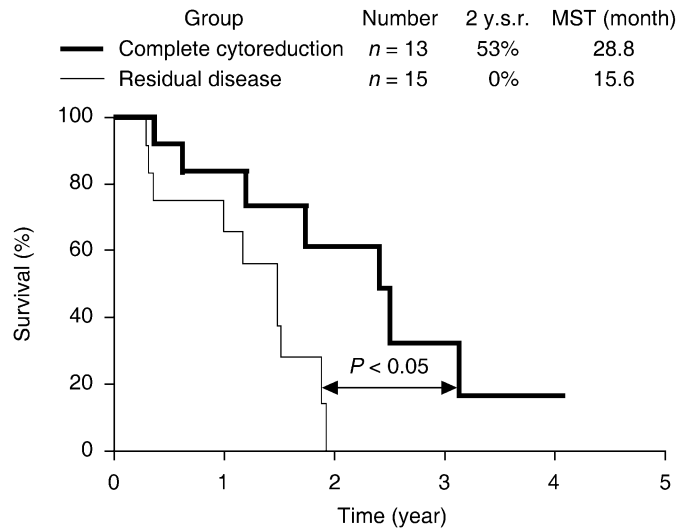


Fig. 3. Survival curves of patients with clinically detectable peritoneal dissemination. Patients who received complete cytoreduction by peritonectomy after neoadjuvant intraperitoneal–systemic chemotherapy survived significantly better than those with residual disease (incomplete cytoreduction group). 2 y.s.r., 2-year survival rate; MST, median survival time.

Future chemotherapy using novel antimetabolites

The administration of antimetabolic fluoropyrimidines such as doxifluridine (5'-DFUR) and UFT has been used either alone or in combination with other antitumor drugs in chemotherapy for advanced gastrointestinal carcinomas. However, these regimens are not considered to be standard treatments because their therapeutic efficacy is inadequate. The development of new anticancer drugs has provided an opportunity for progress in cancer chemotherapy. Several recent clinical studies introducing new anticancer drugs and combination therapies have been reported to show promising results.^(9,10)

TS-1, which is composed of tegafur, gimestat (CDHP) and otastat potassium at a molar ratio of 1 : 0.4 : 1, is the standard first-line anticancer drug used in the treatment of gastric cancer. Many recent reports have shown TS-1 to be a promising drug for advanced and recurrent gastric cancer with metastasis, including peritoneal dissemination.^(9,54–58) We reported the effect of TS-1 for potentially curable patients with peritoneal dissemination (P0/Cy1 status) as a type of postoperative chemotherapy.⁽⁵⁸⁾ After a radical gastrectomy, 35 patients were treated with TS-1 for 28 consecutive days with 14 days rest, and the schedule was repeated every 6 weeks (TS-1 group). The patients in the TS-1 group survived significantly longer than the control group without chemotherapy. The 2-year survival rates of the control and TS-1 groups were 9 and 53%, respectively (Fig. 4). The Cox proportional hazard model showed TS-1 treatment as an independent prognostic factor, and the relative risk by TS-1 treatment was 0.17-fold lower than that of the control group. Major adverse reactions included myelosuppression and gastrointestinal toxicities, but they were generally mild and there were no treatment-related deaths. From these results, we propose TS-1 treatment to be safe and effective as a postoperative chemotherapy for patients with a P0/Cy1 status. At present, clinical studies of TS-1 combined with taxanes or cisplatin in patients with advanced gastric cancer have been evaluated.^(9,59,60) It has been reported that docetaxel and S-1 combination therapy are highly active and well tolerated in advanced or recurrent gastric cancer.⁽⁵⁷⁾

Capecitabine is an orally administered fluoropyrimidine anticancer drug used in the treatment of metastatic breast and

Group	Number	1 y.s.r.	2 y.s.r.	MST (month)
— TS-1 group	n = 35	89%	53%	21.1
— Control group	n = 66	44%	9%	9.1

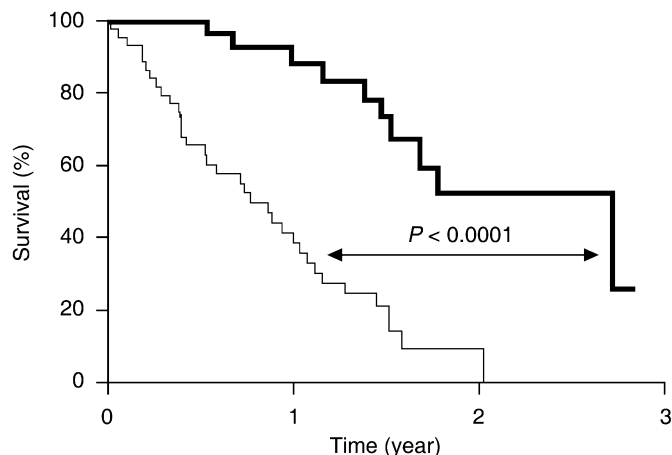


Fig. 4. Survival improvement by TS-1 in patients with peritoneal free cancer cells without macroscopic peritoneal dissemination (P0/Cy1 status). After radical gastrectomy, 35 patients were treated with oral TS-1 (80 mg/m²) for 28 consecutive days with 14 days rest, and the schedule was repeated every 6 weeks (TS-1 group). The other 66 patients did not receive any chemotherapy (control group). Patients in the TS-1 group survived significantly longer than those in the control group ($P < 0.0001$). The Cox proportional hazard model showed TS-1 treatment as an independent prognostic factor, and the relative risk for TS-1 treatment was 0.17-fold lower than that for the control group. Major adverse reactions included myelosuppression and gastrointestinal toxicities, but they were generally mild and there were no treatment-related deaths. 1 y.s.r and 2 y.s.r., 1-year and 2-year survival rates; MST, median survival time.

colorectal cancers. The therapeutic efficacy of capecitabine has been investigated in patients with advanced gastric cancer.^(61–64) Sakamoto *et al.* reported that the administration of capecitabine for the treatment of chemotherapy-naïve patients with unresectable advanced or metastatic gastric cancer showed promising activity and was well tolerated as a first-line therapy for advanced and metastatic gastric cancer.⁽⁶⁵⁾ In addition, the combination of capecitabine plus oxaliplatin every 3 weeks (XELOX regimen) in patients with previously untreated and non-resectable advanced gastric adenocarcinoma has been carried out in Korea.⁽⁶¹⁾

Although the oral fluoropyrimidine antimetabolites are promising agents for advanced gastric cancer, the potent therapeutic effects of non-fluoropyrimidine antimetabolites as typified by 2'-deoxy-2',2'-difluorocytidine (gemcitabine) on various solid tumors have recently been demonstrated in preclinical and clinical studies. Gemcitabine, an antimetabolic fluorinated deoxycytidine analog, is used commonly to treat non-small cell lung cancer, pancreatic cancer, bladder cancer and breast cancer. Among the antitumor 2'-deoxycytidine analogs used clinically, such as Ara-C and its prodrugs, only gemcitabine has been proven to be effective as a single agent against solid tumors. Although gemcitabine has no significant antitumor activity as a single agent in gastric cancer, De Lange *et al.* reported that cisplatin and gemcitabine had moderate efficacy in patients with advanced gastric cancer, with manageable toxicity, and that objective responses were observed in 30% of the patients, including two complete remissions and 10 partial remissions.⁽⁶⁶⁾ In a multi-center phase II trial to evaluate gemcitabine plus FOLFOX-4 (oxaliplatin, folinic acid and 5-FU) in 36 patients with advanced gastric cancer, the gemcitabine plus FOLFOX-4 regimen showed sufficient results to warrant a further evaluation of this multidrug combination in randomized phase III trials.⁽⁶⁷⁾

Furthermore, newly developed cytosine nucleoside analogs such as 4'-thio-FAC, CNDAC and ECyd have been shown to have potent antitumor activity against a wide variety of solid tumors, including murine tumors and human adenocarcinomas.^(68–70) Miura *et al.* previously demonstrated that oral administration of the novel nucleoside analog 4'-thio-FAC, which is a strong inhibitor of DNA polymerase α , showed a marked inhibitory effect on the development of ascites and the survival of nude mice implanted with MKN-45-P cells into the peritoneal cavity.⁽¹¹⁾ Moreover, Zajchowski *et al.* reported that daily oral administration of 4'-thio-FAC significantly inhibited the growth of gemcitabine-resistant BxPC-3 pancreatic tumors and also induced a regression of gemcitabine-refractory Capan-1 tumors.⁽⁷¹⁾ 4'-thio-FAC may thus be a potentially effective and therapeutic agent for advanced and metastatic cancers.

Clinical phase I studies of CNDAC and ECyd are now ongoing in the USA. A 2'-deoxycytidine analog, CNDAC, is metabolically activated by cellular kinases including deoxycytidine kinase (DCK), Ara-C and gemcitabine.⁽⁷²⁾ CNDAC 5'-triphosphate strongly inhibits DNA chain elongation by DNA polymerases. However, ECyd is a potent inhibitor of RNA polymerases.^(73,74) ECyd requires the activity of uridine/cytidine kinase 2 to produce the corresponding active metabolite (ECyd 5'-triphosphate).⁽⁷⁵⁾ Therefore, resistant cells harboring a mutation in the *DCK* gene show a crossresistance to 2'-deoxycytidine analogs, whereas ECyd can effectively inhibit growth of 2'-deoxycytidine analog-resistant cells. Kazuno *et al.* reported that ECyd shows potent antitumor activity against an established gemcitabine-resistant human pancreatic cancer cell line, which originated from MIAPaCa-2.⁽⁷⁰⁾ We recently investigated the therapeutic effects of CNDAC, Ara-C, gemcitabine and ECyd on a peritoneal dissemination model using MKN-45-P. When either CNDAC or ECyd was injected intraperitoneally into the peritoneal cavity of MKN-45-P-bearing mice every day from day 1 to day 21, both CNDAC and ECyd significantly prolonged survival time in MKN-45-P-bearing mice (Fig. 5). In contrast, gemcitabine and Ara-C were ineffective in this model. Furthermore, no survival benefit was obtained after the administration of TS-1 (12 mg/kg) alone in this model.⁽⁷⁶⁾

Currently, new nucleoside antimetabolites besides CNDAC and ECyd, such as tezacitabine and troxacitabine, are being investigated in clinical trials to evaluate their antitumor activity against solid tumors.⁽⁷⁷⁾ These non-fluoropyrimidine nucleosides may improve the poor prognosis of patients with advanced cancers involving peritoneal dissemination.

Conclusion

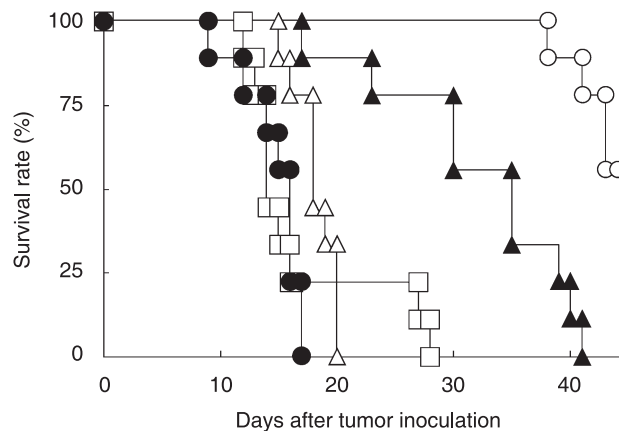
Peritoneal dissemination is established through at least two different processes: *trans*-mesothelial metastasis and *trans*-lymphatic metastasis. Such multimodality of peritoneal dissemination formation and isolated location in the peritoneal cavity make it difficult to treat advanced gastric cancer with peritoneal dissemination. At present, multimodal therapy with NIPS and peritonectomy is the best approach for curative treatment. However, the metabolism and pharmacodynamics of anticancer agents such as taxane and 5-FU injected into the peritoneal cavity remain obscure. Further basic and pharmacological approaches are required to establish the standard regimen for treating peritoneal dissemination. The non-fluoropyrimidine nucleoside antimetabolites may become good candidates for novel intra-peritoneal combination chemotherapies. For example, combination therapy of the oral fluoropyrimidine and the non-fluoropyrimidine nucleoside antimetabolites may be a worthwhile regimen for treatment of peritoneal dissemination in the future.

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Symbol	Treatment	Dose (mg/kg) day 1–21, daily	Survival rate T/C and mean survival
○	CNDAC (<i>n</i> = 9)	5	>250% and >42 days (<i>P</i> < 0.01)
△	Ara-C (<i>n</i> = 9)	5	106% and 17.9 days
●	Gemcitabine (<i>n</i> = 9)	5	89% and 14.6 days
▲	ECyd (<i>n</i> = 9)	5	184% and 30.9 days (<i>P</i> < 0.01)
□	Control (<i>n</i> = 9)	5	100% and 16.8 days

Fig. 5. Antitumor effects of nucleoside analogs on peritoneal dissemination of MKN-45-P. MKN-45-P cells (1×10^7) were inoculated into the peritoneal cavity of nude mice on day 0. Survival curves were constructed using the Kaplan–Meier method. 2'-Deoxycytidine analogs (CNDAC, Ara-C and gemcitabine) at a dose of 5 mg/kg were injected intraperitoneally every day from day 1 to day 21. 1-(3-C-ethynyl- β -D-ribo-pentofuranosyl) cytosine was administered at a dose of 0.1 mg/kg on the same schedule. T/C, treatment group/control group.



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