

## A Preliminary Study of Single Intraperitoneal Administration of Paclitaxel Followed by Sequential Systemic Chemotherapy with S-1 plus Paclitaxel for Advanced Gastric Cancer with Peritoneal Metastasis

MOTOHIRO IMANO<sup>1,2</sup>, YING-FENG PENG<sup>1</sup>, TATSUKI ITOH<sup>3</sup>, MASAYASU NISHIKAWA<sup>1</sup>, TAKAO SATOU<sup>3</sup>, ATSUSHI YASUDA<sup>1</sup>, KEISUKE INOUE<sup>1</sup>, HIROAKI KATO<sup>1</sup>, MASAYUKI SHINKAI<sup>1</sup>, MASAHIRO TSUBAKI<sup>4</sup>, TAKUSHI YASUDA<sup>1</sup>, HARUHIKO IMAMOTO<sup>1</sup>, SHOZO NISHIDA<sup>4</sup>, HIROSHI FURUKAWA<sup>1</sup>, YOSHIFUMI TAKEYAMA<sup>1,2</sup>, KIYOKATA OKUNO<sup>1</sup> and HITOSHI SHIOZAKI<sup>1</sup>

<sup>1</sup>Surgery and <sup>3</sup>Pathology, Kinki University Faculty of Medicine, Osaka, Japan;

<sup>2</sup>Cancer Center, Kinki University Hospital, Osaka, Japan;

<sup>4</sup>Division of Pharmacotherapy, Kinki University Faculty of Pharmacy, Osaka, Japan

**Abstract.** *Aim:* A preliminary study with the aim of evaluating the safety and efficacy of a single intraperitoneal administration of paclitaxel, combined with intravenous administration of paclitaxel plus S-1, was carried out in gastric cancer patients with peritoneal metastasis. *Patients and Methods:* Paclitaxel was administered intraperitoneally at 80 mg/m<sup>2</sup>. After one to two weeks, S-1 was administered at 80 mg/m<sup>2</sup>/day for 14 consecutive days, followed by seven days' rest. Paclitaxel was administered intravenously at 50 mg/m<sup>2</sup> on days 1 and 8. The safety, pharmacokinetic analysis and efficacy of this therapy were investigated. *Results:* Fifteen patients were enrolled in this study. The toxic effects of the intraperitoneal chemotherapy were mild. The toxic effects with the systemic chemotherapy were acceptable. The ratio of (AUC<sub>peri</sub>)/(AUC<sub>pla</sub>) was 1065:1 in the pharmacokinetic analysis. The one-year overall survival rate was 10/15 (66.7%). *Conclusion:* A single intraperitoneal administration of paclitaxel combined with intravenous administration of paclitaxel plus S-1 is a well-tolerated and feasible treatment for patients with gastric cancer with peritoneal metastasis.

Gastric cancer (GC) is one of the leading causes of cancer deaths worldwide (1), and one of the most frequent causes of death from gastric cancer is peritoneal metastasis (PM) (2).

*Correspondence to:* Motohiro Imano, MD, PhD, Surgery, Kinki University Faculty of Medicine, 377-2 Ohno-higashi Osaka-Sayama, Osaka 589-8511, Japan. Tel: +81 723660221, Fax: +81 723683382, e-mail: imano@med.kindai.ac.jp

**Key Words:** Intraperitoneal chemotherapy, paclitaxel, S-1, gastric cancer, peritoneal metastasis.

In a multicenter prospective study of patients with GC with PM, the median survival time was only 3.1 months (2); no standard therapy has been established for such patients (3, 4).

Intraperitoneal (*i.p.*) administration of paclitaxel was developed to enhance antitumor activity against PM. The clearance of paclitaxel from the peritoneal cavity is delayed due to its high molecular weight and bulky structure, and the advantage of intraperitoneal exposure to paclitaxel has been demonstrated through high intraperitoneal/plasma ratios by investigations looking at the area under the drug concentration -time curve (AUC) (5, 6).

However, this treatment has two problems. One concerns the antitumor effect on disseminated lesions in the peritoneum, because penetration of *i.p.* paclitaxel into the peritoneal surfaces is limited and the effective diffusion distance into the tissues has been reported to be just 100  $\mu$ m (7). Therefore, *i.p.* paclitaxel is less effective in treating large disseminated lesions. The other disadvantage concerns the antitumor effects on the primary tumor or the metastatic lesions. *i.p.* paclitaxel is not effective against such neoplasms because the clearance of paclitaxel from the peritoneal cavity is delayed. Therefore, to enhance the therapeutic effect of paclitaxel, combination therapy with systemic chemotherapy would be required.

S-1 is a combination of tegafur, gimeracil and oteracil at a molar ratio of 1:0.4:1, and is designed to have an enhanced antitumor effect and to reduce gastrointestinal toxicity (8). In recent phase III studies on unresectable and/or recurrent GC, S-1 demonstrated significant activity and led to a response rate (RR) of 27-31% and median survival times (MST) of 10.5-11.4 months (9, 10). Paclitaxel has been administered to patients with GC, and the RR was reported to be 22-40%, with an MST of 8.0-8.6 months (11, 12).

Paclitaxel and S-1 have two favourable characteristics for the treatment of PM, namely a high efficacy against diffuse-type adenocarcinomas that can easily disseminate into the peritoneum, and a high penetration rate into the peritoneal cavity (13, 14). Additionally, several clinical trials have already reported on the safety and efficacy of S-1 plus paclitaxel combination therapy (15, 16). Therefore, combined treatment with *i.p.* paclitaxel and systemic S-1 plus paclitaxel has the potential to overcome the problems associated with *i.p.* paclitaxel monotherapy.

In this preliminary study, the safety and efficacy of our new regimen (a single *i.p.* paclitaxel administration followed by systemic chemotherapy of S-1 plus intravenous paclitaxel) were evaluated for the treatment of PM of GC.

## Patients and Methods

**Patients.** Patients were enrolled in this study between May 2003 and December 2004. During this period, we performed staging laparoscopy for the patients in whom the presence of PM was suspected, but who lacked non-curative factors, such as distant metastasis to liver, lung, or lymph nodes except for the possibility of PM. In these patients, the eligibility criteria required for enrolment in this study included: i) adequate bone marrow function (leucocyte count of 3,000-12,000 mm<sup>3</sup>, neutrophil count  $\geq$ 1500/mm<sup>3</sup>, and platelet count  $\geq$ 100,000/mm<sup>3</sup>); ii) adequate liver function (total serum bilirubin  $\leq$ 1.5 mg/dl and serum transaminase  $\leq$ two times the normal upper limit); iii) adequate renal function (serum creatinine  $\leq$ 1.5 mg/dl); iv) Eastern Clinical Oncology Group scale performance status of 1 or less; v) age 20-75 years; vi) no other severe medical conditions or active malignancies; and vii) no previous systemic chemotherapy.

In accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration of 1975, as revised in 1983, written informed consent was obtained from patients before the initiation of treatment. Patients who were expected to be eligible were informed before treatment about the therapeutic strategy, emphasizing its potential benefits as well as the possible risks of mortality and morbidity. Informed consent was obtained from all patients at the time of laparoscopy.

**Treatment.** For the patients with PM, paclitaxel diluted in 1 l of normal saline was administered intraperitoneally at a dose of 80 mg/m<sup>2</sup> at the end of staging laparoscopy (5). After one to two weeks, S-1 was administered orally twice, daily at a dose of 80 mg/m<sup>2</sup>/day for 14 consecutive days, followed by seven days' rest. Paclitaxel was administered intravenously at a dose of 50 mg/m<sup>2</sup> on days 1 and 8 (15). The cycle was repeated every three weeks until observation of unacceptable toxicity or disease progression.

**Evaluation of toxicity.** Toxicity was measured using the common toxicity criteria of the National Cancer Institute, Version 2.0 (17).

**Pharmacokinetic analysis.** Pharmacokinetic studies were performed on 8 patients who gave informed consent. Peritoneal samples and plasma samples were obtained during drug administration and 0.5, 1, 2, 3, 4, 6, 24 and 48 h after drug instillation. Samples were collected in heparinised tubes, centrifuged, and the supernatants

Table I. *Patients' characteristics.*

Characteristic	Value
Median age, years (range)	60 (22-75)
Male/female	9/6
ECOG performance status 0/1	13/2
Histological type (n=15)	
Intestinal	3
Diffuse	12

ECOG: Eastern Cooperative Oncology Group; histopathologic typing: based on Lauren's system.

were stored at -20°C, until required. Paclitaxel concentrations were measured using a high-performance liquid chromatography assay, as previously described (18). The AUC from 0-48 h in the peritoneal fluid (AUC peri, 0-48 h) and in plasma (AUC pla, 0-48 h) was estimated using the trapezoidal method.

**Progression onset regions (POR).** PORs were determined as initial progressive regions and/or new occurrence of metastatic lesions on multi-detector row computed-tomography.

**Survival analysis.** Survival analyses were performed using the Kaplan -Meier method. The follow-up period was determined from the date of staging laparoscopy to death. Survival analysis was conducted using the statistical software GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA).

## Results

**Patients' characteristics.** Between May 2003 and December 2004, we performed staging laparoscopy in 22 patients. Of these patients, 15 were enrolled in this study and fully evaluated for toxicity, and the overall survival (OS) rate was calculated. Follow-up time was 5.25 years (to March 2010) after the end of registration. Patients' characteristics are listed in Table I.

**Safety.** The patients underwent a median of eight cycles, with a range from 2 to 20, and systemic chemotherapy was discontinued in all patients due to disease progression.

Hematological and non-hematological toxic effects are listed in Table II. The incidence of grade 3 hematological and non-hematological effects of *i.p.* chemotherapy was 13.3% and 0%, respectively, and these effects included anemia (6.6%) and leucopenia (6.6%). No grade 4 toxic effects were observed. Furthermore, in systemic chemotherapy, the incidence of grade 3 or 4 hematological and non-hematological effects was 53.3% and 0%, respectively, and such effects included anemia (20%), leucopenia (20%), neutropenia (26.6%) and elevated aspartate aminotransferase and alanine aminotransferase (6.6%). None of the patients experienced abdominal pain (Table II). No treatment-related death occurred.

Table II. Adverse events associated with intraperitoneal and systemic chemotherapy.

Grade (CTCAE v2.0)	No. of patients (%)									
	Intraperitoneal chemotherapy					Systemic chemotherapy				
	1	2	3	4	3/4	1	2	3	4	3/4
<b>Hematological toxicity</b>										
Anemia	2 (13.3)	1 (6.6)	1 (6.6)	0 (0)	1 (6.6)	1 (6.6)	3 (20)	2 (13.3)	1 (6.6)	3 (20)
Leucopenia	1 (6.6)	0 (0)	0(0)	0 (0)	0(0)	2 (13.3)	3 (20)	3 (20)	0 (0)	3 (20)
Neutropenia	1 (6.6)	0 (0)	1 (6.6)	0 (0)	1 (6.6)	3 (20)	2 (13.3)	3 (20)	1 (6.6)	4 (26.6)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AST elevation	3 (20)	0(0)	0 (0)	0 (0)	0 (0)	4 (26.6)	0 (0)	1 (6.6)	0 (0)	1 (6.6)
ALT elevation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.6)	1 (6.6)	0 (0)	1 (6.6)
Bilirubin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1(6.6)	2 (13.3)	1 (6.6)	0 (0)	1 (6.6)
Creatinine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Non-hematological toxicities</b>										
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3)	0(0)	0 (0)	0 (0)	0 (0)
Anorexia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (26.6)	0(0)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3)	0(0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3)	0(0)	0 (0)	0 (0)	0 (0)
Abdominal pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neuropathy-sensory	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (20)	0 (0)	0 (0)	0 (0)	0 (0)

AST: Aspartate aminotransferase; ALT:alanine aminotransferase.

**Pharmacokinetic analysis.** High *i.p.* drug concentrations were observed over a long period. The maximal *i.p.* concentration was, on average, 238.3-times higher than the maximal plasma concentration, which was reached after 2 h. The ratio of AUC peri/AUC pla was 1065:1. Figure 1 shows the curves of mean ( $\pm$ SD) *i.p.* and plasma paclitaxel concentrations versus time in these patients.

**Overall survival (OS).** The OS was calculated for all 15 patients, and the one-year OS rate was 10/15 (66.7%), the two-year OS rate was 4/15 (26.7%), and the median survival time (MST) was 15.8 months (Figure 2).

**PORs.** Most region as POR was the primary tumor (8/15, 53.3%). Surprisingly, the patients who had malignant ascites as POR only comprised 33.3% (5/15). The remaining two patients had liver metastasis as POR.

## Discussion

In this study, since grade 3 hematological toxic effects were only observed in two patients (anemia and neutropenia) with a single *i.p.* paclitaxel, and because no grade 4 toxicity occurred, we consider a single administration of *i.p.* paclitaxel to be a safe treatment option. With systemic chemotherapy, neutropenia had been the main toxicity. Previous studies have reported higher incidence rates of neutropenia and occurrences of more severe toxicities (15, 16). Additionally, non-hematological toxicity in the present study was relatively mild,

and no patients discontinued their participation due to severe adverse events. Thus, we consider this regimen to be a feasible treatment for patients with advanced GC with PM.

In our study, high *i.p.* drug concentrations were observed over a long period and mean peak plasma levels reached the cytotoxic threshold level of 0.1  $\mu$ mol/l in pharmacokinetic analysis. In our previous study on the *i.p.* chemotherapy after gastrectomy with *en-bloc* D2 lymph node dissection, mean peak plasma levels did not reach the cytotoxic threshold level. Additionally, the ratio of AUC peri/AUC pla was reduced by half, compared with the present study (5). The reason behind these phenomena might be due to omentectomy. The omentum is the principal site where ascites are absorbed (19, 20). In brief, absorption of paclitaxel might be encouraged by the presence of omentum.

Our new regimen led to a one-year OS rate of 66.7% with an MST of 15.8 months. Recent studies on unresectable cases or in patients with recurrent GC found one-year OS rates of about 50% (9, 10). Moreover, because patients with GC with PM generally have a particularly poor prognosis, our results are considered encouraging.

In patients with ovarian and gastric cancer with PM, the clinical efficacy of *i.p.* paclitaxel has been verified by clinical trials (21, 22). However, within these trials, it was necessary to implant a peritoneal access port for multiple *i.p.* paclitaxel administrations. In the Gynecological Oncology Group study, Walker *et al.* reported that 41.5% of patients (85/205 eligible patients) had catheter complications or possible *i.p.* infusion- or catheter-related problems, and such patients were unable to

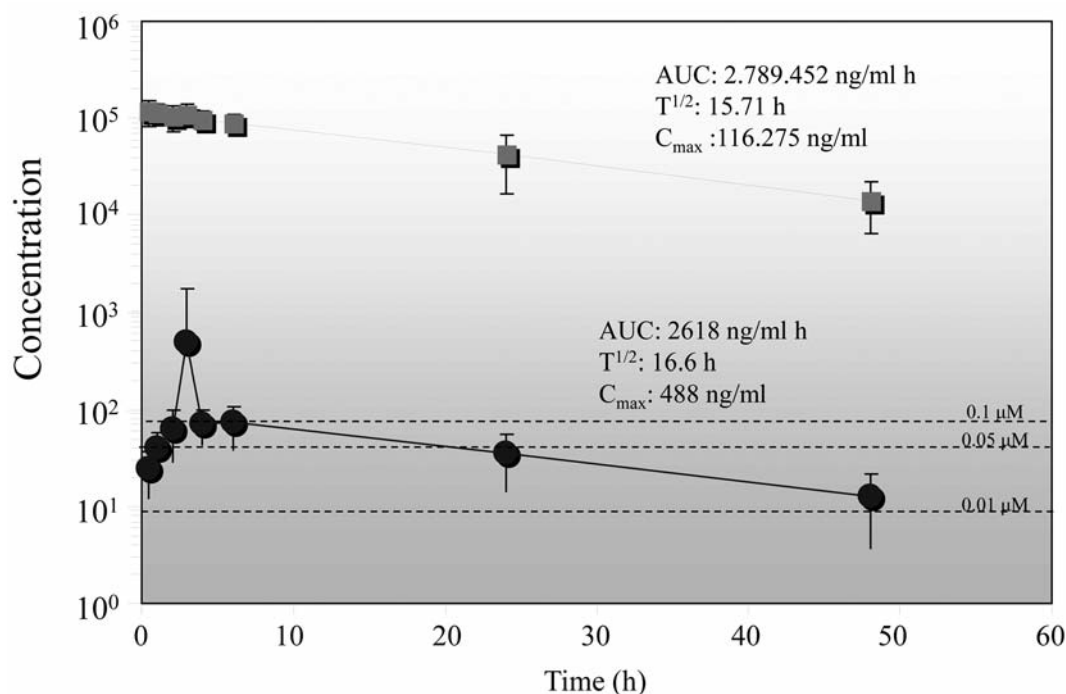


Figure 1. Pharmacokinetic analysis of the intraperitoneal and plasma concentrations of paclitaxel. High intraperitoneal concentrations were maintained for 48 h, during which time the mean plasma peak levels reached the cytotoxic threshold. The intraperitoneal maximum drug concentration ( $C_{max}$ ) was, on average, 238.3-times higher than the plasma  $C_{max}$ . AUC: Area under the blood concentration time curve,  $T_{1/2}$ : half-life period,  $C_{max}$ : maximum drug concentration.

undergo the full number of *i.p.* paclitaxel cycles (23). In our study, a single *i.p.* administration of paclitaxel, which does not require a peritoneal access port and has been shown to be efficacious against free intraperitoneal cancer cells (5) was used. For these reasons, our new regimen might be excellent.

For our results, the most common POR was the primary tumor, and not malignant ascites. These patients had an obstructed stomach due to the increased size of the primary lesion. Heartgrink *et al.* stated that palliative gastrectomy may be beneficial for patients where the tumor load is restricted to one metastatic site (24). Based on these results we consider that for these patients, the use of gastrectomy might improve their prognosis.

## Conclusion

In conclusion, our novel regimen was well-tolerated by patients with GC with PM. A phase II study of its utility should be conducted.

## Acknowledgements

The Authors would like to express their appreciation to Dr. Harumasa Ohyanagi, Vice Board Director of the University of KinDAI Himeji, for his expert comments on the manuscript. We also wish to thank Miss Fusako Kamada for her technical assistance.

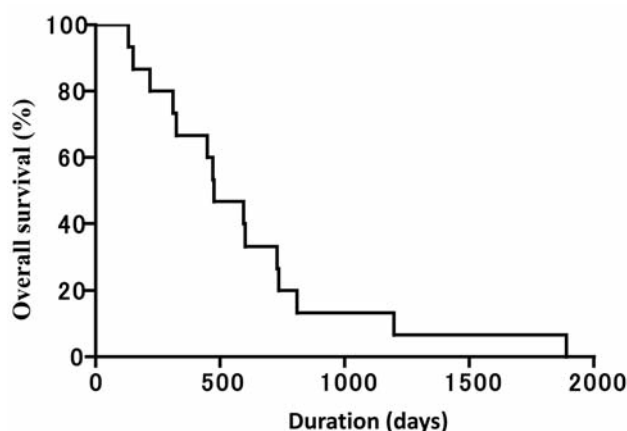


Figure 2. Overall survival. Kaplan-Meier survival curves for 15 eligible patients.

## References

- 1 Parkin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108, 2005.
- 2 Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumar E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, Francois Y, Vignal J and Gilly FN: Peritoneal carcinomatosis from non-gynecologic malignancies:

- Results of the EVOCAPE 1 multicentric prospective study. *Cancer* 88: 358-363, 2000.
- 3 Oh SY, Kwon HC, Lee S, Lee DM, Yoo HS, Kim SH, Jang JS, Kim MC, Jeong JS and Kim HJ: A phase II study of oxaliplatin with low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) for gastric cancer patients with malignant ascites. *Jpn J Clin Oncol* 37: 930-935, 2007.
- 4 Sugarbaker PH and Yonemura Y: Clinical pathway for the management of resectable gastric cancer with peritoneal seeding: Best palliation with a ray of hope for cure. *Oncology* 58: 96-107, 2000.
- 5 Imano M, Imamoto H, Itoh T, Satou T, Peng YF, Yasuda A, Kato H, Shiraishi O, Shinkai M, Yasuda T, Takeyama Y, Okuno K and Shiozaki H: Safety of intraperitoneal administration of paclitaxel after gastrectomy with en-bloc D2 Lymph node dissection. *J Surg Oncol* 105: 43-47, 2012.
- 6 Mohamed F, Marchettini P, Stuart OA, Yoo D and Sugarbaker PH: A comparison of hetastarch and peritoneal dialysis solution for intraperitoneal chemotherapy delivery. *Eur J Surg Oncol* 29: 261-265, 2003.
- 7 Kyle AH, Huxham LA, Yeoman DM and Minchinton AI: Limited tissue penetration of taxanes: A mechanism for resistance in solid tumors. *Clin Cancer Res* 13: 2804-2810, 2007.
- 8 Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K and Fukushima M: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 7: 548-557, 1996.
- 9 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H and Takeuchi M: S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): A phase III trial. *Lancet Oncol* 9: 215-221, 2008.
- 10 Boku N: Chemotherapy for metastatic disease: Review from JCOG trials. *Int J Clin Oncol* 13: 196-200, 2008.
- 11 Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordani P, Menichetti ET and Catalano G: Phase II study of paclitaxel in pretreated advanced gastric cancer. *Anticancer Drugs* 9: 307-310, 1998.
- 12 Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, Matsui T, Kojima H, Takase T, Ohashi N, Fujiwara M, Sakamoto J and Akimasa N: A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 study). *Anticancer Res* 27: 2667-2671, 2007.
- 13 Mori T, Fujiwara Y, Yano M, Tamura S, Yasuda T, Takiguchi S and Monden M: Prevention of peritoneal metastasis of human gastric cancer cells in nude mice by S-1, a novel oral derivative of 5-fluorouracil. *Oncology* 64: 176-182, 2003.
- 14 Kobayashi M, Sakamoto J, Namikawa T, Okamoto K, Okabayashi T, Ichikawa K and Araki K: Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. *World J Gastroenterol* 12: 1412-1415, 2006.
- 15 Narahara H, Fujitani K, Takiuchi H, Sugimoto N, Inoue K, Uedo N, Tsukuma H, Tsujinaka T, Furukawa H and Taguchi T: Phase II study of a combination of S-1 and paclitaxel in patients with unresectable or metastatic gastric cancer. *Oncology* 74: 37-41, 2008.
- 16 Mochiki E, Ohno T, Kamiyama Y, Aihara R, Haga N, Ojima H, Nakamura J, Ohsawa H, Nakabayashi T, Takeuchi K, Asao T and Kuwano H: Phase I/II study of S-1 combined with paclitaxel in patients with unresectable and/or recurrent advanced gastric cancer. *Br J Cancer* 95: 1642-1647, 2006.
- 17 Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, Gunderson L, McCormick B, Morrisintegral M, Rich T, Shipley W and Curran W: Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 47: 13-47, 2000.
- 18 Longnecker SM, Donehower RC, Cates AE, Chen TL, Brundrett RB, Grochow LB, Ettinger DS and Colvin M: High-performance liquid chromatographic assay for taxol in human plasma and urine and pharmacokinetics in a phase I trial. *Cancer Treat Rep* 71: 53-59, 1987.
- 19 Lukas G, Brindle SD and Greengard P: The route of absorption of intraperitoneally administered compounds. *J Pharmacol Exp Ther* 178: 562-564, 1971.
- 20 Hirabayashi K and Graham J: Genesis of ascites in ovarian cancer. *Am J Obstet Gynecol* 106: 492-497, 1970.
- 21 Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL and Burger RA: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 354: 34-43, 2006.
- 22 Ishigami H, Kitayama J, Kaisaki S, Hidemura A, Kato M, Otani K, Kamei T, Soma D, Miyato H, Yamashita H and Nagawa H: Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. *Ann Oncol* 21: 67-70, 2010.
- 23 Walker JL, Armstrong DK, Huang HQ, Fowler J, Webster K, Burger RA and Clarke-Pearson D: Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: A Gynecologic Oncology Group Study. *Gynecol Oncol* 100: 27-32, 2006.
- 24 Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ and van de Velde CJ: Value of palliative resection in gastric cancer. *Br J Surg* 89: 1438-1443, 2002.

Received May 16, 2012

Revised July 23, 2012

Accepted July 24, 2012