Table 4: Randomized controlled trials comparing D1 with D2/D3.

Study	Country	Comparison	Postoperative morbidity	Postoperative mortality	5-year survival
Dutch trial (1989–1993)	Netherlands	D1 (n = 380) D2 (n = 331)	25% 43% (P < .001)	4% 10% (P = .004)	45% 47% HR 1.00 (95% CI, 0.82–1.22)
MRC trial (1987–1994)	UK	D1 (n = 200) D2 (n = 200)	28% 46% (P < .001)	6.5% 13% (P = .04)	35% 33% HR 1.10 (95% CI, 0.87–1.39)
Taiwanese trial (1993–1999)	Taiwan	D1 (n = 110) D3 (n = 111)	7.3% 17.1% (P = .012)	0% 0%	53.6% 59.5% HR 0.49 (95% CI, 0.32–0.77)
IGCSG trial (1999–2002)	Italy	D1 (n = 76) D2 (n = 86)	10.5% 16.3% (P < .029)	0% 1.3% (N.S)	Under analysis

Recently, 15-year follow-up results of a randomized nationwide Dutch D1D2 trial were reported. The overall 15-year survival was 21% (82 patients) for the D1 group and 29% (92 patients) for the D2 group (P = .34). The gastric-cancer related death rate was significantly higher in the D1 group (48%, 182 patients) compared with that in the D2 group (37%, 123 patients), whereas death due to other diseases was similar in both groups [19].

The authors indicated in the interpretation that because a safer, spleen-preserving D2 resection technique had become available in high-volume centers, D2 lymphadenectomy should be the recommended surgical approach for patients with resectable (curable) gastric cancer.

In the British study, postoperative complications were significantly higher in the D2 group (46%) than in the D1 group (28%; P < .001), and the postoperative mortality was also significantly higher in the D2 group (13%) than in the D1 group (6.5%; P = .04) [6].

In this study, splenectomy was performed for many patients with distal gastrectomy and pancreaticosplenectomy was carried out in 56% of patients allocated to the D2 group and 4% of the D1 group. The high frequency of postoperative complications was influenced by the excessive surgery, which contributed to a misunderstanding of the definition of D2 gastrectomy defined by the Japanese Gastric Cancer Association. The 5-year survival rate was 33% in the D1 group and 35% in the D2 group, which did not significantly differ between the two groups [20].

Unlike these two large European trials, the Italian Gastric Cancer Study Group (IGCSG) has shown the safety of D2 dissection with pancreas preservation in a one-arm phase I-II trial [9]. Between 1994 and 1996, 191 eligible patients were entered in the study. The overall morbidity rate was 20.9%. Surgical complications were observed in 16.7% of patients and reoperation was necessary in six patients and was successful in all cases. The overall hospital mortality rate was 3.1%; it was higher after total gastrectomy (7.46%) than after distal gastrectomy (0.8%). This study concluded that postoperative morbidity and mortality rates were favorably comparable to those reported after the standard Western gastrectomy and that the more extensive Japanese procedure with pancreas preservation can be regarded as a safe radical treatment for gastric cancer in selected Western patients treated at experienced centers.

A small-scale RCT comparing of the morbidity and mortality of D1 to D2 gastrectomy was performed by IGCSG [10].

Of 162 patients randomized, 76 were allocated to D1 and 86 to D2 gastrectomy. The overall postoperative morbidity rate was 13.6%. Complications developed in 10.5% of patients after D1 and in 16.3% of patients after D2 gastrectomy. This difference was not statistically significant (P < .29). The overall postoperative mortality rate was 0.6% (one death); it was 1.3% after D1 and 0% after D2 gastrectomy. This study confirmed that, at very experienced centers, morbidity and mortality after extended gastrectomy could be as low as those after D1 gastrectomy.

Another single-institutional small-scale RCT has reported from Taiwan that there were no significant differences in the postoperative and mortality between patients undergoing D3 and D1 gastrectomy [21, 22]. This was the only trial that showed a significantly higher 5-year disease-specific survival in patients with D3 surgery than in those with D1 surgery (Table 4).

Therefore, D2 gastrectomy is becoming accepted as a safe treatment for gastric cancer at experienced centers, in western countries.

4. D2 versus D3

In Japan, gastrectomy with more radical extended lymphadenectomy had been performed since 1980's at many specialized centers in order to improve the prognosis of patients with advanced gastric cancer [23–26]. The incidence of microscopic metastasis in the paraaortic nodes (section no. 16) in patients with gastrectomy undergoing D3 lymph node dissection ranged from 6% to 33%, and the 5-year

Table 5: Randomized controlled trials comparing D2 with D2 plus para-aortic lymph nodes.

Study	Country	Comparison	Postoperative morbidity	Postoperative mortality	5-year survival
JCOG trial (1995–2001)	Japan	D2 (n = 263) D2+ PALN (n = 260)	20.9% 28.1% (P = .067)	0.8% 0.8% (P = .99)	69.2% 70.3% HR 1.03 (95% CI, 0.77–1.37)
Polish trial (1999–2003)	Poland	D2 (n = 141) D2+ PALN (n = 134)	27.7% 21.6% (P = .248)	4.9% 2.2% (P = .37)	Under analysis
East Asian trial (1995–2002)	Japan, Korea, and Chinese Taiwan area	D2 (n = 135) D2+ PALN (n = 134)	26% 39% (P = .023)	0.7% 3.7% (P = .107)	52.6% 55.4% (P = .801)

D2: gastrectomy with D2 lymph node dissection. PALN: para-aortic lymph node dissection.

survival rate had been reported to range from 12% to 23% in patients undergoing gastrectomy with D3 dissection. Extending these previous findings regarding the favorable results of D3 dissection, the Japanese Clinical Oncology Group (JCOG) conducted a randomized clinical trial between 1995 and 2001 to compare D2 gastrectomy alone with D2 plus paraaortic lymph node dissection (PAND) [27]. A total of 523 patients with T2b, T3, and T4 gastric cancer were registered and randomly assigned to D2 alone group (263 patients) or D2 plus PAND group (260 patients).

The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9% and 28.1%, respectively (P = .07). There were no significant differences between the two groups in the frequencies of anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia, or death from any cause within 30 days after surgery (the mortality was 0.8% in each group). The 5-year overall survival rate was 69.2% for the group assigned to D2 lymphadenectomy alone and 70.3% for the group assigned to D2 lymphadenectomy plus PAND; the hazard ratio for death was 1.03. Moreover, there were no significant differences in recurrence-free survival between the two groups.

Recently, meta-analyses of D2 lymphadenectomy versus D2 with PAND were reported [28]. Three RCTs including the PGCSG study in Poland [29], EASOG study in Japan, Korea, and Chinese Taiwan area [30, 31], and JCOG-9501 study in Japan [27] were eligible (Table 5). Another analysis included 4 RCTs and 4 nonrandomized studies were identified [32]. These meta-analyses showed that D2+ PAND can be performed as safely as a standard D2 resection without increasing postoperative mortality but failed to benefit overall survival in patients with advanced gastric cancer.

Gastrectomy with D2 lymphadenectomy plus PAND cannot be recommended as a routine practice for the surgical treatment of gastric cancer.

5. Mediastinal Lymph Node Dissection for Gastric Cancer

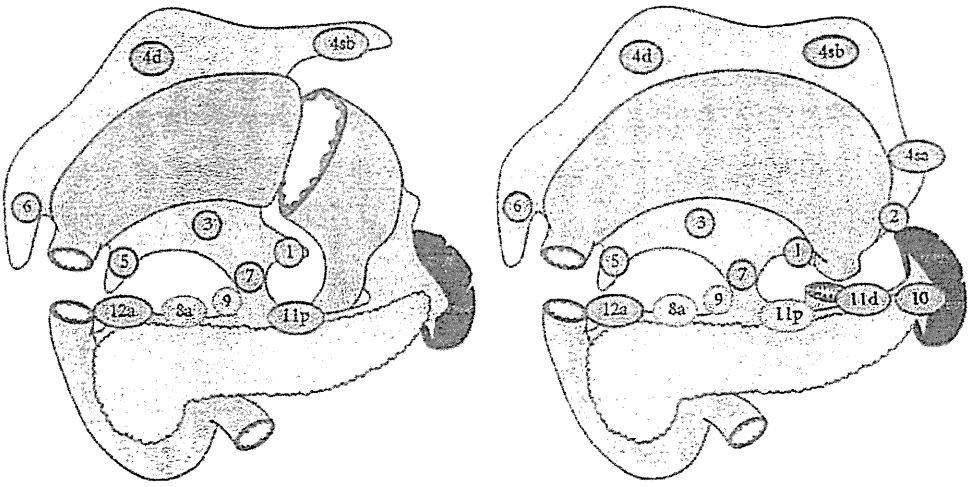
For patients with esophageal invasion from gastric cancer, it is necessary to perform mediastinal resection included the lower esophagus and the periesophageal lymph nodes and to confirm that the esophageal cut end is negative by performing histological examination using frozen section as necessary [33]. Conventionally, this mediastinal procedure was done through the left thoracoabdominal approach (LTA), because the frequency of lymph node metastasis was reported to be high with about 20–40% and an adequate margin from the tumor could be secured. However, a mediastinal procedure was enabled through the abdominal-transhiatal approach (TH) with advances in surgical methods using a circular stapler in recent years.

In Japan, an RCT comparing LTA versus TH for Siewert type II and III tumors with esophageal invasion of 3 cm or less was carried out by JCOG [34]. Between 1995 and 2003, 167 patients were enrolled from 27 Japanese hospitals and randomly assigned to TH (n = 82) or LTA (n = 85), although the projected sample size was 302. After the first interim analysis, the predicted probability of LTA having a significantly better overall survival than TH at the final analysis was only 3.65%; therefore, the trial was closed. The 5-year overall survival was 52.3% in the TH group and 37.9% in the LTA group. The hazard ratio of death for LTA compared with TH was 1.36 (0.89–2.08, P = .92). Three patients died in hospital after LTA but none after TH. Morbidity after LTA was worse than that after TH with rates of 49% and 34%, respectively.

This study concluded that LTA could not be performed for gastric cancer with esophageal invasion of 3 cm or less, because LTA did not improve survival compared to TH and resulted in increased morbidity.

6. Splenectomy or Pancreaticosplenectomy in the Treatment of Cancer of the Upper Third of the Stomach

In Japan, pancreaticosplenectomy for LN dissection around the splenic artery (station no. 11) and splenic hilus (station no. 10) had been widely performed, because this procedure was proposed as a radical dissection of metastatic LN along the splenic artery [35, 36]. However, Japanese retrospective analyses proved that there was no survival benefit of these



(a) Distal gastrectomy (b) Total gastrectomy

FIGURE 2: Lymph node dissection according to the Japanese gastric cancer treatment guideline 2010 of the 3rd edition reproduced form [14] with permission. D1 distal gastrectomy consists of LN dissection of station nos. 1, 3, 4sb, 4d, 5, 6, and 7 and D1 total gastrectomy consists of station nos. 1–6 and 7 (blue circle). Yellow circles indicate the lymph nodes that belong to D1+, and red circles indicate those to D2.

procedures [37, 38]. Recently, pancreas-preserving splenectomy has been considered a safe and effective procedure without decreasing surgical curability [39, 40].

In the JCOG 9501 study, pancreas-preserving splenectomy was generally performed with low surgical mortality [27, 41]. In this study, only 22 of 523 patients underwent pancreaticosplenectomy and 59% of patients (13 of 22 cases) developed postoperative complications.

In this pancreas-preserving procedure, the splenic artery is generally divided at the distal site after branching-off of the great pancreatic artery in Sasako's modification and the splenic vein is preserved as distal as possible in order to prevent pancreatic fistula and pancreatic atrophy and consequent glucose intolerance [42].

In Western countries as well, pancreaticosplenectomy had a marked adverse effect on both mortality and morbidity in two RCTs [5, 6].

Currently, pancreaticosplenectomy is considered beneficial only when the primary tumor or metastatic LN directly invades the pancreas, but is not performed for prophylactic dissection of lymph nodes around the splenic artery (station no. 11).

According to the Japanese experience with LN dissection at the splenic hilus with splenectomy, the incidence of hilar node metastasis ranged 15–21% for tumors located at or infiltrate to the proximal third of the stomach. About 20–25% of patients with LN metastasis have survived over 5 years following LN dissection with splenectomy [35]. However, hilar nodal metastasis was reported to be not found in the early gastric cancer base on retrospective data [43, 44]. Splenectomy is recommended for curative resection of the proximal advanced gastric cancer with infiltration to the greater curvature in the Gastric Cancer Treatment Guidelines 2010 [14].

Two RCTs compared gastrectomy with splenectomy and gastrectomy alone in patients with gastric cancer were reported with regard to the effectiveness and safety [45, 46].

Csendes et al. reported 187 patients who underwent total gastrectomy between 1985 and 1992; these patients were randomized into two groups, gastrectomy with splenectomy and gastrectomy alone. Postoperative complications were more frequent in the splenectomy group than in the surgery alone group, including postoperative fever over 38°C (50% versus 39%: $P < .04$), pulmonary complications (39% versus 24%: $P < .008$), and subphrenic abscess (11% versus 4%: $P < .05$). There were no significant differences between the groups in hospital mortality (4.4% for splenectomy versus 3.1% for gastrectomy alone) or in the 5-year survival rate (42% for splenectomy versus 36% for gastrectomy alone) [45].

The other trial reported by Yu et al. was carried out in Korea between 1995 and 1999. Two hundred seven patients with gastric cancer were divided randomly into two groups, total gastrectomy (103 patients) and total gastrectomy plus splenectomy (104 patients). Postoperative mortality was 8.7% in total gastrectomy alone group and 15.4% in total gastrectomy plus splenectomy group, but there was no significant difference between the groups. Hospital mortality was 1.0% in total gastrectomy alone and 1.9% in total gastrectomy plus splenectomy group; there was no significant difference between the two groups.

The 5-year survival rates did not differ statistically between the gastrectomy alone group (48.8%) and gastrectomy plus splenectomy group (54.8%). There was no 5-year survivor among patients with lymph node metastasis at the splenic hilum in either group [46].

Therefore, these results did not support the effectiveness of prophylactic dissection at the splenic hilum during

splenectomy in patients undergoing total gastrectomy for proximal gastric cancer.

7. Future Perspectives

In Japan and Korea, gastrectomy with D2 LN dissection is the gold standard of treatment for advanced gastric cancer. In order to improve the prognosis of these patients, adjuvant chemotherapy after D2 gastrectomy is thought to be effective and several studies have been reported [47, 48]. Recently, a meta-analysis based on the individual data of 3838 patients from 17 different trials with median follow-up 7 years was reported and indicated a modest but statistically significant benefit associated with adjuvant chemotherapy after curative resection of gastric cancer [49]. In Japan, adjuvant chemotherapy with S-1 is a standard treatment for patients with stage II/III gastric cancer after curative gastrectomy with D2 LN dissection [48]. Moreover, to improve the survival of patients with advanced gastric cancer, neoadjuvant chemotherapy and/or chemotherapy with combination setting or new agents, such as molecular targeting agents, are thought to be necessary in addition to performing D2 gastrectomy with safety and reliability [50].

Last year, the Japanese Classification of Gastric Carcinoma was revised to conform with the TNM classification of UICC in many respects. In the new guidelines for the Diagnosis and Treatment of Carcinoma of the Stomach, D1, D1+, and D2 gastrectomy were described according to the type of gastrectomy, making the guidelines easier to understand. A global study using unified criteria is necessary to establish a safe and effective worldwide treatment standard including gastrectomy with LN dissection.

References

[1] P. Pisani, D. M. Parkin, F. Bray, and J. Ferlay, "Estimates of the worldwide mortality from 25 cancers in 1990," *International Journal of Cancer*, vol. 83, no. 1, pp. 18–29, 1999.

[2] F. Lordick and J. R. Siewert, "Perioperative chemotherapy vs. surgery alone in resectable gastroesophageal carcinoma," *Results of the MAGIC Study. Chirun*, vol. 77, pp. 1166–1167, 2006.

[3] J. S. Macdonald, S. R. Smalley, J. Benedetti et al., "Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction," *The New England Journal of Medicine*, vol. 345, no. 10, pp. 725–730, 2001.

[4] T. Kajitani, "The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification," *Japanese Journal of Surgery*, vol. 11, no. 2, pp. 127–139, 1981.

[5] J. Bonenkamp, I. Songun, J. Hermans et al., "Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients," *The Lancet*, vol. 345, no. 8952, pp. 745–748, 1995.

[6] A. Cuschieri, P. Fayers, J. Fielding et al., "Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial," *The Lancet*, vol. 347, no. 9007, pp. 995–999, 1996.

[7] R. Biffi, A. Chiappa, F. Luca et al., "Extended lymph node dissection without routine spleno-pancreatectomy for treatment of gastric cancer: low morbidity and mortality rates in a single center series of 250 patients," *Journal of Surgical Oncology*, vol. 93, no. 5, pp. 394–400, 2006.

[8] F. Roviello, D. Marrelli, P. Morgagni et al., "Survival benefit of extended D2 lymphadenectomy in gastric cancer with involvement of second level lymph nodes: a longitudinal multicenter study," *Annals of Surgical Oncology*, vol. 9, no. 9, pp. 894–900, 2002.

[9] M. Degiuli, M. Sasako, A. Ponti, T. Soldati, F. Danese, and F. Calvo, "Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian gastric cancer study group prospective multicenter surgical study," *Journal of Clinical Oncology*, vol. 16, no. 4, pp. 1490–1493, 1998.

[10] M. Degiuli, M. Sasako, M. Calgaro et al., "Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial," *European Journal of Surgical Oncology*, vol. 30, no. 3, pp. 303–308, 2004.

[11] Japanese Gastric Cancer Association, "Japanese classification of gastric carcinoma—2nd English edition," *Gastric Cancer*, vol. 1, pp. 10–24, 1998.

[12] Japanese Gastric Cancer Association, *Japanese Classification of Gastric Cancer*, Kanehara & Co. Ltd, Tokyo, Japan, 14th edition, 2010.

[13] K. Maruyama, M. Sasako, T. Kinoshita et al., "Should systematic lymph node dissection be recommended for gastric cancer?" *European Journal of Cancer*, vol. 34, no. 10, pp. 1480–1489, 1998.

[14] Japanese Gastric Cancer Association, *Gastric Cancer Treatment Guidelines*, Kanehara & Co. Ltd, Tokyo, Japan, 2010.

[15] F. L. Greene, D. L. Page, and I. D. Fleming, Eds., *AJCC Cancer Staging Manual: TNM Classification of Malignant Tumors*, Springer, New York, NY, USA, 6th edition, 2002.

[16] S. B. Edge, D. R. Byrd, C. C. Compton, A. G. Fritz, F. L. Greene, and A. Trotti, *AJCC Cancer Staging Handbook*, Springer, New York, NY, USA, 7th edition, 2010.

[17] H. H. Hartgritik, C. J. H. van de Velde, H. Putter et al., "Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch Gastric Cancer Group Trial," *Journal of Clinical Oncology*, vol. 22, no. 11, pp. 2069–2077, 2004.

[18] A. M. G. Bunt, J. Hermans, M. C. Boon et al., "Evaluation of the extent of lymphadenectomy in a randomized trial of Western- versus Japanese-type surgery in gastric cancer," *Journal of Clinical Oncology*, vol. 12, no. 2, pp. 417–422, 1994.

[19] I. Songun, H. Putter, E. M. K. Kranenbarg, M. Sasako, and C. J. H. van de Velde, "Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial," *The Lancet Oncology*, vol. 11, no. 5, pp. 439–449, 2010.

[20] A. Cuschieri, S. Weeden, J. Fielding et al., "Patient survival after D1 and D2 dissections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Cooperative Group," *British Journal of Cancer*, vol. 79, pp. 1522–1530, 1999.

[21] C. W. Wu, C. A. Hsiung, S. S. Lo et al., "Nodal dissection for patients with gastric cancer: a randomised controlled trial," *The Lancet Oncology*, vol. 7, no. 4, pp. 309–315, 2006.

[22] C. W. Wu, C. A. Hsiung, S. S. Lo, M. C. Hsieh, L. T. Shia, and J. Whang-Peng, "Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer," *British Journal of Surgery*, vol. 91, no. 3, pp. 283–287, 2004.

[23] H. Isozaki, K. Okajima, K. Fujii et al., "Effectiveness of paraaortic lymph node dissection for advanced gastric cancer," *Hepato-Gastroenterology*, vol. 46, no. 25, pp. 549–554, 1999.

[24] M. Baba, S. Hokita, S. Natsugoe et al., "Paraaortic lymphadenectomy in patients with advanced carcinoma of the upper-third of the stomach," *Hepato-Gastroenterology*, vol. 47, no. 33, pp. 893–896, 2000.

[25] C. Kunisaki, H. Shimada, H. Yamaoka et al., "Indications for paraaortic lymph node dissection in gastric cancer patients with paraaortic lymph node involvement," *Hepato-Gastroenterology*, vol. 47, no. 32, pp. 586–589, 2000.

[26] S. Takashima and T. Kosaka, "Results and controversial issues regarding a para-aortic lymph node dissection for advanced gastric cancer," *Surgery Today*, vol. 35, no. 6, pp. 425–431, 2005.

[27] M. Sasako, T. Sano, S. Yamamoto et al., "D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer," *The The New England Journal of Medicine*, vol. 359, no. 5, pp. 453–462, 2008.

[28] X. Z. Chen, J. K. Hu, Z. G. Zhou et al., "Meta-analysis of effectiveness and safety of D2 plus para-aortic lymphadenectomy for resectable gastric cancer," *Journal of the American College of Surgeons*, vol. 210, no. 1, pp. 100–105, 2010.

[29] J. Kulig, T. Popiela, P. Kolodziejczyk, M. Sierzega, and A. Szczepanik, "Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial," *American Journal of Surgery*, vol. 193, no. 1, pp. 10–15, 2007.

[30] Y. Yonemura, C. C. Wu, N. Fukushima et al., "Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons," *Hepato-Gastroenterology*, vol. 53, no. 69, pp. 389–394, 2006.

[31] Y. Yonemura, C. C. Wu, N. Fukushima et al., "East Asia Surgical Oncology Group. Randomized clinical trial of D2 and extended paraaortic lymph adenectomy in patients with gastric cancer," *International Journal of Clinical Oncology*, vol. 13, pp. 132–137, 2008.

[32] Z. Wang, J. Q. Chen, and Y. F. Cao, "Systematic review of D2 lymphadenectomy versus D2 with para-aortic nodal dissection for advanced gastric cancer," *World Journal of Gastroenterology*, vol. 16, no. 9, pp. 1138–1149, 2010.

[33] K. Koufuji, K. Shirouzu, K. Aoyagi et al., "Surgery and clinicopathological features of gastric adenocarcinoma involving the esophago-gastric junction," *Kurume Medical Journal*, vol. 52, no. 3, pp. 73–79, 2005.

[34] M. Sasako, T. Sano, S. Yamamoto et al., "Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial," *Lancet Oncology*, vol. 7, no. 8, pp. 644–651, 2006.

[35] K. Okajima and H. Isozaki, "Splenectomy for treatment of gastric cancer: Japanese experience," *World Journal of Surgery*, vol. 19, no. 4, pp. 537–540, 1995.

[36] Y. Noguchi, T. Imada, A. Matsumoto, D. G. Colt, and M. F. Brennan, "Radical surgery for gastric cancer. A review of the Japanese experience," *Cancer*, vol. 64, no. 10, pp. 2053–2062, 1989.

[37] K. Kitamura, S. Nishida, D. Ichikawa et al., "No survival benefit from combined pancreaticosplenectomy and total gastrectomy for gastric cancer," *British Journal of Surgery*, vol. 86, no. 1, pp. 119–122, 1999.

[38] Y. Kodera, Y. Yamamura, Y. Shimizu et al., "Lack of benefit of combined pancreaticosplenectomy in D2 resection for proximal-third gastric carcinoma," *World Journal of Surgery*, vol. 21, no. 6, pp. 622–628, 1997.

[39] K. Maruyama, M. Sasako, T. Kinoshita, T. Sano, H. Katai, and K. Okajima, "Pancreas-preserving total gastrectomy for proximal gastric cancer," *World Journal of Surgery*, vol. 19, no. 4, pp. 532–536, 1995.

[40] H. Furukawa, M. Hiratsuka, O. Ishikawa et al., "Total gastrectomy with dissection of lymph nodes along the splenic artery: a pancreas-preserving method," *Annals of Surgical Oncology*, vol. 7, no. 9, pp. 669–673, 2000.

[41] T. Sano, M. Sasako, S. Yamamoto et al., "Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501," *Journal of Clinical Oncology*, vol. 22, no. 14, pp. 2767–2773, 2004.

[42] P. A. Clavien, M. G. Sarr, and Y. Fong, "Atlas of upper gastrointestinal and hepato-pancreatico-biliary surger," in *Total Gastrectomy with Radical Systemic Lymphadenectomy*, M. Sasako, Ed., pp. 179–188, Springer, New York, NY, USA, 2007.

[43] K. Yoshino, Y. Yamada, F. Asanuma, and K. Aizawa, "Splenectomy in cancer gastrectomy: recommendation of spleen-preserving for early stages," *International Surgery*, vol. 82, no. 2, pp. 150–154, 1997.

[44] M. Ikeguchi and N. Kaibara, "Lymph node metastasis at the splenic hilum in proximal gastric cancer," *American Surgeon*, vol. 70, no. 7, pp. 645–648, 2004.

[45] A. Csendes, P. Burdiles, J. Rojas, I. Braghetto, J. C. Diaz, and F. Maluenda, "A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma," *Surgery*, vol. 131, no. 4, pp. 401–407, 2002.

[46] W. Yu, G. S. Choi, and H. Y. Chung, "Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer," *British Journal of Surgery*, vol. 93, no. 5, pp. 559–563, 2006.

[47] D. Cunningham, W. H. Allum, S. P. Stenning et al., "Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer," *The New England Journal of Medicine*, vol. 355, no. 1, pp. 11–20, 2006.

[48] S. Sakuramoto, M. Sasako, T. Yamaguchi et al., "Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine," *The New England Journal of Medicine*, vol. 357, no. 18, pp. 1810–1820, 2007.

[49] X. Paoletti, K. Oba, T. Burzykowski et al., "Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis," *JAMA—Journal of the American Medical Association*, vol. 303, no. 17, pp. 1729–1737, 2010.

[50] Y. J. Bang, E. Van Cutsem, A. Feyereislova et al., "Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial," *The Lancet*, vol. 376, no. 9742, pp. 687–697, 2010.

Clinical Study

Oncology

Oncology 2011;80:296–300
DOI: 10.1159/000329090

Received: December 12, 2010
Accepted after revision: May 2, 2011
Published online: July 18, 2011

Phase II Feasibility Study of Adjuvant S-1 plus Docetaxel for Stage III Gastric Cancer Patients after Curative D2 Gastrectomy

Shigeyuki Tamura[a] Kazumasa Fujitani[b] Yutaka Kimura[c] Takeshi Tsuji[e] Jin Matsuyama[f] Shohei Iijima[g] Hiroshi Imamura[h] Kentaro Inoue[d] Kenji Kobayashi[i] Yukinori Kurokawa[b] Hiroshi Furukawa[h] the Osaka Gastrointestinal Cancer Chemotherapy Study Group

Department of Surgery, [a]Kansai Rosai Hospital, Amagasaki, [b]National Hospital Organization, Osaka National Hospital, [c]NTT West Osaka Hospital, and [d]Kansai Medical University, Osaka, [e]Wakayama Rosai Hospital, Wakayama, [f]Yao Municipal Hospital, Yao, [g]Minoh City Hospital, Minoh, [h]Sakai Municipal Hospital, Sakai, and [i]Kinki Central Hospital, Itami, Japan

Key Words
Gastric cancer · Adjuvant chemotherapy · S-1 · Docetaxel · Gastrectomy · D2 lymph node dissection

Abstract
Objective: The aim of this prospective study was to evaluate the feasibility and safety of adjuvant S-1 plus docetaxel in patients with stage III gastric cancer. ***Methods:*** We enrolled 53 patients with pathological stage III gastric cancer who underwent D2 gastrectomy. They received oral S-1 (80 mg/m^2/day) administration for 2 consecutive weeks and intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (1 cycle). The treatment was started within 45 days after surgery and repeated for 4 cycles, followed by S-1 monotherapy (4 weeks on, 2 weeks off) until 1 year after surgery. The feasibility of the 4 cycles of chemotherapy, followed by S-1 administration, was evaluated. ***Results:*** A total of 42 patients (79.2%, 95% CI 65.9–82.9) tolerated the planned 4 cycles of treatment with S-1 and docetaxel, and 34 patients (64.2%, 95% CI 49.8–76.9) completed subsequent S-1 monotherapy for 1 year. Grade 4 neutropenia was observed in 28% and grade 3 febrile neutropenia in 9% of the patients, while grade 3 nonhematological toxicities were relatively low. ***Conclusions:*** Adjuvant S-1 plus docetaxel therapy is feasible and has only moderate toxicity in stage III gastric cancer patients. We believe that this regimen will be a candidate for future phase III trials seeking the optimal adjuvant chemotherapy for stage III gastric cancer patients.

Introduction

The principal aims of adjuvant chemotherapy for curatively resected gastric cancer are to prevent distant or local recurrence and improve the survival of patients. In Japan, several studies concerning postoperative adjuvant chemotherapy for patients with gastric cancer have been performed since 1960, but none of these studies demonstrated therapeutic benefits of adjuvant chemotherapy [1–6].

The National Surgical Adjuvant Study Group for Gastric Cancer study evaluated postoperative chemotherapy for patients with T2, N1–2 gastric cancer from 1998 using uracil-tegafur (an oral fluoropyrimidine prodrug) for 18 months, excluding stage I gastric cancer, based on an analysis of previous studies. Although this study was interrupted because of the introduction of S-1 and the start

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–2414/11/0806–0296$38.00/0

Accessible online at:
www.karger.com/ocl

Shigeyuki Tamura
Department of Surgery
Kansai Rosai Hospital
Amagasaki, Hyogo 660-8511 (Japan)
E-Mail stamura@kanrou.net

Table 1. Patient characteristics

		Patients (n = 53)
Age, years	Median	65
	Range	43–78
Gender	Male	42
	Female	11
ECOG PS	0	31
	1	22
Pathological type	Intestinal	23
	Diffuse	29
	Others	1
Stage[1]	IIIA	36
	IIIB	17
T stage[2]	pT2	21
	pT3	30
	pT4	2
N stage[2]	pN0	1
	pN1	22
	pN2	30
M stage[2]	M0	53
	M1	0
Stage[2]	IIIA	36
	IIIB	16
	IV (T4, N1)	1

ECOG PS = Eastern Cooperative Oncology Group performance status.
[1] Japanese classification. [2] TNM classification.

Table 2. Adverse events of 4 cycles of chemotherapy with S-1 plus docetaxel (n = 53)

	G1	G2	G3	G4	≥G3, %
Hematologic					
Anemia	20	11	2	0	3.3
Leukopenia	7	17	7	3	18.9
Neutropenia	4	4	11	15	49.1
Thrombocytopenia	7	0	0	0	3.8
Febrile neutropenia	–	–	5	0	9.4
Nonhematologic					
AST/ALT	7	0	0	0	0
Total bilirubin	4	3	0	0	0
Nausea	9	3	3	0	5.7
Vomiting	2	2	0	0	0
Anorexia	16	7	5	0	9.4
Fatigue	12	8	3	0	5.7
Stomatitis	5	1	1	0	1.9
Diarrhea	6	3	0	0	0
Alopecia	5	3	–	–	0

National Cancer Institute Common Toxicity Criteria, version 3.0. AST = Aspartate aminotransferase; ALT = alanine aminoransferase.

studies, including ultrasonograpy, computed tomography and gastrointestinal endoscopy. Patients underwent abdominal computed tomography at 6-month intervals during the first 2 years after surgery, at 1-year intervals thereafter until 5 years after surgery, and also underwent gastrointestinal endoscopy at 1-year intervals.

Statistical Analysis

The calculation of the sample size for the study was based on an expected feasibility rate of 75% and a threshold feasibility rate of 50%, using a 2-sided α error of 0.05 and a statistical power of 90%. The planned sample size was 50 patients, allowing for a 20% dropout rate. The feasibility rate was evaluated by exact binominal test. Statistical analysis was done using R software version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

We enrolled 53 patients from 13 institutions for this study, 42 men and 11 women with a median age of 65 years (range 43–78), between May 2007 and August 2008. Thirty-six patients had stage IIIA disease and 17 patients had stage IIIB disease. The demographic and clinicopathological characteristics of these patients are listed in table 1.

Toxicity

The most frequent grade 3–4 hematological toxicity during 4 cycles of this regimen was neutropenia, which was observed in 26 of 53 patients (49.1%) (table 2). Grade 3 febrile neutropenia was observed in 5 patients (9%). Additional grade 3–4 hematological toxicities consisted of leukopenia in 10 patients (18.9%) and anemia in 2 patients (3.8%). Nonhematological toxicities of grade ≥3 involved nausea in 5.7%, anorexia in 9.4% and fatigue in 5.7%. There was no grade 4 nonhematological toxicity in any patient.

No treatment-related deaths occurred within 30 days after completion of this regimen.

Feasibility

The feasibility of the planned 4 cycles of treatment was 79.2% (95% CI 65.9–89.2; $p < 0.001$ under the null hypothesis) with 42 out of 53 patients (table 3). Reasons for discontinuation of this regimen were adverse events in 9 patients, by physician's decision in 1 patient, and 1 patient postponed the treatment schedule due to personal rea-

Table 3. Feasibility of protocol treatment

	S-1 plus docetaxel for 4 cycles	S-1 plus docetaxel and S-1 monotherapy for 1 year
Patients	53	53
Completed	42	34
Not completed	11	19
Treatment completing rate	79.2% (65.9–89.2)	64.2% (49.8–76.9)

Figures in parentheses are 95% CIs.

sons. A total of 42 patients completed 4 cycles of S-1 and docetaxel, but 8 patients did not follow the planned S-1 monotherapy: 3 due to recurrent cancer, 2 due to toxicity, 1 due to patient refusal, 1 due to the physician's decision, and 1 due to personal reasons.

The relative performance of S-1 and docetaxel for 4 cycles of chemotherapy was 79.6 and 87.8%, respectively. Moreover, the compliance rates of S-1 patients were 84.9, 73.6, 69.8 and 64.2% (95% CI 49.8–76.95) at 3, 6, 9 and 12 months after surgery, respectively.

Discussion

This phase II study demonstrated that postoperative adjuvant S-1 plus docetaxel therapy of 4 cycles is feasible, with a feasibility rate of 79.2%. Moreover, the compliance of S-1 treatment was similar to those of the ACTS-GC study up to 1 year after surgery: 84.9 versus 87.4% at 3 months, 73.6 versus 77.9% at 6 months, 69.8 versus 70.8% at 9 months and 64.2 versus 65.8% at 12 months, respectively [8].

Since there were few gastrointestinal toxicities during an additional 4 courses of docetaxel, this combination regimen seemed to be highly tolerable. These results may have important implications for future adjuvant treatment strategies for stage III gastric cancer.

In Japan, for metastatic or recurrent gastric cancer, S-1 plus cisplatin is now considered to be one of the standard regimens based on a phase III trial (SPIRITS study) [16].

The results of the SPIRITS study (S-1 vs. S-1 plus cisplatin) established the superiority of the S-1 plus cisplatin combination over S-1 monotherapy [15]. The rate of response to combination therapy versus monotherapy was 54 versus 31% ($p = 0.0018$), and the median survival time was 13.0 versus 11.0 months ($p = 0.0366$).

Therefore, S-1 plus cisplatin is considered to be a candidate for an experimental arm in the next adjuvant chemotherapy trial.

More recently, adjuvant chemotherapy studies using S-1 plus cisplatin have been reported for patients with resected gastric cancer [16, 17]. Five courses of S-1 plus cisplatin appear to be too toxic as postgastrectomy treatment for clinical stage II/III patients who underwent gastrectomy but turned out to be stage IV gastric cancer, so that the median relative dose intensities of S-1 and cisplatin were only 37 and 40%, respectively [16]. Moreover, a feasibility study of adjuvant chemotherapy with 3 courses of S-1 plus cisplatin followed by S-1 monotherapy until 1 year after surgery demonstrated that 3 courses of combined chemotherapy were not feasible because of the high incidence of grade 3–4 toxicities including neutropenia (40%), anorexia (28%) and nausea (8%) [17]. In this clinical trial, they suggested the modified protocol, the first chemotherapy cycle of which consisted of S-1 monotherapy; then, cisplatin was added to cycles 2, 3 and 4, followed by S-1 monotherapy up to 1 year after surgery. This amended protocol is more feasible than the original protocol, because of relatively few grade 3–4 toxicities including neutropenia (37%), anorexia (8%) and nausea (3%) and should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial [17].

Nausea and anorexia are commonly observed adverse reactions after the administration of cisplatin, and dehydration due to impaired oral food intake could increase the renal toxicity of cisplatin, especially in patients immediately after gastrectomy.

On the other hand, preclinical pharmacokinetic studies on docetaxel have shown that its hepatobiliary excretion is the major route of elimination, while renal excretion is minimal (<5%) [18–20]. Thus, it seems that docetaxel is a suitable anticancer agent for patients immediately after surgery. Moreover, S-1 plus docetaxel can be given in outpatient clinics, while S-1 plus cisplatin usually requires hospitalization to ensure hydration; thus, the former reduces the inconvenience to both patients and clinicians.

In both Japan and Korea, phase III studies of S-1 alone versus S-1 and docetaxel (JACCRO GC03 study) as chemotherapy for advanced gastric cancer are ongoing and the results should be reported soon [21].

If the results of the JACCRO GC03 study are favorable, it seems that the present regimen will become a promising candidate for adjuvant chemotherapy in stage III gastric cancer.

In conclusion, postoperative adjuvant chemotherapy with S-1 and docetaxel of 4 cycles and S-1 monotherapy afterwards until 1 year after surgery is considered to be feasible for patients who have undergone gastrectomy for gastric cancer.

This should be regarded as a potential experimental arm together with S-1 plus cisplatin for the next adjuvant phase III study comparing S-1 plus other drug combination chemotherapy and S-1 alone as adjuvant chemotherapy for patients who have undergone curative resection with D2 lymph node dissection for stage III gastric cancer.

Acknowledgements

We are indebted to the physicians and all of the clinical study teams at the participating institutions. We also thank Mr. Toshio Shimokawa for his scientific advice, and Ms. Akiko Hotta and Ms. Hiroko Maruyama for their excellent secretarial assistance at the Osaka Gastrointestinal Cancer Chemotherapy Study Group data center. The authors are also indebted to Prof. J. Patrick Barron of the Department of International Medical Communications of Tokyo Medical University for his review of the manuscript.

References

1 Nakajima T, Fukami A, Ohashi I, Kajitani T: Long-term follow-up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. Int J Clin Pharmacol Biopharm 1978;16:209–216.

2 Nakajima T, Fukami A, Takagi K, Kajitani T: Adjuvant chemotherapy with mitomycin C, and with a multi-drug combination of mitomycin C, 5-fluorouracil and cytosine arabinoside after curative resection of gastric cancer. Jpn J Clin Oncol 1980;10:187–194.

3 Nakajima T, Takahashi T, Takagi K, Kuno K, Kajitani T: Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. J Clin Oncol 1984;2:1366–1371.

4 Nakajima T, Okabayashi K, Nakazato H, Iwanaga T, Ohta K, Kinoshita T, Kitou T, Yamamura Y, Furukawa H, Hiratsuka M: Adjuvant chemotherapy with MFC-related regimens for patients with gastric cancer after curative gastrectomy. Jpn J Soc Cancer Ther 1994;29:654–662.

5 Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, Goto M: Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomized trial. Lancet 1999;354:273–277.

6 Nashimoto A, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, Sasako M, Kunii Y, Motohashi H, Yamamoto S, Gastric Cancer Surgical Study Group, Japan Clinical Oncology Group: Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol 2003;21:2282–2287.

7 Nakajima T, Kinoshita T, Nashimoto A, Sairenji M, Yamaguchi T, Sakamoto J, Fujiya T, Inada T, Sasako M, Ohashi Y, National Surgical Adjuvant Study of Gastric Cancer Group: Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg 2007;94:1468–1476

8 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810–1820.

9 Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, Shirao K, Matsumura Y, Gotoh M: Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 2003;89:2207–2212.

10 Yoshida K, Ninomiya M, Takakura N, Hirabayashi N, Takiyama W, Sato Y, Todo S, Terashima M, Gotoh M, Sakamoto J, Nishiyama M: Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin Cancer Res 2006;12:3402–3407.

11 Mochiki E, Ohno T, Kamiyama Y, Aihara R, Haga N, Ojima H, Nakamura J, Ohsawa H, Nakabayashi T, Takeuchi K, Asao T, Kuwano H, North Kanto Gastric Cancer Study Group: Phase I/II study of S-1 combined with paclitaxel in patients with unresectable and/or recurrent advanced gastric cancer. Br J Cancer 2006;95:1642–1647.

12 Inokuchi M, Yamashita T, Yamada H, Kojima K, Ichikawa W, Nihei Z, Kawano T, Sugihara K: Phase I/II study of S-1 combined with irinotecan for metastatic advanced gastric cancer. Br J Cancer 2006;94:1130–1135.

13 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma - 2nd English edition. Gastric Cancer 1998;1:10–24.

14 Sobin LH, Witteking C: International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, ed 6. New York, Wiley, 2002.

15 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, 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 2008;9:215–221.

16 Kodera Y, Ishiyama A, Yoshikawa T, Kinoshita T, Ito S, Yokoyama H, Mochizuki Y, Ito H, Tsuburaya A, Sakamoto J, Nakao A, Chubu Clinical Cancer Group: A feasibility study of postoperative chemotherapy with S-1 and cisplatin (CDDP) for gastric carcinoma (CCOG0703). Gastric Cancer 2010;13:197–203.

17 Takahari D, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, Kinoshita T, Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T, Sasako M: Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. Cancer Chemother Pharmacol 2010, Epub ahead of print.

18 Mori K, Kamiyama Y, Kondo T, Kano Y, Kodama T: A phase II study of docetaxel and infusional cisplatin in advanced non-small cell lung cancer. Chemotherapy 2005;51:120–125.

19 Bruno R, Sanderink GJ: Pharmacokinetics and metabolism of taxotere (docetaxel). Cancer Surv 1993;17:305–313.

20 Clarke SJ, Rivory LP: Clinical pharmacokinetics of docetaxel. Clin Pharmacokinet 1999;36:99–114.

21 Fujii M: Chemotherapy for advanced gastric cancer: chemotherapy for advanced gastric cancer: ongoing phase III study of S-1 alone versus S-1 and docetaxel combination (JACCRO GC03 study). Int J Clin Oncol 2008;13:201–205.

J Gastrointest Surg (2012) 16:2190–2196
DOI 10.1007/s11605-012-2059-3

ORIGINAL ARTICLE

Phase II Study of Single Intraperitoneal Chemotherapy Followed by Systemic Chemotherapy for Gastric Cancer with Peritoneal Metastasis

Motohiro Imano · Atsushi Yasuda · Tatsuki Itoh · Takao Satou · Ying-Feng Peng · Hiroaki Kato · Masayuki Shinkai · Masahiro Tsubaki · Yasutaka Chiba · Takushi Yasuda · Haruhiko Imamoto · Shozo Nishida · Yoshifumi Takeyama · Kiyokata Okuno · Hiroshi Furukawa · Hitoshi Shiozaki

Received: 3 August 2012 / Accepted: 12 October 2012 / Published online: 26 October 2012

Abstract
Background We conducted a phase II study involving a single administration of intraperitoneal chemotherapy with paclitaxel followed by sequential systemic chemotherapy with S-1+ paclitaxel for advanced gastric cancer patients with peritoneal metastasis.
Methods Gastric cancer patients with peritoneal metastasis were enrolled. Paclitaxel (80 mg/m^2) was administered intraperitoneally at staging laparoscopy. Within 7 days, patients received systemic chemotherapy with S-1 (80 mg/m^2/day on days 1–14) plus paclitaxel (50 mg/m^2 on days 1 and 8), followed by 7-days rest. The responders to this chemotherapy underwent second-look laparoscopy, and gastrectomy with D2 lymph node dissection was performed in patients when the disappearance of peritoneal metastasis had been confirmed. The primary endpoint of the study was overall survival rate.
Results Thirty-five patients were enrolled. All patients were confirmed as having localized peritoneal metastasis by staging laparoscopy. Eventually, gastrectomy was performed in 22 patients. The median survival time of the total patient population and those patients in which gastrectomy was performed was 21.3 and 29.8 months, respectively. The overall response rate was 65.7 % for all patients. The frequent grade 3/4 toxic effects included neutropenia and leukopenia.
Conclusions Sequential intraperitoneal and intravenous paclitaxel plus S-1 was well tolerated in gastric cancer patients with peritoneal metastasis.

M. Imano (✉) · A. Yasuda · Y.-F. Peng · H. Kato · M. Shinkai · T. Yasuda · H. Imamoto · Y. Takeyama · K. Okuno · H. Furukawa · H. Shiozaki
Surgery, Kinki University Faculty of Medicine,
377-2 Ohno-higashi,
Osaka-Sayama, Osaka 589-8511, Japan
e-mail: imano@med.kindai.ac.jp

M. Imano · Y. Takeyama
Cancer Center, Kinki University Hospital,
377-2 Ohno-higashi,
Osaka-Sayama, Osaka 589-8511, Japan

T. Itoh · T. Satou
Pathology, Kinki University Faculty of Medicine,
377-2 Ohno-higashi,
Osaka-Sayama, Osaka 589-8511, Japan

M. Tsubaki · S. Nishida
Division of Pharmacotherapy,
Kinki University Faculty of Pharmacy,
3-4-1 Kowakae,
Higashi-Osaka, Osaka 577-5802, Japan

Y. Chiba
Division of Biostatistics, Clinical Research Center,
Kinki University Faculty of Medicine,
377-2 Ohno-higashi,
Osaka-Sayama, Osaka 589-8511, Japan

Keywords Gastric cancer · Peritoneal metastasis · Intraperitoneal chemotherapy · Gastrectomy

Introduction

Gastric cancer (GC) is a life-threatening disease worldwide. Recent advances in the treatment of GC have improved clinical outcomes.[1] However, GC patients with peritoneal metastasis (PM) still have a poor overall prognosis.[2] Recently, numerous modalities have been tried in the treatment of PM, such as aggressive surgery, intraperitoneal chemotherapy (IPC), and hyperthermia. However, none of these modalities have shown a satisfactory clinical outcome.[3–5] Consequently, there is no standard treatment for patients with PM.

S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) and paclitaxel (PTX) have a high rate of transition into the peritoneal cavity and a high efficacy against the diffuse type of adenocarcinoma which can easily disseminate.[6,7] Therefore, S-1 and PTX are suitable for PM systemic chemotherapy. In addition, in advanced and/or recurrent gastric cancer patients, several previous trials involving combination chemotherapy with S-1 and intravenous paclitaxel have reported on the safety and efficacy for measurable lesions.[8,9]

PTX has another advantage in the treatment of PM; when administered intraperitoneally it exhibits delayed clearance from the peritoneal cavity because of its high molecular weight and bulky structure. In our recent study we demonstrated the possible effectiveness of PTX for IPC.[10] The advantage of IPC exposure is best expressed as the achievement of a maximal concentration and area under the curve (AUC) ratios of the drug, between the peritoneal cavity and the peripheral blood.[10] Our study showed that the average maximal concentration and AUC ratios for paclitaxel were 1,065:1.[10] However, the clinical effects of intraperitoneal chemotherapy using PTX are unclear.

Therefore, we have developed a new regimen that involves the addition of a single intraperitoneal (IP) administration of PTX to the established systemic chemotherapy regimen of S-1 and PTX for the treatment of PM from GC. In our preliminary study, we confirmed the safety of the regimen.[10] In the present study, we carried out a phase II clinical trial to evaluate the efficacy, response, and safety of this novel multimodal treatment for GC.

Patients and Methods

This study was a prospective phase II study carried out between January 2005 and October 2008. During this period, we performed staging laparoscopy for patients in whom the presence of PM was suspected, for example, a nodular and irregular outer border of the thickened gastric wall, nodules on the peritoneal surface, or a small amount of ascites detected by multi-detector row CT (MDCT). Additionally, with the exception of possible PM, there was a lack of non-curative factors such as distant metastasis to the liver, lung, or lymph nodes. In these patients, the following eligibility criteria that were required for enrolment in this study included: (1) the presence of GC confirmed by histopathology; (2) the presence of PM confirmed by staging laparoscopy; (3) a performance status (Eastern Cooperative Oncology Group [ECOG]) <2; (4) age younger than 75 years; (5) no prior chemotherapy or surgery for gastric or other cancers; (6) adequate bone marrow function (leukocyte count >3,000 ml^{-1} and platelet count >100,000 ml^{-1}), (7) adequate liver function (serum bilirubin level <1.5 $mg dl^{-1}$ and serum transaminase levels less than twice the upper limit of the normal level); (8) adequate renal function, serum creatinine level <1.5 $mg dl^{-1}$; (9) no other severe medical conditions, such as symptomatic infectious disease, intestinal pneumonia, active hemorrhage/bleeding, or obstructive bowel disease; and (10) no current pregnancy or lactation. In accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration of 1964, as revised in 1975 and 1983, written informed consent was obtained from the patients before the initiation of treatment and especially before surgery. Patients predicted to be eligible were informed about the therapeutic strategy, emphasizing its potential benefits as well as the possible risk of mortality and morbidity, prior to treatment and especially surgery. Informed consent was given by all patients.

Intraperitoneal Chemotherapy After Staging Laparoscopy

After PM was confirmed at staging laparoscopy, PTX was administered at a dose of 80 mg/m^2.[10] In each patient, PTX dissolved in isotonic saline to a final volume of 1 L was instilled into the peritoneal cavity at the end of the staging laparoscopy. Drainage of the drug solution was not carried out.[10]

Post IPC Systemic Chemotherapy

One week after IPC, S-1 was administered orally twice daily at a dose of 80 mg/m^2/day for 14 consecutive days, followed by 7-days rest. PTX was administered i.v. at a dose of 80 mg/m^2 on days 1 and 8 as previously reported.[8] The treatment course was repeated every 3 weeks until the observation of unacceptable toxicity, disease progression, or responses which might enable a macroscopically curative operation.

Evaluation of Toxicity, Tumor Response, and Indication of Gastrectomy with En Bloc D2 Lymph Node Dissection

Toxicity was measured using the common toxicity criteria of the National Cancer Institute, Version 2.0. In the patients

who had a target lesion, we evaluated the antitumor effects after two and five courses of the treatment and classified them based on the RECIST guidelines. Regarding the patients who had no target lesions, we evaluated the antitumor effects based on the wall thickness of the primary tumor by means of MDCT using the air filling technique. The area in the stomach where the wall thickness was measured corresponded to the area with a biopsy proven tumor mass. A patient was considered a responder in the case of tumor response or a 30 % improvement in wall thickness in one transverse, coronal, and sagittal image and was evaluated using second-look laparoscopy. In cases where there were negative PM findings at second-look laparoscopy, we performed gastrectomy with en bloc D2 lymph node dissection.

Gastrectomy with En Bloc D2 Lymph Node Dissection

The surgical procedure was either total gastrectomy for proximal tumors or subtotal gastrectomy when the primary tumor was located distally in the stomach, with a 5 cm "safe" margin. In all cases, an en bloc D2 lymph node dissection was performed according to the Japanese Gastric Cancer Association guidelines.[11]

Postoperative Chemotherapy

At more than 1 week after the operation, we performed postoperative chemotherapy. Initially one or two courses of weekly PTX,[12] followed by S-1 (80 mg/m^2/day, on days 1–14, every 3 weeks) was administered for more than 1 year or until recurrence was confirmed. Treatment after recurrence was at the physician's discretion.

Statistical Analysis

The JCOG 9205 study reported that the median survival time was 7.1 months (95 % confidence interval (CI), 5.8–8.2 months) in the 5-FU alone arm in patients with advanced and/or recurrent GC.[13] In our study, the median survival time is expected to be shorter than that in the JCOG9205 study owing to the fact that we evaluated patients who had PM. However, the median survival time of the patients whose treatment included an operation is expected to be longer than was the case in the JCOG9205 study. Based on these findings, on the premise that the threshold median survival time is 5 months and the expected median survival time is 9 months, the necessary number of subjects was calculated to be 32 with alpha=0.1 (one-tailed) and beta=0.2. The planned sample size was set at 35, with the consideration of approximately 10 % of patients being ineligible. The accrual time was 3 years and the follow-up time was 2 years after closure of recruitment. The primary endpoint of this study was overall survival. Secondary endpoints were response rate (RR) and safety.

Survival analyses were performed using the Kaplan–Meier method. The survival period was calculated from the first staging laparoscopy date to death or the day of most recent follow-up. Statistical analysis was conducted using the statistical software GraphPad Prism 5 (GraphPad Software Inc, La Jolla, CA, USA).

The clinicopathologic classifications were determined according to the criteria of the TNM Classification of Malignant Tumours, seventh edition. Toxicity and operative complications were measured using the common toxicity criteria of the National Cancer Institute, version 2.0.

Results

During the accrual time, we performed staging laparoscopy in 43 patients. Of these patients, only 35 with PM were enrolled in the current study and fully evaluated. The PM lesions were located mainly on the diaphragm, falciform ligament, and peritoneum. The remaining eight patients could not be enrolled in this study, because they did not have PM. Patient characteristics are listed in Table 1. All patients showed PM at first staging laparoscopy and underwent at least five cycles of systemic chemotherapy. Second-look laparoscopy was performed in 23 patients who were judged as responders according to our criteria. Gastrectomy with lymph node dissection was performed in 22 out of the 23 patients (96.6 %). In the remaining patient who still had PM at the second-look laparoscopy, gastrectomy was not performed. The flow diagram of the treatment protocol is shown in Fig. 1.

Table 1 Patient characteristics and tumor response (n=35)

	Number of patients	
Median age, years (range)	64 (32–75)	
Male/female	23/12	
ECOG performance status 0/1	35/0	
Histological type		
Intestinal	10	
Diffuse	25	
Tumor response		
RECIST guidelines (n=13)		
Complete response	1	8 %
Partial response	7	54 %
Stable disease	3	23 %
Progressive disease	2	15 %
Wall thickness (n=22)		
Over 30 % decrease	15	68 %
Increase	7	32 %

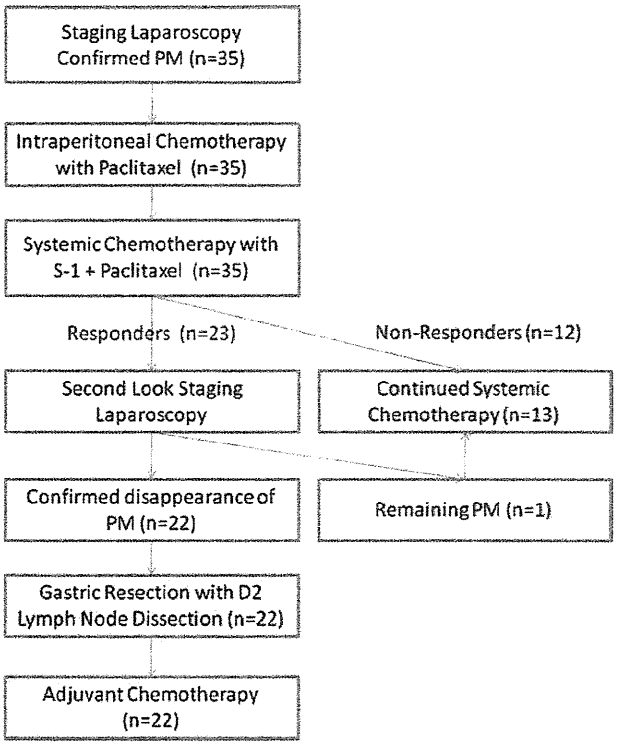


Fig. 1 Flow diagram of the treatment protocol. *PM* patients with peritoneal metastasis

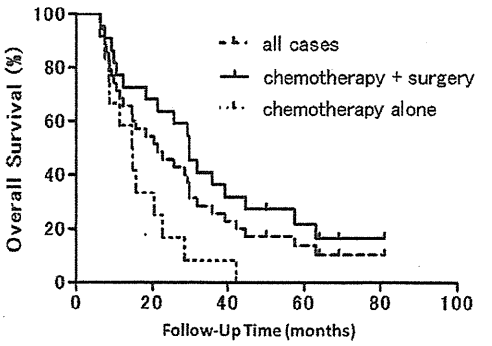


Fig. 2 Kaplan–Meier survival curve for the 35 eligible patients and the patients grouped according to whether or not surgery was carried out. (1) The 35 eligible patients: median survival was 21.3 months with a 1- and 2-year survival rate of 68.6 and 45.7 %, respectively. (2) Chemotherapy+surgery group: median survival was 29.7 months with 1- and 2-year survival rates of 77.3 and 63.6 %, respectively. (3) Chemotherapy alone group: median survival was 14.7 months with a 2-year survival rate of 15.4 %

Survival

At the time of analysis, 31 patients had died and the median follow-up time for the remaining four patients was 69.1 months. The median survival time (MST) of all patients was 21.3 months (95 % CI, 11.4 to 29.8 months), and the 1-year, 2-year, and 5-year overall survival (OS) rates were 68.6 % (95 % CI, 53.2 to 84.0 %), 45.7 % (95 % CI, 29.2 to 62.2 %) and 13.7 % (95 % CI, 2.1 to 25.4 %), respectively. In the patient that underwent gastrectomy, the 1-, 2-, and 5-year OS rates were 77.3 % (95 % CI, 59.8 to 94.8 %), 63.6 % (95 % CI, 43.5 to 83.7 %), and 21.8 % (95 % CI, 4.1 to 39.5 %), respectively, and MST was 29.7 months (95 % CI, 12.3 to 44.6 months). In the patient that received chemotherapy only, the 1- and 2-year OS rates were 53.8 % (95 % CI, 26.7 to 80.9 %) and 15.4 % (95 % CI, 0.0 to 35.0 %), respectively, and the MST was 14.7 months (95 % CI, 7.8 to 20.4 months). There was no patient survival beyond 5 years. The Kaplan–Meier survival curve is shown in Fig. 2.

Response

Thirteen patients had measurable target lesions and the remainder did not. Classification of the patients who had target lesions and were assessed for RR was based on the RECIST guidelines. The RR was 61.5 % (8/13), with one patient showing a complete response, and seven patients showing a partial response. While, out of the 22 patients without a measurable target lesion, a 30 % decrease in wall thickness was seen in 15/22 (68.2 %) (Table 1). Therefore, according of our evaluation of antitumor effects, 23/35 (65.7 %) patients were diagnosed as "responders".

Toxic Reactions

Hematological and non-hematological toxic reactions are listed in Table 2. No patient experienced abdominal pain or any other toxicity related to IPC. During IPC, a grade 3 toxicity reaction was noted in three patients (8.6 %). There were no grade 4 toxicity reactions. However, during systemic chemotherapy the grade 4 toxic reaction of neutropenia was observed in two patients. Frequent grade 3/4 toxic effects included leukopenia (5.7 %), neutropenia (20 %), alanine aminotransferase (ALT) elevation (2.9 %), and bilirubin (2.9 %). There were no treatment-related deaths.

Outcome of Second-Look Laparoscopy

The 23 patients that we diagnosed as responders underwent second-look laparoscopy. Unfortunately, only one patient who was judged as a responder due to a change in wall thickness remained with PM. Therefore, radical resection of all gross and microscopic disease (R0) after induction chemotherapy was accomplished in 22 patients.

Surgical Outcome

Gastrectomy was performed in 22 patients, including total gastrectomy in 19 and distal gastrectomy in three. In almost

Table 2 Adverse events associated with intraperitoneal and systemic chemotherapy

Number of patients (%)										
	Intraperitoneal chemotherapy					Systemic chemotherapy				
Grade (CTCAE v2.0)	1	2	3	4	3/4	1	2	3	4	3/4
Hematological toxicities										
Anemia	7 (20)	5 (14.2)	2 (5.7)	0 (0)	2 (5.7)	20 (57.1)	9 (25.7)	0 (0)	0 (0)	0 (0)
Leucopenia	4 (11.4)	3 (8.6)	1 (2.9)	0 (0)	1 (2.9)	7 (20)	10 (29)	2 (5.7)	0 (0)	2 (5.7)
Neutropenia	4 (11.4)	2 (5.7)	1 (2.9)	0 (0)	1 (2.9)	2 (5.7)	7 (20)	5 (14.2)	2 (5.7)	7 (20)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AST elevation	2 (5.7)	1 (2.9)	0 (0)	0 (0)	0 (0)	6 (17.1)	0 (0)	0 (0)	0 (0)	0 (0)
ALT elevation	4 (11.4)	0 (0)	1 (2.9)	0 (0)	1 (2.9)	6 (17.1)	1 (2.9)	1 (2.9)	0 (0)	1 (2.9)
Bilirubin	1 (2.9)	3 (8.6)	0 (0)	0 (0)	0 (0)	6 (17.1)	3 (8.6)	1 (2.9)	0 (0)	1 (2.9)
Creatinine	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0)
Non-hematological toxicities										
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (17)	2 (6)	0 (0)	0 (0)	0 (0)
Anorexia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	13 (37)	2 (6)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (17)	2 (6)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (11)	1 (2.9)	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	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (20)	0 (0)	0 (0)	0 (0)	0 (0)

all patients, we found a decrease in the size of the main tumor at the time of gastrectomy. The operative complication rate was 9 %, including one case of anastomotic leakage and pancreatic fistula. The details of the 22 patients and the postoperative final tumor stage are listed in Table 3.

Postoperative Chemotherapy

Postoperative chemotherapy was initiated in all 22 patients that underwent gastrectomy, and was completed in all patients. The adverse events of the postoperative chemotherapy were relatively mild, and throughout the treatment period, there were no grade 4 toxic effects.

Discussion

In the current study, our new combination regimen showed a 1-year OS rate of 68.6 % with a MST of 21.3 months. Recent studies targeting unresectable or recurrent GC patients have shown a 1-year OS rate of about 50 %. Our survival results are encouraging in that patents with PM are generally considered to show a particularly poor prognosis.

PM is currently treated with systemic chemotherapy as a palliative, not curative therapy.[14] In brief, there are no GC patients with PM that who survived for over 5 years that had only received chemotherapy.[15] Otherwise, R0 resection is indispensable for curing the gastric cancer. Therefore, we must carefully consider the advantages and disadvantages associated with surgery for GC patients with PM. We might perform gastrectomy on patients who exhibit a response to chemotherapy. In our study, the patients with gastrectomy showed a 1-year OS rate of 77.2 % with a MST of 29.7 months. Additionally, three patients who survived beyond 5 years had undergone gastrectomy. To care for the GC patients, R0 resection was required. Therefore, the GC patients in which PM disappeared after chemotherapy might undergo gastrectomy. Consequently, the survival rates of patients who underwent gastrectomy after chemotherapy were better than those of patients who received chemotherapy alone. This finding indicated that our treatment strategy was appropriate for these patients.

Generally, the effects of chemotherapy are determined by tumor response. However, the evaluation of tumor response in GC patients with PM is difficult because they frequently do not have a target lesion. Therefore, we have developed a new evaluation technique for the chemotherapeutic effect using MDCT with the air filling technique. Using this technique, PM was found to have disappeared in 14 out of 15 (93.3 %) patients who were judged as being responders. Thus, our new evaluation technique was useful in these patients.

With regard to intraperitoneal chemotherapy, toxicity reactions were mild, with only grade 3 toxicity reactions being noted in three patients. Therefore, intraperitoneal chemotherapy with PTX was safe in these patients. During

Table 3 Surgery, pathological results, and postoperative complications in 22 patients

	n	%
Type of resection		
Total gastrectomy	19	86.3
Distal gastrectomy	2	9.0
Pancreaticoduodenectomy	1	4.5
R0 resection rate	22	100
D2 lymph node dissection	22	100
Tumor stage		
CR	1	4.5
M	1	4.5
SM	2	9.0
MP	1	4.5
SS	16	72.7
SE	1	4.5
Nodal stage		
N0	10	45.5
N1	2	9.0
N2	5	22.7
N3a	1	4.5
N3b	4	18.2
Postoperative complications		
Anastomotic leakage	1 (Gr. 2)	4.5
Bleeding	0	0
Intestinal occlusion	0	0
Intra-abdominal abscess	0	0
Pancreatic fistula	1 (Gr. 2)	4.5
Pneumonia	0	0
Surgical site infection	0	0
Death resulting from complication	0	0
Any postoperative complication	2	9.0

Gr. toxicity grade according to the Clavien–Dindo classification

systemic chemotherapy, neutropenia was the main toxic effect; it was more frequent and severe with S-1 plus PTX chemotherapy.[8,9] Non-hematological toxicity effects were relatively mild and were similar to those reported in previous studies.[8,9]

In the present study, the postoperative morbidity rate was 9 %. In previous studies, postoperative morbidity of the patients after chemotherapy for advanced gastric cancer has been reported to occur with a frequency of 31–44.9 %.[16–18] These results indicated that our novel multimodal treatment for GC with PM is feasible and effective.

In conclusion, novel multimodal treatment for GC with PM was well tolerated and active in GC patients with PM. This regimen should be evaluated further in a randomized phase III trial.

Acknowledgments 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 Ms. Fusako Kamada for her technical assistance.

Funding The study was not supported by any grant.

References

1. Siewert JR, Bottcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. Br J Surg 1993; 80: 1015–1018.
2. Allum WH, Powell DJ, McConkey CC, Fielding JW. Gastric cancer: a 25-year review. Br J Surg 1989; 76: 535-540.
3. Sugarbaker PH, Yonemura Y. Clinical pathway for the management of resectable gastric cancer with peritoneal seeding: best palliation with a ray of hope for cure. Oncology 2000; 58: 96-107.
4. Fujimoto S, Takahashi M, Kobayashi K, Kure M, Mutou T, Masaoka H, Ohkubo H. Relation between clinical and histologic outcome of intraperitoneal hyperthermic perfusion for patients with gastric cancer and peritoneal metastasis. Oncology 1993; 50: 338-343.
5. Ajani JA. Standard chemotherapy for gastric carcinoma: is it a myth? J Clin Oncol 2000; 18: 4001-4003.
6. Kobayashi M, Sakamoto J, Namikawa T, Okamoto K, Okabayashi T, Ichikawa K, Araki K. Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. World J Gastroenterol 2006; 12: 1412-1415.
7. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, Miyata Y, Taguchi T. Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 2001; 12: 1133-1137.
8. Narahara H, Fujitani K, Takiuchi H, Sugimoto N, Inoue K, Uedo N, Tsukuma H, Tsujinaka T, Furukawa H, Taguchi T. Phase II study of a combination of S-1 and paclitaxel in patients with unresectable or metastatic gastric cancer. Oncology 2008; 74: 37-41.
9. Mochiki E, Ohno T, Kamiyama Y, Aihara R, Haga N, Ojima H, Nakamura J, Ohsawa H, Nakabayashi T, Takeuchi K, Asao T, 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 2006; 95: 1642-1647.
10. Imano M, Peng YF, Itoh T, Nishikawa M, Satou T, Yasyda A, Inoue K, Kato H, Shinkai M, Tsubaki M, Yasuda T, Imamoto H, Nishida S, Furukawa H, Takeyama Y, Okuno K, Shiozaki H. 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. Anticancer Res 2012; 32: 4071-4076.
11. Japanese Gastric Cancer A. Japanese Classification of Gastric Carcinoma - 2nd English Edition. Gastric Cancer 1998; 1: 10-24.
12. Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006; 9: 14-18.
13. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 2003; 21: 54-59.

14. Iwasa S, Nakajima TE, Nakamura K, Takashima A, Kato K, Hamaguchi T, Yamada Y, Shimada Y. First-line fluorouracil-based chemotherapy for patients with severe peritoneal disseminated gastric cancer. Gastric Cancer 2012; 15(1):21-6
15. Bozzetti F, Yu W, Baratti D, Kusamura S, Deraco M. Locoregional treatment of peritoneal carcinomatosis from gastric cancer. J Surg Oncol 2008; 98: 273-276.
16. Okabe H, Ueda S, Obama K, Hosogi H, Sakai Y. Induction chemotherapy with S-1 plus cisplatin followed by surgery for treatment of gastric cancer with peritoneal dissemination. Ann Surg Oncol 2009; 16: 3227-3236.
17. Fujiwara Y. Neoadjuvant intraperitoneal and systemic chemotherapy for gastric cancer patients with peritoneal dissemination. Ann Surg Oncol 2011; 8(13):3726–3731
18. Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito S, Kawashima Y, Fukushima N. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. Br J Surg 2009; 96: 1015–1022.

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

[1]*Surgery and* [3]*Pathology, Kinki University Faculty of Medicine, Osaka, Japan;*
[2]*Cancer Center, Kinki University Hospital, Osaka, Japan;*
[4]*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^2. After one to two weeks, S-1 was administered at 80 mg/m^2/day for 14 consecutive days, followed by seven days' rest. Paclitaxel was administered intravenously at 50 mg/m^2 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 peri)/(AUC pla) 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). 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 μm (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).

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.

0250-7005/2012 $2.00+.40

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^3, neutrophil count ≥1500/mm^3, and platelet count ≥100,000/mm^3); ii) adequate liver function (total serum bilirubin ≤1.5 mg/dl and serum transaminase ≤two times the normal upper limit); iii) adequate renal function (serum creatinine ≤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 laparocsopy.

Treatment. For the patients with PM, paclitaxel diluted in 1 l of normal saline was administered intraperitoneally at a dose of 80 mg/m^2 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^2/day for 14 consecutive days, followed by seven days' rest. Paclitaxel was administered intravenously at a dose of 50 mg/m^2 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 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.

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.

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.*

	No. of patients (%)									
	Intraperitoneal chemotherapy					Systemic chemotherapy				
Grade (CTCAE v2.0)	1	2	3	4	3/4	1	2	3	4	3/4
Hematological toxicity										
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)
Biliburin	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)
Non-hematological toxicities										
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: Asparatate 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 (±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 μmol/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

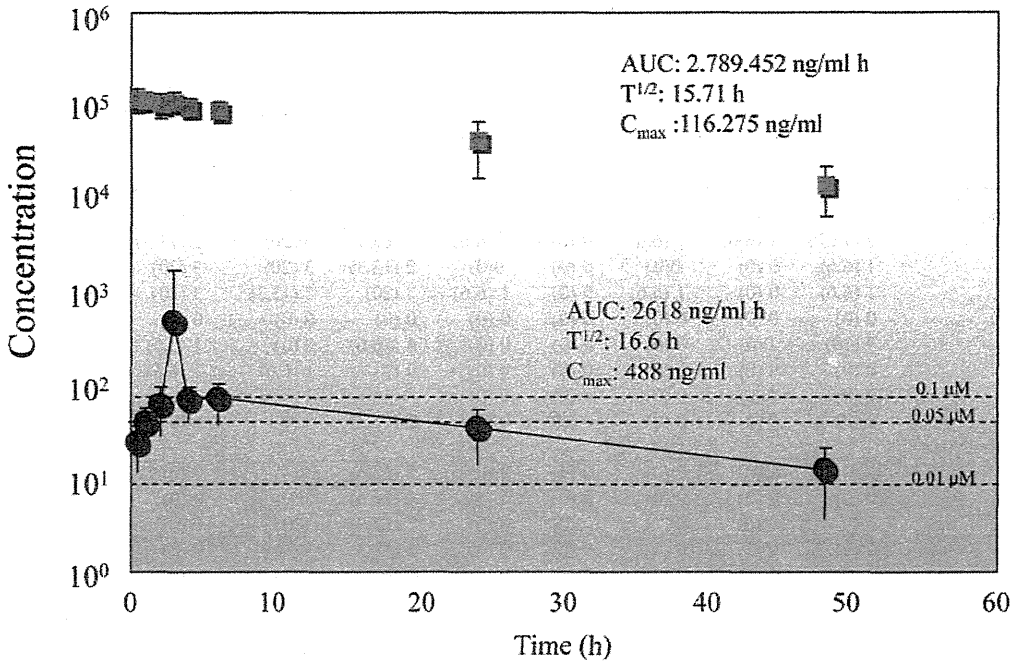


Figure 1. *Pharmacokinetic analysis of the intraperitoneal and plasma concentrations of paclitaxel. High intraperitoneal concentrations were maintained for 48 h, during which time the mean plasma peak levels reached the cytotoxic threshold. The intraperitoneal maximum drug concentration (Cmax) was, on average, 238.3-times higher than the plasma Cmax. AUC: Area under the blood concentration time curve, T1/2: half-life period, Cmax: 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.

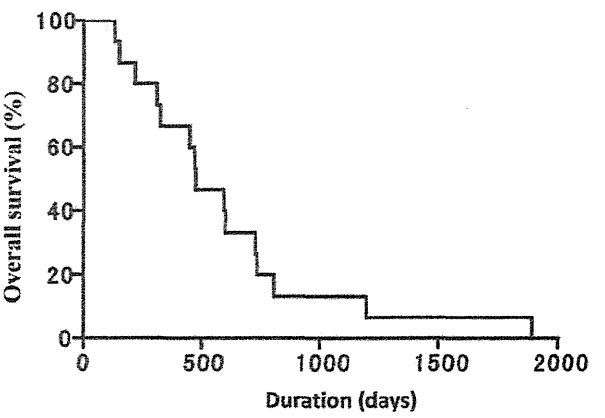


Figure 2. *Overall survival. Kaplan-Meier survival curves for 15 eligible patients.*

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.

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, Fontaumard E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, Francois Y, Vignal J and Gilly FN: Peritoneal carcinomatosis from non-gynecologic malignancies: