

# Feasibility Study of S-1 plus Weekly Docetaxel Combined with Concurrent Radiotherapy in Advanced Gastric Cancer Refractory to First-line Chemotherapy

KAZUMASA FUJITANI<sup>1</sup>, TOSHIMASA TSUJINAKA<sup>1</sup>, HIDEYA YAMASAKI<sup>2</sup>,  
MOTOHIRO HIRAO<sup>1</sup>, KEN YOSHIDA<sup>2</sup> and YUKINORI KUROKAWA<sup>1</sup>

*Departments of <sup>1</sup>Surgery and <sup>2</sup>Radiology, National Osaka Medical Center, Osaka, Japan*

**Abstract.** *Background:* As there is no standard treatment for advanced gastric cancer refractory to first-line chemotherapy, the feasibility of S-1 plus weekly docetaxel combined with concurrent radiotherapy was evaluated. *Patients and Methods:* Ten patients were enrolled in this study. Patients were given S-1 at a daily dose of 40 mg/m<sup>2</sup> and docetaxel at a weekly dose of 20 mg/m<sup>2</sup> for 5 consecutive weeks, with concurrent radiotherapy (RT) amounting to a total irradiation dose of 45 Gy or 50.4 Gy. *Results:* Hematological toxicities were grade 3 or less except for anemia. Non-hematological toxicities were all grade 2 or less, apart from one grade 3 asthenia. There was one treatment-related death, resulting from melena, in a patient with a mechanical device in the radiation field. Planned treatment was delivered with relative dose intensity for S-1, docetaxel and RT as 94%, 98% and 97%, respectively. Median survival time of 297 days was obtained, with an objective response seen in 2 patients and symptom relief achieved in all patients. *Conclusion:* S-1 plus weekly docetaxel combined with concurrent RT exhibited a tolerable toxicity profile with sufficient symptom palliation and prolonged survival in patients with advanced gastric cancer refractory to first-line chemotherapy.

Surgical resection remains the mainstay for curative treatment of advanced gastric cancer (AGC). However, even when a complete resection can be achieved, postoperative recurrence may occur. Once the disease relapses, it seems lethal. Treatment mainstream for the recurrent disease is chemotherapy. Various chemotherapy regimens have been studied in patients with AGC. Although a median survival time

(MST) of 6-11 months has been obtained (1-6), the therapeutic impact of these results on survival is considered to be modest and there has been no generally accepted standard regimen for the treatment of AGC so far. However, S-1 (an oral fluoropyrimidine) plus cisplatin has recently shown an MST of 13 months in a phase III trial and holds promise of becoming a standard first-line treatment for AGC (7). Contrary to these developments in first-line chemotherapy for AGC, standard regimen for second-line therapy still remains unclear as there have been no randomized phase III studies.

As for radiotherapy (RT), another treatment modality for AGC, several studies have shown the efficacy of RT against AGC concurrently used with chemotherapy either preoperatively (8-11) or postoperatively (12). High pathological complete response (pCR) rates of 20% to 30% and good local control obtained by chemoradiotherapy (CRT) suggest that CRT could also be a candidate for post first-line therapy in patients with AGC.

Although infusional 5-fluorouracil (5-FU) has been used most commonly with RT because of its radiosensitizing property (8-12), other agents such as cisplatin (11) and paclitaxel (9, 10) have also been used in combination with 5-FU. There has been no generally accepted standard chemotherapy regimen combined with RT against AGC.

S-1 is an active agent against AGC (13), composed of tegafur (1-(2-tetrahydrofuryl)-5-fluorouracil; FT) and two modulating agents, 5-chloro-2,4-dihydropyridine (CDHP) and potassium oxonate (Oxo), at a molar ratio of 1:0.4:1 (14). FT is converted primarily in the liver to 5-FU, a conventional radiosensitizer. CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase (DPD) which degrades 5-FU, and is also known to have a radiosensitizing property. Therefore, S-1 can be anticipated as a suitable agent for CRT against AGC because of its radiosensitizing properties as well as its cytotoxic activity. Recently, synergism of S-1 with RT has been confirmed in human cancer xenografts (15, 16).

Docetaxel, another active agent for AGC, has also been identified clinically as an effective radiosensitizer in various types of cancer with weekly dosing (17, 18). Docetaxel

*Correspondence to:* Kazumasa Fujitani, M.D., Department of Surgery, National Osaka Medical Center, 2-1-14, Hoenzaka, Chuo-ku, Osaka 540-0006, Japan. Tel: +81 669421331, Fax: +81 669436467, e-mail: fujitani@onh.go.jp

*Key Words:* Feasibility study, S-1, weekly docetaxel, concurrent radiotherapy, advanced gastric cancer.

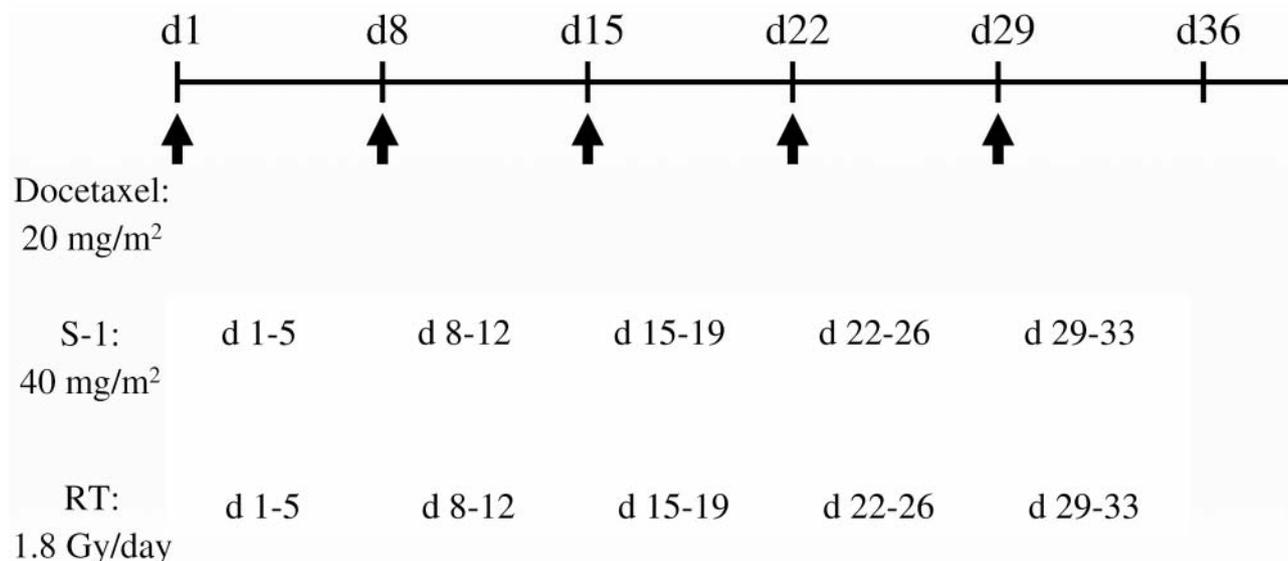


Figure 1. Treatment schedule. RT, radiotherapy.

synchronizes the cell cycle to the G<sub>2</sub>/M-phase, which is the most vulnerable period for radiation (19), and shows synergistic cytotoxicity with RT in various human cancer cell lines *in vitro* (20, 21).

Anticipating radiosensitizing effects as well as tumoricidal effects by S-1 and docetaxel, we conducted the present feasibility study of CRT employing S-1 and weekly docetaxel in patients with AGC refractory to first-line chemotherapy.

### Patients and Methods

**Eligibility criteria.** Tumor assessment was performed within 4 weeks before entry, and a complete blood cell count, liver and renal function tests were carried out within 2 weeks prior to entry. Patients enrolled in this study were required to fulfill the following criteria: (i) histologically proven unresectable or recurrent GC with measurable lesions, (ii) performance status of 1 or less on the Eastern Cooperative Oncology Group (ECOG) scale, (iii) life expectancy of at least 3 months, (iv) age of 80 years or younger, (v) at least one prior chemotherapy for the disease before entry, (vi) no prior radiation therapy, (vii) adequate bone marrow function (WBC count 3,000-12,000/mm<sup>3</sup>, platelet count ≥100,000/mm<sup>3</sup>, and hemoglobin ≥8.0 g/dl), hepatic function (total bilirubin ≤2.0 mg/dl, serum transaminases ≤3.0 x upper institutional limit), and renal function (serum creatinine ≤1.5 mg/dl), (viii) tolerance of oral feeding, (ix) no other severe medical conditions, (x) no other concurrent active malignancy, and (xi) provision of written informed consent.

**Treatment schedule.** The treatment schedule is illustrated in Figure 1. S-1 was given orally twice daily after meals at a dose of 40 mg/m<sup>2</sup>/day every Monday through Friday for 5 consecutive weeks. The dose of S-1 was assigned according to the body surface area (BSA) of the patient as follows: BSA<1.25 m<sup>2</sup>, 40 mg/day; 1.25 m<sup>2</sup>≤ BSA<1.5 m<sup>2</sup>,

50 mg/day; and BSA≥1.5 m<sup>2</sup>, 60 mg/day. Docetaxel was administered intravenously at a dose of 20 mg/m<sup>2</sup> over 60 minutes before irradiation with a standard antiemetic prophylaxis every Monday for 5 consecutive weeks. Radiotherapy was also delivered concurrently with chemotherapy every Monday through Friday for 5 consecutive weeks. A total irradiation dose of 45 Gy was delivered in 25 fractions of 1.8 Gy over 5 weeks to the former 5 patients and 50.4 Gy in 28 fractions of 1.8 Gy over 5.5 weeks to the latter 5 patients, consecutively.

Chemotherapy was continued if the biological parameters still conformed to the eligibility criteria, except for the leukocyte count (≥2,000/mm<sup>3</sup>) and the platelet count (≥75,000/mm<sup>3</sup>). When the patient developed non-hematological toxicity of grade 3 or more, chemotherapy was suspended.

**Radiation fields encompassed the tumor with a 2-cm margin.** The fields were modified as needed to shield at least two-thirds of one kidney. Linear accelerators delivered the radiation dosage using 10-MV photons and, if necessary, a three-dimensional conformal technique was used to spare the heart, lungs and spinal cord, and to minimize the radiation dose to the small bowel and liver. While undergoing RT, patients were evaluated weekly by a radiation oncologist. The RT schedule was interrupted if the patient developed grade 4 leukopenia, neutropenia, and/or thrombocytopenia.

Granulocyte colony-stimulating factor (G-CSF) was used when grade 4 leukopenia and/or neutropenia were observed. The treatment was continued unless disease progression or intolerable toxicity occurred.

**Evaluation of toxicity and efficacy.** A complete blood cell count and measurements of liver and renal function were assessed at least every week during the treatment. Non-hematological toxicities were also verified at least every week by patient interview and physical examination. Toxicity was graded according to the National Cancer Institute (NCI) common toxicity criteria version 3.0.

Within 4 weeks after the completion of CRT, patients were evaluated with abdominal computed tomography (CT) scans and assessed for locoregional control according to the RECIST criteria. A

Table I. *Patient characteristics.*

Patient no.	Gender	Age (years)	PS	Prior Gx	T, N stage	Histology	Prior chemotherapy	Target tumor	RT dose (Gy)
1	M	68	1	Total	T2N3	Intestinal	S1/CPT, TXL	Lymph node	45
2	F	74	1	Total	T4N1	Diffuse	S1/CDDP	Local	45
3	M	57	1	Distal	T3N1	Intestinal	S1/CPT	Lymph node	45
4	M	71	1	Total	T3N1	Diffuse	S1, CPT/CDDP, TXL	Lymph node	45
5	M	57	1	(-)	T3N2	Diffuse	S1/CDDP/TXL, S1/CDDP	Local	45
6	M	69	0	Distal	T2N3	Intestinal	S1/CDDP, S1/CPT	Lymph node	50.4
7	M	67	1	Total	T3N1	Diffuse	S1	Local	50.4
8	F	76	1	Distal	T3N2	Diffuse	S1	Lymph node	36*
9	M	71	0	Total	T3N3	Intestinal	S1/CDDP, CPT/CDDP, TXL, TXT	Lymph node	50.4
10	M	75	1	(-)	T3N1	Diffuse	S1/CPT, S1/CDDP	Lymph node	50.4

M, Male; F, female; PS, performance status; Gx, gastrectomy; CPT, irinotecan; TXL, paclitaxel; CDDP, cisplatin; TXT, docetaxel; RT, radiotherapy. Asterisk indicates the case of treatment-related death (TRD), in whom RT was discontinued at the dose of 36 Gy.

complete response (CR) was defined as complete disappearance of the tumor by CT scan. A partial response (PR) was defined as shrinkage in  $\geq 30\%$  of the tumor diameter. An increase in  $\geq 20\%$  of the tumor diameter, or the appearance of new lesions, was defined as progressive disease (PD). Stable disease (SD) was defined as not qualifying as a CR, PR or PD. Patients were also assessed for symptom relief.

Overall survival (OS) time since the initiation of CRT to the date of death of any cause or confirmed survival was recorded, and the Kaplan-Meier method was used to draw the survival curve. Patients who were alive at the time of our analysis were censored for survival.

## Results

**Patient characteristics.** The clinical characteristics of the patients are shown in Table I. Ten patients, 8 males and 2 females with a median age of 70.0 years (range: 57-76), entered this single-center study between October 2006 and October 2008. All the patients had a performance status of 0 or 1. Five patients had previously undergone total gastrectomy and 3 had distal gastrectomy, while two patients had no gastrectomy because of the presence of distant metastasis (M1). T stage of the primary tumor was T2 in 2 patients, T3 in 7, and T4 in 1. N stage of the primary tumor was N1 in 5 patients, N2 in 2, and N3 in 3. Histologically, 4 patients had intestinal-type adenocarcinoma and 6 patients had diffuse-type adenocarcinoma. Prior chemotherapy had been given in all patients, with 1 regimen in 4 patients, 2 regimens in 4 patients, 3 regimens in 1 patient, and 4 regimens in 1 patient. As a target tumor of RT, lymph node relapse was observed in 6 patients and local recurrence in 2 patients after prior gastrectomy, while 2 patients with M1 disease had primary tumor and lymph node, respectively.

**Toxicity.** All the patients were assessable for toxicity. Table II lists all adverse events. Hematological toxicities were grade 3 or less in all the patients but one. A 76-year-old female

Table II. *Toxicities recorded during the study.*

	NCI-CTC Grade (n)			
	1	2	3	4
Leukopenia	2	2	2	
Neutropenia	2	4	1	
Anemia	5	0	3	1*
Thrombocytopenia	2	1*		
Stomatitis	2			
Diarrhea	2	1		
Anorexia	4	1		
Nausea	5			
Vomiting	1			
Asthenia	7	1	1	
T-bil		1		
AST/ALT		1		

Asterisk indicates the case of treatment-related death (TRD).

developed grade 4 anemia accompanied by melena and grade 2 thrombocytopenia, resulting in treatment-related death (TRD) immediately after the discontinuation of the treatment despite hospitalization and blood transfusion. Non-hematological toxicities were all grade 2 or less, apart from grade 3 asthenia observed in one patient who had chemotherapy withheld for the last three days during the treatment. No patient suffered from febrile neutropenia of grade 3 or more, neuropathy of any grade or radiation dermatitis over grade 2.

S-1 administration was skipped in 4 patients: for 3 days in 2 and for 5 days in 2, due to grade 3 leukopenia in 2, grade 3 asthenia in 1, and TRD in 1, respectively. Docetaxel was delivered as scheduled in all the patients but one, who

Table III. *Clinical efficacy.*

Patient no.	Response	Presenting symptom	Symptom relief	Alive/Dead
1	PR	Pain	Disappeared	D
2	SD	Pain and dysphagia	Improved	D
3	PR	None		D
4	SD	None		D
5	SD	Dysphagia	Improved	A
6	SD	None		A
7	SD	Dysphagia	Improved	D
8	SD	Obstructive jaundice with PTCD		D (treatment-related)
9	SD	None		D
10	SD	None		D

PR, partial response; SD, stable disease; PTCD, percutaneous transhepatic cholangiodrainage.

could not receive the fifth weekly dose of docetaxel because of TRD during the treatment. Received dose intensity was 37.6 mg/m<sup>2</sup> per day for S-1 and 19.6 mg/m<sup>2</sup> per week for docetaxel, corresponding to a relative dose intensity of 94% and 98% , respectively.

RT was conducted as scheduled in 9 out of 10 patients, excluding the case of TRD in whom RT was discontinued after reaching a dose of 36 Gy. The relative dose intensity of RT was 97% .

*Clinical efficacy.* The objective response to treatment is shown in Table III. A PR was achieved in 2 patients while the remaining 8 patients showed SD, yielding a disease control rate of 100% .

Just prior to the CRT, two patients with lymph node recurrence each complained of pain or obstructive jaundice. Of the other 3 patients presenting with dysphagia because of local relapse around the esophagojejunal anastomosis in 2 and primary tumor of the gastroesophageal junction in 1, one complained of pain as well. After the completion of CRT, pain disappeared in 1 and decreased in 1, respectively. Dysphagia improved in all 3 patients, greatly facilitating oral intake.

The MST of all patients after the commencement of CRT was 297 days, as shown in Figure 2. Seven patients died of disease progression, and one patient suffered from TRD. Additional chemotherapy was given after the completion of CRT in 5 out of 10 patients.

**Discussion**

The first-line treatment for recurrent gastric cancer remains chemotherapy, despite the lack of a generally accepted standard regimen. Recent advances have yielded a prolonged MST of 13 months for AGC (7). Contrary to this development in first-line chemotherapy for AGC, the optimal modality for post first-line therapy is uncertain due to the lack

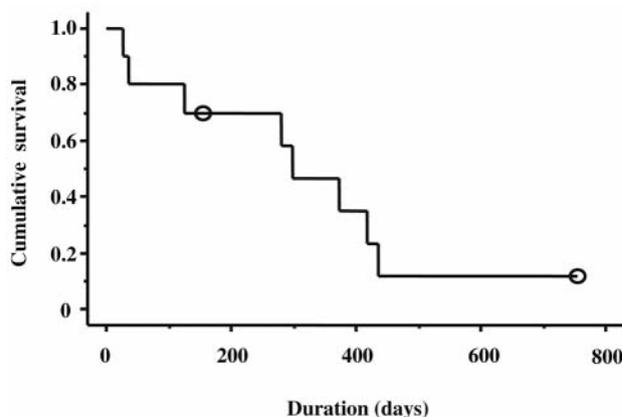


Figure 2. Overall survival. Circles indicate the censored cases.

of any randomized phase III studies. On the other hand, CRT has demonstrated superior local control against AGC when used preoperatively (8-10) and significant improvement in overall survival as adjuvant therapy (12). These findings lead us to a growing interest in CRT as a post first-line treatment in patients with recurrent gastric cancer.

Concurrent CRT commonly employs infusional 5-FU at a dose of around 300 mg/m<sup>2</sup> because of its radiosensitizing property (8-10). In this study, S-1, composed of tegafur and CDHP, was administered instead of infusional 5-FU because tegafur is converted to 5-FU and CDHP is also radiosensitizing. S-1 at a dose of 40 mg/m<sup>2</sup>/day, the amount delivered in this study, is known to be equivalent to protracted venous infusion of 5-FU at a dose of 250 mg/m<sup>2</sup>/day in terms of the area under the plasma concentration time curve (AUC) of 5-FU (22). In addition, S-1, being an oral fluoropyrimidine, can avoid the need for inconvenient and troublesome indwelling catheters and portable pump systems required for infusional 5-FU, which makes a striking

difference from conventional 5-FU-based regimens. Recently, S-1 plus low-dose cisplatin combined with RT has been reported to show a high response rate of 65% as an initial treatment for incurable or unresectable AGC (23).

Docetaxel is another potent radiosensitizer as well as being an active agent for AGC. Through its synchronization of the cell cycle to the G<sub>2</sub>/M phase (19), docetaxel shows synergistic effect with RT on cancer cells (20, 21). When used concurrently with RT, docetaxel is usually administered on a weekly basis at a dose of 10-20 mg/m<sup>2</sup>/week (17, 18). Weekly docetaxel is considered to inhibit progression of the tumor by shortening the interval between drug administration, and is known to show a better overall tolerability profile than 3-week dosing (24).

In anticipation of additive radiosensitizing effects as well as tumoricidal effects by both S-1 and docetaxel, we combined these two drugs with RT in patients with recurrent gastric cancer refractory to first-line chemotherapy.

The overall toxicity of this combination therapy was highly acceptable, as shown in Table II. Hematological toxicities were favorable except for grade 4 anemia which was related to a TRD. Non-hematological toxicities were also mild, apart from grade 3 asthenia observed in only one patient. In a recent phase II study of S-1 plus cisplatin combined with RT for AGC, the incidence of adverse reactions above grade 3 was 6.7% for anemia, 66.7% for leukopenia, 33.3% for thrombocytopenia, 6.7% for diarrhea, 23.3% for anorexia, 23.3% for nausea, and 6.7% for renal dysfunction, including 13.3% for grade 4 bone marrow toxicity (23). Likewise, a high incidence of grade 4 toxicities over 20% was reported when continuous infusion of 5-FU plus weekly paclitaxel was given concurrently with RT preoperatively (10). Although there are limitations to comparing different studies because of variations in the agents, dosage and schedule of chemotherapy, as well as the extent of prior treatment, the toxicity profile of this combination therapy seems highly acceptable compared with those reported in other studies. Such a low toxicity profile enabled the high relative dose intensity of chemotherapeutic agents and RT obtained in this combination therapy.

However, of note, one TRD was observed in this study. A 76-year-old female, who had a percutaneous transhepatic cholangiodrainage (PTCD) tube inserted in the radiation field because of obstructive jaundice due to lymph node recurrence, developed TRD accompanied by melena and grade 4 anemia. Although the origin of gastrointestinal (GI) bleeding was unknown because the patient received neither endoscopy nor angiography, RT might have been implicated as bleeding from the PTCD tube placed in the radiation field was observed. The incidence of GI complications associated with RT delivered to the right upper quadrant of abdomen has been reported to be 5.9% for gastric ulcer, 9.2% for duodenal

ulcer, 5.9% for gastroduodenitis, 1.3% for perforation, 7.2% for bleeding, and 0.7% for fatal bleeding in patients with irradiated hepatocellular carcinoma (25). In addition, when delivering CRT, careful management of the patient is needed to monitor the safety of the treatment, especially in patients with mechanical devices present in the radiation field. As for the irradiated patients with esophageal stenting for advanced esophageal cancer, high morbidity rates are reported, including formation or worsening of esophageal fistulae (28%), massive hematemesis or GI bleeding (21%), and TRD (21%), with an overall grade 3-5 nonhematological toxicity rate of 51% (26). Considering the risk of life-threatening complications during RT, palliative intubation of mechanical devices in the radiation field might have to be delayed until CRT appears to have failed.

The objective response to treatment is shown in Table III. A PR was achieved in 2 patients, while the remaining 8 patients showed SD. Although high pathological CR rates of 13-26% as well as good response to CRT were observed when it was delivered as an initial treatment for AGC (10, 23), the response rate (RR) of 20% obtained in this study might be reasonable, given that all the patients had failed to respond to first-line chemotherapy. Significant correlations have been reported between the response to first-line chemotherapy and the response to subsequent CRT in patients with head and neck cancer and non-small cell lung cancer (27, 28). Generally, in patients with AGC refractory to first-line chemotherapy, objective response to second-line treatment is considered to be around 20% (29-31). In addition, it is of interest that an objective response to CRT was achieved only in patients with intestinal-type GC. The associations of intestinal-type GC with good response to CRT and better OS by CRT have already been reported elsewhere (12, 32).

Patients were also assessed for symptom relief. Satisfactory palliation of clinical symptoms such as pain and dysphagia was achieved in all patients. The three most frequent symptoms caused by AGC are pain, bleeding (hematemesis, melena), and obstruction (dysphagia, vomiting) (32, 33). These can have a significant impact on a patient's quality of life. RT has been used to alleviate these symptoms and control rates for pain, bleeding and obstruction have been reported to be 25-86%, 54-70% and 25-81%, respectively (32, 33).

The MST of all patients recruited into this study was 297 days from the commencement of CRT, as shown in Figure 2. This result is considered acceptable because MST obtained by second-line chemotherapy has been reported to be 8-9 months in patients with AGC refractory to first-line chemotherapy (29-31). In addition, the MST of 10 months shown in this study was comparable to the period of 12-14 months previously reported in patients with unresectable GC treated with CRT as first-line treatment (34, 35).

In conclusion, S-1 plus weekly docetaxel combined with concurrent RT was demonstrated to exhibit a tolerable toxicity profile with sufficient palliation of clinical symptoms and prolonged survival in patients with unresectable or recurrent GC refractory to first-line chemotherapy. Despite the limited number of patients treated in this study, we believe that this regimen could be a candidate for additional testing in phase II trials, paying careful consideration to the added risk of life-threatening complications associated with palliative intubation of mechanical devices in the radiation field.

### Acknowledgements

We are indebted to Professor J. Patrick Barron, Tokyo Medical University, for linguistic revision.

### References

- Kim NK, Park YS, Heo DS, Suh C, Kim SY, Park KC, Kang YK, Shin DB, Kim HT, Kim HJ, Kang WK, Suh CI and Bang YJ: A phase III randomized study of 5-fluorouracil and cisplatin *versus* 5-fluorouracil, doxorubicin, and mitomycin C *versus* 5-fluorouracil alone in the treatment of advanced gastric cancer. *Cancer 71*: 3813-3818, 1993.
- Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A and Meehan M: Randomized trial comparing epirubicin, cisplatin, and fluorouracil *versus* fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol 15*: 261-267, 1997.
- Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H and 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 21*: 54-59, 2003.
- Cutsem EV, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML and Ajani JA: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol 24*: 4991-4997, 2006.
- Kang Y, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinister M, Salas MP, Suarez T and Santamaria J: Randomized phase III trial of capecitabine/cisplatin (XP) *vs.* continuous infusion of 5FU/cisplatin (FP) as first-line therapy in patients with advanced gastric cancer: efficacy and safety results. *J Clin Oncol 24(18S)*: 183s, LBA4018, 2006.
- Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J and Norman AR: Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med 358*: 36-46, 2008.
- 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.
- Ajani JA, Mansfield PF, Janjan N, Morris J, Pisters PW, Lynch PM, Feig B, Myerson R, Nivers R, Cohen DS and Gunderson LL: Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol 22*: 2774-2780, 2004.
- Ajani JA, Mansfield PF, Crane CH, Wu TT, Lunagomez S, Lynch PM, Janjan N, Feig B, Faust J, Yao JC, Nivers R, Morris J and Pisters PW: Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. *J Clin Oncol 23*: 1237-1244, 2005.
- Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, Greskovich JF, Anne PR, Bradley JD, Willett C and Rich TA: Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG9904): Quality of combined modality therapy and pathologic response. *J Clin Oncol 24*: 3953-3958, 2006.
- Allal AS, Zwahlen D, Brundler MA, de Peyer R, Morel P, Huber O and Roth AD: Neoadjuvant radiochemotherapy for locally advanced gastric cancer: long-term results of a phase I trial. *Int J Radiat Oncol Biol Phys 63*: 1286-1289, 2005.
- MacDonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM and Martenson JA: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med 345*: 725-730, 2001.
- Boku N, Yamamoto S, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Kimura A and Ohtsu A: Randomized phase III study of 5-fluorouracil (5-FU) alone *versus* combination of irinotecan and cisplatin (CP) *versus* S-1 alone in advanced gastric cancer. (JCOG 9912). *J Clin Oncol 25(18S)*: 200s, LBA 4513, 2007.
- 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.
- Harada K, Kawaguchi S, Supriatno, Kawashima Y, Yoshida H and Sato M: S-1, an oral fluoropyrimidine anticancer agent, enhanced radiosensitivity in a human oral cancer cell line *in vivo* and *in vitro*: involvement possibility of inhibition of survival signal, Akt/PKB. *Cancer Lett 226*: 161-168, 2005.
- Nakata E, Fukushima M, Takai Y, Nemoto K, Ogawa Y, Nomiya T, Nakamura Y, Milas L and Yamada S: S-1, an oral fluoropyrimidine, enhances radiation response of DLD-1/FU human colon cancer xenografts resistant to 5-FU. *Oncol Rep 16*: 465-471, 2006.
- Koukourakis MI, Kourousis C, Kamilaki M, Koukouraki S, Giatromanolaki A, Kakolyris S, Kotsakis A, Androulakis N, Bahlitzanakis N and Georgoulas V: Weekly docetaxel and concomitant boost radiotherapy for non-small cell lung cancer. A phase I/II dose escalation trial. *Eur J Cancer 34*: 838-844, 1998.
- Fujii M, Tsukuda M, Satake B, Kubota A, Kida A, Kohno N, Okami K and Inuyama Y: Phase I/II trial of weekly docetaxel and concomitant radiotherapy for squamous cell carcinoma of the head and neck. *Int J Clin Oncol 9*: 107-112, 2004.
- Chaffey JT and Hellman S: Differing responses to radiation of murine bone marrow stem cells in relation to the cell cycle. *Cancer Res 31*: 1613-1615, 1971.

- 20 Choy H, Rodriguez F, Koester SK, Hilsenbeck S and Von Hoff DD: Synergistic effects of taxol/taxotere on radiation sensitivity of human tumor cell lines. *Int J Radiat Oncol Biol Phys* 24: 274-275, 1992.
- 21 Hennequin C, Giocanti N and Favaudon V: Interaction of ionizing radiation with paclitaxel (taxol) and docetaxel (taxotere) in Hela and SQ20B cells. *Cancer Res* 56: 1842-1850, 1996.
- 22 Yamada Y, Hamaguchi T, Goto M, Muro K, Matsumura Y, Shimada Y, Shirao K and Nagayama S: Plasma concentrations of 5-fluorouracil and F- $\beta$ -alanine following oral administration of S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, as compared with protracted venous infusion of 5-fluorouracil. *Br J Cancer* 89: 816-820, 2003.
- 23 Saikawa Yoshiro, Kubota Tetsuro, Kumagai Koshi, Nakamura Rieko, Kumai Koichiro, Shigematsu Naoyuki, Kubo Atsushi, Kitajima Masaki and Kitagawa Yuko: Phase II study of chemoradiotherapy with S-1 and low-dose cisplatin for inoperable advanced gastric cancer. *Int J Radiat Oncol Biol Phys* 71: 173-179, 2008.
- 24 Hainsworth JD: Practical aspects of weekly docetaxel administration schedules. *Oncologist* 9: 538-545, 2004.
- 25 Yang MH, Lee JH, Choi MS, Park HS, Rhee PL, Kim JJ, Paik SW, Rhee JC and Lim DH: Gastrointestinal complications after radiation therapy in patients with hepatocellular carcinoma. *Hepatogastroenterology* 52: 1759-63, 2005.
- 26 Nishimura Y, Nagata K, Katano S, Hirota S, Nakamura K, Higuchi F, Soejima T and Sai H: Severe complications in advanced esophageal cancer treated with radiotherapy after intubation of esophageal stents: a questionnaire survey of the Japanese Society for Esophageal Diseases. *Int J Radiat Oncol Biol Phys* 56: 1327-1332, 2003.
- 27 Ensley JF, Jacobs JR, Weaver A, Kinzie J, Crissman J, Kish JA, Cummings G and Al-Sarraf M: Correlation between response to cisplatin-combination chemotherapy and subsequent radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. *Cancer* 54: 811-814, 1984.
- 28 Bouillet T, Morere JF, Mazon JJ, Piperno-Neuman S, Boaziz C, Haddad E and Breau JL: Induction chemotherapy followed concomitant combined radiotherapy and chemotherapy in stage III non-small cell bronchial carcinoma. *Cancer Radiother* 1: 121-131, 1997.
- 29 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. *Anti-Cancer Drug* 9: 307-10, 1998.
- 30 Koizumi W, Kurihara M, Satoh A, Takiuchi H, Tanabe S, Shimada K, Iwasaki R and Saigenji K: Phase I/II study of bi-weekly irinotecan plus cisplatin in the treatment of advanced gastric cancer. *Anticancer Res* 25: 1257-1262, 2005.
- 31 Kodaera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, Matsui T, Kojima H, Takase T, Ohashi N, Fujiwara M, Sakamoto J and Nakao A: A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 study). *Anticancer Res* 27: 2667-2672, 2007.
- 32 Kim MM, Rana V, Janjan NA, Das P, Phan AT, Delclos ME, Mansfield PF, Ajani JA, Crane CH and Krishnan S: Clinical benefit of palliative radiation therapy in advanced gastric cancer. *Acta Oncol* 26: 1-7, 2007.
- 33 Tey J, Back MF, Shakespeare TP, Mukherjee RK, Lu JJ, Lee KM, Wong LC, Leong CN and Zhu M: The role of palliative radiation therapy in symptomatic locally advanced gastric cancer. *Int J Radiat Oncol Biol Phys* 67: 385-388, 2007.
- 34 Moertel CG, Childs DS, Reitemeier RJ, Colby MY and Holbrook MA: Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* 2: 865-867, 1969.
- 35 O'Connell MJ, Gunderson LL, Moertel CG and Kvols LK: A pilot study to determine clinical tolerability of intensive combined modality therapy for locally unresectable gastric cancer. *Int J Radiat Oncol Biol Phys* 11: 1827-1831, 1985.

*Received March 31, 2009*

*Revised June 2, 2009*

*Accepted June 12, 2009*