

## A Phase I Study of Concurrent Chemoradiotherapy Using Oral S-1 for Head and Neck Cancer

YASUSHI FUJIMOTO<sup>1</sup>, SATOSHI KATO<sup>1</sup>, YOSHIYUKI ITOH<sup>2</sup>, SHINJI NAGANAWA<sup>2</sup> and TSUTOMU NAKASHIMA<sup>1</sup>

Departments of <sup>1</sup>Otorhinolaryngology and <sup>2</sup>Radiology,  
Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

**Abstract.** *Aim: S-1 is a novel oral anticancer agent containing a combination of two modulators and tegafur. We conducted a phase I study of concurrent chemoradiotherapy with S-1 for head and neck cancer. Patients and Methods: S-1 was administered once daily, and radiotherapy was performed by 2 Gy/day, five days/week, for a total of 30 fractions. S-1 dosage was started at level 1 (55.3 mg/m<sup>2</sup>/day), and was increased to level 2 (66.7 mg/m<sup>2</sup>/day). Results: A total of 12 patients were registered. Concerning hematological toxicities, no grade  $\geq 3$  or more hematological toxicity was confirmed at any level. With regard to non-hematological toxicities, at level 2, three cases of grade 3 mucositis and two cases of grade 3 dermatitis were confirmed. Conclusion: The results showed that the maximum tolerated dose was level 2 and that dose-limiting toxicity was mucositis. Having determined that the recommended dose is level 1, we have begun the phase II clinical study.*

The treatment of locally advanced squamous cell carcinoma of head and neck (SCCHN) has evolved gradually from surgery as the mainstay of treatment to concurrent chemoradiotherapy (CCRT). CCRT is now accepted as a standard treatment for patients with locally advanced SCCHN without surgical treatment (1). Meta-analyses by Pignon *et al.* showed an improved 5-year survival of approximately 8% with CCRT compared radiotherapy alone (2). While there are undisputed advantages to CCRT for locoregional control, it increases toxicity when compared with radiotherapy-alone (3). Quality of life (QOL) after

treatment is also very important. In terms of SCCHN, chemotherapy mainly consists of a platinum analog, mainly cisplatin, and continuous intravenous infusion of 5-fluorouracil (5-FU), especially in neoadjuvant chemotherapy studies. Bolus administration of cisplatin is the most well-known regimen in CCRT studies (1). However, whilst these regimens have strong positive impacts, they produce severe adverse effects at the same time. Patients of an advanced age or with co-morbidities such as renal dysfunction or cardiovascular disease, or those who refuse hospitalization, or those who do not have locally advanced tumor, cannot or need not be treated with strong chemoradiation. Therefore, a suitable anticancer drug that can be delivered to such patients during radiotherapy is required.

S-1, a novel oral anticancer agent, is a combination of tegafur (a prodrug of 5-FU), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase responsible for 5-FU catabolism) and oteracil potassium (an inhibitor of 5-FU phosphorylation in the gastrointestinal tract and a suppressor of gastrointestinal toxicities) (4). In the present clinical study, we conducted a dose-escalation study to determine the recommended dose (RD) of S-1 for concurrent chemoradiation for head and neck cancer. The purpose of this study was to identify the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT) of S-1, and the RD of this combination therapy.

### Patients and Methods

**Eligibility criteria.** We conducted a phase I study of patients with head and neck cancer (excluding thyroid cancer) who visited the Department of Otolaryngology, Nagoya University Hospital from February 2004 to June 2007.

Patients enrolled in this study were those without distal metastasis, or with recurrence only in the head and neck region who had not received radiotherapy for the planned area of irradiation, and were scheduled to receive chemotherapy for the first time. The ages of participants ranged from 20 to 75 years, and the performance status (PS) ranged from 0 to 2. In all cases, the function of the major organs (bone marrow, liver and kidney) was maintained, and survival of three months or more was expected.

This article is freely accessible online.

Correspondence to: Yasushi Fujimoto, Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. Tel: +81 527442323, Fax: +81 527442325, e-mail: yasushifujimoto1@mac.com

**Key Words:** Concurrent chemoradiotherapy, mucositis, recommended dose, S-1, head and neck cancer.

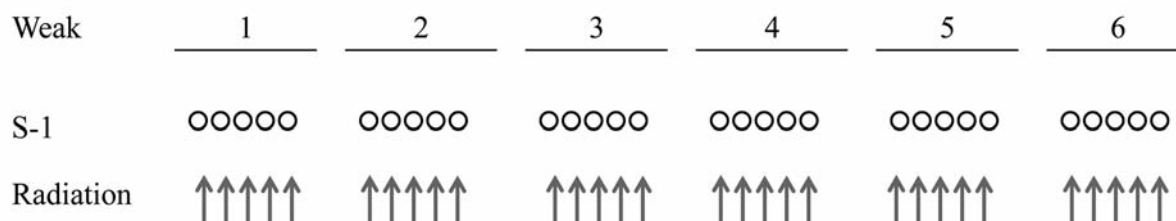


Figure 1. The treatment schedule: S-1 was concomitantly administered once daily after breakfast, and radiotherapy was performed by irradiating at 2 Gy/day, five days/week, for a total of 30 fractions (total dose, 60 Gy).

The present study was approved by the Investigational Review Board of the hospital (no.158034), and informed consent was obtained from all participants prior to enrollment.

**Drug administration methods and timing of irradiation.** S-1 was given in tablet form as formulated by Taiho Pharmaceutical Co. (Tokyo, Japan). It was concomitantly administered once daily after breakfast, and radiotherapy was performed by irradiating with 2 Gy/day, five days/week, for a total of 30 fractions (total dose, 60 Gy). Oral S-1 and radiotherapy were started on the same day, and radiotherapy was performed between 3 and 6 h after taking oral S-1. S-1 was not administered on Saturdays and Sundays, when radiotherapy was not performed (Figure 1).

**Radiation therapy.** Radiotherapy was planned for all patients after appropriate immobilization, using a thermoplastic mask and 3D-computed tomography-based techniques. Conventional radiotherapy was performed with 4 MV or 6 MV at 2 Gy/fraction/day (5). The irradiation field was changed according to lymph node status. In cases of N0 disease, the field contained the primary site and levels I to III of the neck on the ipsilateral side. The dose was delivered to 40 Gy/20 fractions. The portal was then reduced to only the primary site in order to protect the spinal cord. The total dose delivered to the primary tumor was 60 Gy/30 fractions. In cases treated with operation of nodal stage N1 to N2a and N2b disease, the field contained the primary site and levels I to V of the neck on the ipsilateral side. The dose was delivered to 40 Gy/20 fractions. The portal was then reduced to the primary site and the excised lymph node region with lymph node metastases. The dose to the spinal cord ranged from 40 to 45 Gy. The total dose delivered to the primary tumor bed and the metastatic lymph node sites was 60 Gy/30 fractions.

**Dosage and drug-escalation methods.** We planned the dose-escalation study of S-1 as follows: S-1 dosage was started at level 1 (55.3 mg/m<sup>2</sup>/day), and was increased to level 2 (66.7 mg/m<sup>2</sup>/day) and then level 3 (80 mg/m<sup>2</sup>/day). Concerning the transition of dose levels, therapy was performed on six patients at each level, and if DLT occurred in three or fewer of the six patients, the dose level was then increased by one. If at this level the number of patients with DLT was four or more, registration was stopped at that point. The MTD was the dose level at which registration was stopped, and the RD was one dose level below the MTD.

**Definition of DLT.** In the present study, DLT was defined as follows: i) grade 4 neutropenia or leucopenia; ii) grade 3 or more thrombocytopenia; 3) grade 3 or more non-hematological toxicity

as subjective or objective adverse reactions in areas outside the area of irradiation; iv) grade 3 or more mucositis or dermatitis caused by radiotherapy as subjective or objective adverse reactions within the area of irradiation, or grade 4 or more radiation-induced esophageal or pharyngeal dysphagia; v) the need to administer a total dose of S-1 <75% of the initial planned dose (equivalent to administration for 20 consecutive days) (critical toxicity); or vi) the need for a drug-free period 2 or more weeks of the 6-week therapeutic period used in the present study. MTD was the dose level at which any of these events were seen. The Japanese version of the National Cancer Institute-Common Toxicity Criteria (JCOG) was used to grade toxicities (6).

## Results

**Patients' background (Table I).** All 12 patients who were enrolled in the dose-escalation study were eligible, and their safety was assessed. Nine males and three females with a median age of 59 (range=42-71) years were treated. Histological type was squamous carcinoma except for two adenocarcinoma cases. The diagnosis of 12 patients was oropharyngeal cancer in 5 patients, laryngeal in 2, maxillary in 1, hypopharyngeal in one, submandibular gland in one, parotid gland in 1, and the primary unknown disease was in 1 patient. Eleven patients were postoperative cases and one was a new case.

**Adverse events (Table II) and RD.** At first, this combination study was performed on three patients at level 1, but none of the three developed DLT at this level. We, therefore, advanced to level 2. Since four of the six patients developed DLT at level 2, the MTD was decided at this level. A further three patients were treated at level 1.

As far as hematological toxicities were concerned, three cases of grade 1 decreased hemoglobin were seen at both levels 1 and 2, but no grade 3 or more hematological toxicity was confirmed at any level. With regard to non-hematological toxicities, at level 1, grade 2 or less mucositis, nausea/vomiting, dermatitis and anorexia were confirmed, but no grade 3 or more adverse effects were observed. One patient (case 3) who discontinued at 50 Gy refused further radiotherapy.

Table I. Clinical features of the total patient cohort.

Case no.	Age/Gender (years)	PS	Tumor site	TNM stage		S-1 (mg/m <sup>2</sup> /day)	Radiation (Gy)
				Clinical	Pathological		
Level 1							
1	67/F	0	Submandibular gland	T2N0M0	T4aN1M0	55.3	60
2	42/M	0	Oropharynx	TxN2bM0	T1N2bM0	55.3	60
3	59/F	1	Oropharynx	T3N1M0	T2N1M0	55.3	50
4	53/M	0	Larynx	T4aN2bM0	T4aN2bM0	55.3	60
5	59/M	0	Oropharynx	T3N0M0	T3N0M0	55.3	60
6	71/M	1	Oropharynx	T2N0M0	-	55.3	60
Level 2							
7	61/M	0	Hypopharynx	T4aN3M0	T4aN3M0	66.7	60
8	58/M	0	Parotid gland	T4aN2bM0	T4aN2bM0	66.7	60
9	64/M	1	Larynx	T4aN2bM0	T4aN2bM0	66.7	50
10	66/M	0	Primary unknown	TxN2bM0	TxN2bM0	66.7	56
11	56/M	0	Oropharynx	T3N3M0	T3N3M0	66.7	28
12	56/F	0	Maxillary sinus	T4bN1M0	T4bN1M0	66.7	50

PS: Performance status.

Since the adverse event was slight, it was judged that there was no adverse event exceeding grade 3 with these three patients, and they were shifted to level 2. At level 2, three cases of grade 3 mucositis and two cases of grade 3 dermatitis were confirmed. At level 2, DLTs were confirmed in four out of the six patients. Grade 3 mucositis occurred on the 8th, 15th, and 28th days, respectively, and S-1 was mostly discontinued at these times. The patient (case 11) who stopped at 28 Gy did so because of an infection from fistulation of a wounded area.

We returned to level 1 again and added three cases. The third case (case 6) added developed acute abdominal pain at 26 Gy. He underwent an emergency operation and was diagnosed as non-occlusive mesenteric ischemia. Since his general condition improved after the operation, he was treated with radiotherapy alone. He is alive and the tumor has been controlled.

As the above results indicate, the MTD was taken as level 2 and the RD was level 1 (55.3 mg/m<sup>2</sup>/day).

## Discussion

The greater the number of combined techniques, the higher the possibility for better therapy. However, with more techniques comes greater incidence of therapy-induced injuries that hinder treatment and reduce patient QOL. To safely perform chemoradiotherapy with S-1, which should achieve even better results, the present study was conducted to identify the optimal dose of S-1.

The anti-tumor effect of S-1 has been demonstrated in various kinds of solid tumors: advanced gastric cancer, colorectal cancer, and head and neck cancer in several studies

Table II. Adverse events according to dose level of S-1.

Adverse events	NCI-CTC grade				
	1	2	3	4	≥3 (%)
Level 1 N=6					
Anemia	3	0	0	0	0
Leucopenia	3	0	0	0	0
Mucositis	2	3	0	0	0
Nausea/vomitting	1	1	0	0	0
Dermatitis	5	0	0	0	0
Anorexia	1	2	0	0	0
Level 2 N=6					
Anemia	3	0	0	0	0
Leucopenia	2	0	0	0	0
Mucositis	1	0	3	0	50
Nausea/vomitting	1	1	0	0	0
Dermatitis	4	0	2	0	33.3
Anorexia	0	3	0	0	0

(7-10). Moreover, CCRT with S-1 produces enhanced therapeutic efficacy because tegafur is a preform of 5-FU (4). S-1 is routinely administered according to a 4-week administration, followed by 2-week rest regimen for gastric cancer, *etc.* However, the appropriate schedule for S-1 administration in combination with radiation has not yet been determined. Some investigators administered S-1 in a 2-week application followed by a 1-week rest regimen (9), others administered it twice daily on the days of irradiation (Monday to Friday) (10). In the present study, S-1 was administered

Table III. Clinical studies of chemoradiation with S-1 for head and neck cancer.

Authors (reference)		Radiation	S-1 (/day)	MTD	RD	DLT	Adverse events (≥Grade 3)	Total dose of S-1 mg/m <sup>2</sup> (mg/body, 1.5 m <sup>2</sup> )
Tsuji <i>et al.</i> (15) 2006	Phase I	60 Gy/30 fr	60 mg 80 mg 100 mg	100 mg/body	80 mg/body	Dermatitis	Dermatitis (66.7%)	1493 (2240)
Nonoshita <i>et al.</i> (13) 2010	Phase II	70 Gy/35 fr	65 mg/m <sup>2</sup>	–	–	–	Mucositis (56%)	1820 (2730)
Nakayama <i>et al.</i> (17) 2010	Phase I/II	60 Gy/30 fr	80 mg/m <sup>2</sup> Split 1 week Split 2 weeks	–	80 mg/m <sup>2</sup> Split 1 week	–	Mucositis (23%)	2800 (4200)
Ohnishi <i>et al.</i> (14) 2011	Phase II	60-71 Gy	65 mg/m <sup>2</sup>	–	–	–	Mucositis (31.5%)	1820 (2730)
Nakata <i>et al.</i> (16) 2013	Phase I	64-70 Gy/ 32-35 fr	40 mg/m <sup>2</sup> 60 mg/m <sup>2</sup> 80 mg/m <sup>2</sup>	80 mg/m <sup>2</sup>	60 mg/m <sup>2</sup>	Anorexia Rhabdomyolysis	Mucositis (33.3%)	2100 (3150)
Present study	Phase I	60 Gy/30 fr	55.3 mg/m <sup>2</sup> 66.7 mg/m <sup>2</sup>	66.7 mg/m <sup>2</sup>	55.3 mg/m <sup>2</sup>	Mucositis	Mucositis (50%)	1659 (2488)

MTD: Maximum tolerated dose; RD: recommended dose; DLT: dose-limiting toxicity.

once daily on the day of irradiation. The optimal schedule for CCRT with S-1 is under investigation. The radiosensitizing effects of 5-FU are influenced by the concentration and duration of 5-FU during radiotherapy (11), and marked effects can reportedly be obtained with ≥200 ng/ml of 5-FU (12). In the phase I clinical study of S-1, blood 5-FU concentrations were compared between once- and twice-daily regimens. Based on blood 5-FU concentration patterns during administration (13), we deduced that radiotherapy should be performed when the blood 5-FU concentration is high with the once-daily regimen. The present clinical study protocol thus employed the once-daily regimen and S-1 was administered orally once daily for six consecutive weeks on the day of irradiation (from Monday to Friday).

We showed some reports of CCRT with S-1 for head and neck cancer in Table III. Various administration methods of S-1 were carried out and the total doses administered also differed (14-18). However, adverse event was mainly mucositis in all reports. Similarly to one report (19) showing that adverse events depend on the irradiated field size if the same chemotherapeutic agents are administered, our cases which had grade 3 side-effects at level 2 in this study were those which had received whole-neck irradiation or irradiation to the whole affected side of the neck. There were several studies in which locally advanced pancreatic cancer was treated with CCRT with S-1 (20-22). The recommended dose of S-1 with concurrent radiotherapy is 80 mg/m<sup>2</sup>/day, and adverse events are mainly leukocytopenia and anorexia. Although these are the same combined therapies, not only does the optimal dose of S-1 differ, but the adverse events

also differ. The reason for this is that 55.3 mg/m<sup>2</sup>/day is not a dose that induces hematological toxicities, and the gastrointestinal toxicity-reducing effects of S-1 are more relevant for abdominal irradiation than for head and neck irradiation. It is hypothesized that gastrointestinal toxicities are suppressed by potassium oxonate in abdominal irradiation, but are not suppressed by potassium oxonate in head-and-neck field irradiation. Therefore, in CCRT using S-1 for head and neck cancer, an indication for disease is considered if the size of the irradiation field of the pharyngo-oral mucosal membrane is not large.

We have already initiated a phase II clinical study for T2N0 laryngeal cancer using the dose established in the present study, and we also plan to assess its therapeutic effects. The greatest characteristic of S-1 is that it is an oral anticancer agent, and in terms of patient QOL, such regimen relieves patients from receiving day-long venous infusions over a 6-week period (23).

In the near future, the present therapy may prove useful in many ways by providing an option for outpatient chemotherapy, and by reducing the economic burden on patients by allowing administration without hospital admission.

## Conclusion

For 12 patients with head and neck cancer, a phase I study was conducted by CCRT with S-1. The results show that the MTD was level 2 (66.7 mg/m<sup>2</sup>/day) and the DLT was mucositis. Having determined that the RD is level 1 (55.3 mg/m<sup>2</sup>/day), we have begun the phase II clinical study.

## Acknowledgements

This work was supported in part by a Health and Labour Sciences Research Grant for Clinical Cancer Research (H23- A-26) from the Ministry of Health, Labour and Welfare, Japan. No additional financial or personal support was provided.

## References

- Argiris A, Karamouzis MV, Raben D and Ferris RL: Head and neck cancer. *Lancet* 371: 1695-1709, 2008.
- Pignon JP, Bourhis J, Domenge C, Designe L, on behalf of the MACH-NC Collaborative Group: Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: Three meta-analyses of updated individual data. *Lancet* 355: 949-955, 2000.
- Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, Forastiere A and Ang KK: Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer. An RTOG analysis. *J Clin Oncol* 26: 3582-3589, 2008.
- Shirasaka T, Shimamoto Y, Ohshima 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.
- Mitsudo K, Shigetomi T, Fujimoto Y, Nishiguchi A, Yamamoto N, Furuse H, Ueda M, Itoh Y, Fuwa N and Tohna I: Organ preservation with daily concurrent chemotherapy using superselective intra-arterial infusion *via* a superficial temporal artery for T3 or T4 head and neck cancer. *Int J Radiat Oncol Biol Phys* 79: 1428-1435, 2011.
- Japan Clinical Oncology Group: Common Terminology Criteria for Adverse Events v4.0-JCOG. <http://www.jcoog.jp/doctor/tool/ctcae4.html>, 2013.
- Koizumi W, Kurihara M, Nakano S, Hasegawa K, The S-1 Cooperative Gastric Cancer Study Group: Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. *Oncology* 58: 191-197, 2000.
- Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K and Taguchi T: the S-1 cooperative Colorectal Carcinoma Study Group: Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. *Br J Cancer* 83: 141-145, 2000.
- Inuyama Y, Kida A, Tsukuda M, Kohno N and Sakata B: Late phase II study of S-1 in patients with advanced head and neck cancer. *Jpn J Cancer Chemother* 28: 1381-1390, 2001.
- Ueno H, Okusaka T, Ikeda M, Takezako Y and Morizane C: Phase II study of S-1 in patients with advanced biliary tract cancer. *Br J Cancer* 91: 1769-1774, 2004.
- Lawrence TS, Blackstock AW and McGinn C: The mechanism of action of radiosensitization of conventional chemotherapeutic agents. *Semin Rad Oncol* 13: 13-21, 2003.
- Byfield JE, Calabro-Jones P, Klisak I and Kulhanian F: Pharmacologic requirements for obtaining sensitization of human tumor cells in vitro to combined 5-fluorouracil or fluorafur and X rays. *Int J Radiat Oncol Biol Phys* 8: 1923-1933, 1982.
- Taguchi T, Inuyama Y, Kanamaru R, Hasegawa K, Akazawa S and Niitani H, S-1 Study Group: Phase I study of S-1. *Jpn J Cancer Chemother* 24: 2253-2264, 1997.
- Nonoshita T, Shioyama Y, Nakamura K, Nakashima T, Ohga S, Yoshitake T, Ohnishi K, Terashima K, Asai K and Honda H: Concurrent chemotherapy with S-1 for T2N0 glottic squamous cell carcinoma. *J Radiat Res* 51: 481-484, 2010.
- Ohnishi K, Nonoshita T, Shioyama Y, Nakamura K, Nakashima T, Ohga S, Yoshitake T, Terashima K, Komune S and Honda H: Concurrent chemotherapy with S-1 as first-line treatment for patients with oropharyngeal cancer. *J Radiat Res* 52: 47-53, 2011.
- Tsuji H, Kiba T, Nagata M, Inoue T, Yukawa H, Yamashita T, Shimode Y, Murata H, Nagata K and Tomoda K: A phase I study of concurrent chemoradiotherapy with S-1 for T2N0 glottis carcinoma. *Oncology* 71: 369-373, 2006.
- Nakata K, Sakata K, Someya M, Miura K, Hayashi J, Hori M, Kakagi M, Himi T, Kondo A and Hareyama M: Phase I study of oral S-1 and concurrent radiotherapy in patients with head and neck cancer. *J Radiat Res* 54: 679-683, 2013.
- Nakayama M, Hayakawa K, Okamoto M, Niibe Y, Ishiyama H and Kotani S: Phase I/II trial of concurrent use of S-1 and radiation therapy for T2 glottic cancer. *Jpn J Clin Oncol* 40: 921-926, 2010.
- Itoh Y and Fuwa N: Simultaneous combination of chemotherapy using protracted infusion of low-dose cisplatin and 5-fluorouracil with radiotherapy. Relationship between the size of the irradiation field and hemotoxicity. *Anticancer Res* 23: 1709-1712, 2003.
- Ikeda M, Okusaka T, Ito Y, Ueno H, Morizane C, Furuse J, Ishii H, Kawashima M, Kagami Y and Ikeda H: A phase I trial of S-1 with concurrent radiotherapy for locally advanced pancreatic cancer. *Br J Cancer* 96: 1650-1655, 2007.
- Shinchi H, Maemura K, Noma H, Mataka Y, Aikou T and Takao S: Phase-I trial of oral fluoropyrimidine anticancer agent (S-1) with concurrent radiotherapy in patients with unresectable pancreatic cancer. *Br J Cancer* 96: 1353-1357, 2007.
- Sudo K, Yamaguchi T, Ishihara T, Nakamura K, Shirai Y, Nakagawa A, Kawakami H, Uno T, Ito H and Saisho H: *Int J Radiat Oncol Biol Phys* 67: 219-224, 2007.
- Itoh Y and Fuwa N: Retrospective analysis: concurrent chemoradiotherapy using protracted continuous infusion of low-dose cisplatin and 5-fluorouracil for T2N0 glottic cancer. *Radiat Med* 24: 277-281, 2006.

Received November 4, 2013

Revised November 18, 2013

Accepted November 20, 2013