Phase I/II study of docetaxel, cisplatin and S-1 in locally advanced, recurrent and metastatic head and neck squamous cell carcinoma

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Received April 3, 2012; Accepted July 13, 2012

DOI: 10.3892/ol.2012.846

Abstract. The purpose of this study was to evaluate the maximum tolerated dose, dose-limiting toxicities and preliminary efficacy of chemotherapy with cisplatin, docetaxel and S-1 (TPS) to treat advanced head and neck squamous cell cancer. S-1 was administered orally twice daily on days 1-14 and docetaxel and cisplatin were injected intravenously on day 8, with one course lasting 4 weeks. The recommended dose obtained from a phase I study was set at docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 80 mg/m^2/day. The phase II study revealed that the overall response rate was 81%, comprising 95% in untreated patients with localized advanced cancer and no distant metastases, 50% in untreated patients with distant metastases and 33% in previously treated patients with recurrence. The overall survival rate of untreated patients with localized advanced cancer and no distant metastases was 95% at 1 year and 64.33% at 2 years. In terms of grade 3 or higher hematotoxicity, neutropenia occurred in 100%, thrombocytopenia in 4% and anemia in 4%. Febrile neutropenia occurred in 46%, with the rate rising to 57% in elderly patients ≥66 years. Grade 3 or higher non-hematotoxicity consisted of loss of appetite in 8%, diarrhea in 8%, hyponatremia in 13% and hypokalemia in 13%. This TPS therapy may be recommended for use as induction chemotherapy. For patients ≤65 years, the appropriate dose was docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 80 mg/m^2, whereas for those ≥66 years, it was docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 60 mg/m^2.

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Key words: head and neck squamous cell carcinoma, chemotherapy, cisplatin, docetaxel, S-1

Introduction

Induction chemotherapy with docetaxel/cisplatin/5-FU (TPF) has been recognized as the standard treatment for locally advanced head and neck squamous cell carcinoma (HNSCC) since TAX323 and TAX324 trials were simultaneously reported in 2007 (1,2). According to the TAX324 trial, a TPF regimen leads to excellent long-term overall survival (OS) and disease-free survival (DFS) compared with treatment with cisplatin and 5-FU (FP) (3). However, despite its favorable therapeutic effect, TPF treatment is associated with several inconvenient factors, including prolonged infusion time for 5-FU, restlessness and catheter-related problems.

In contrast to locally advanced disease, treatment for patients with recurrent and metastatic HNSCC is still a major problem. The efficacy of TPF treatment as adjuvant chemotherapy or as a therapeutic approach against recurrence and metastasis has rarely been reported due to the high frequency of adverse events with this therapy (4,5). Chemotherapy for recurrence or metastasis is important in terms of sustainability as well as effectiveness (6). Although it is recognized that chemotherapy using cetuximab with an FP regimen is a new first-line therapy for the treatment of patients with relapse, this method also requires a long-term infusion (7). In this context, oral 5-FU agents may resolve this problem and reduce the physical and emotional strain on patients (6,8,9). As a result of several phase III studies, treatment that involves changing a continuous drip of 5-FU to S-1 oral administration has been recognized as the standard treatment for gastric cancer. The Japan Clinical Oncology Group (JCOG) 9912 trial revealed that the impact on prognosis of S-1 was not inferior to that of 5-FU in the treatment of metastatic gastric cancer [hazard ratio, 0.83; 95% confidence interval (CI), 0.68-1.01] (10). The SPIRITS trial demonstrated that S-1 was useful as a single agent or in combination with cisplatin (11). Several reports from Asia showed that S-1 is more practical than 5-FU in the treatment of patients with head and neck cancer (12-16). S-1 is an activated prodrug that combines tegafur, gimeracil (5-chloro-2,4-dihydroxypyridine; CDHP) and potassium

oxonate (Oxo) at a molar ratio of 1:0.4:1. CDHP elevates serum levels of 5-FU by inhibiting dihydropyrimidine dehydrogenase. Oxo localizes in the intestinal mucosa and inhibits gastrointestinal toxicity. Thus, S-1 produces an excellent effect compared with conventional 5-FU and simultaneously reduces the side effects (17). The effects of S-1 appear to be comparable to those of 5-FU (18). We report here on a phase I study of combination chemotherapy with cisplatin, docetaxel and S-1 (TPS) in which 5-FU from the TPF regimen was replaced by S-1 to determine the recommended dose (RD) in patients with locally advanced disease or recurrence. In addition, we report the findings on the intermediate outcome of a phase II trial.

Patients and methods

Eligibility criteria. All patients had a histologically confirmed diagnosis of HNSCC with recurrent/metastatic or unresectable locally advanced disease. Patients were required to be aged 20-75 years and have an Eastern Cooperative Oncology Group performance status of 0 to 2 and a life expectancy of 12 weeks or longer. The bone marrow, liver and renal function had to be within predefined limits (white blood cell count, >4,000 mm^{-3}; absolute neutrophil count, >2,000 mm^{-3}; platelet count, >100,000 mm^{-3}; hemoglobin, >10 g/dl; normal bilirubin level; AST and ALT, <1.5 times the upper normal limit; serum creatinine level, <1.2; and creatinine clearance >80 ml/min). The exclusion criteria were previous chemotherapy with a TPF regimen, history of drug hypersensitivity, severe infection, malnutrition, brain metastasis, grade 3-4 peripheral neuropathy, higher than grade 2 edema, diabetes treated with insulin, use of a flucytosine-type drug, women who were pregnant or planning to get pregnant, and cases which the physician judged inappropriate.

Patients were required to give written informed consent. The study protocol was approved by the institutional ethics committee.

Treatment evaluation. S-1 was orally administered twice a day for 2 weeks and cisplatin and docetaxel were infused on day 8. Chemotherapy was planned every 4 weeks for a maximum of three cycles as induction therapy. Thereafter, locoregional treatment was administered. For the treatment of recurrence or metastasis, chemotherapy was planned for a maximum of six cycles. Patients received a 1-h intravenous infusion of docetacel followed by a 2-h intravenous infusion of cisplatin at 60 mg/m^2 with pre-treatment (4,000 ml) and post-treatment hydration (2,000 ml). All patients were given antiemetics ($5\text{-}HT_3$ antagonists and dexamethasone). Prophylactic use of granulocyte colony-stimulating factor (G-CSF) and antibiotics was not allowed, but G-CSF was given to patients who experienced grade 4 neutropenia and febrile neutropenia.

Phase I study

Dose escalation. The dose of cisplatin was fixed at 60 mg/m^2. The dose of docetaxel was increased from 50 mg/m^2 in level 1 to 60 mg/m^2 in levels 2, 3 and 4. The daily dose of S-1 was increased from 40 mg/m^2 in levels 1 and 2 to 60 mg/m^2 in level 3 and 80 mg/m^2 in level 4 (Table I).

Toxicity assessment. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events, version 3.0. A dose-limiting toxicity (DLT) was defined as follows: 1, febrile neutropenia lasting >5 days; 2, grade 4 thrombocytopenia; 3, grade 3 or 4 non-hematological toxic effects except nausea, vomiting and alopecia; 4, cessation of treatment due to an adverse event lasting >15 days; or 5, shortening of S-1 administration due to an adverse event for less than 9 days. A minimum of three assessable patients was treated at each dose level. If one or two of the three patients at a given dose level experienced DLT, three additional patients were accrued at the same dose level. The maximum tolerated dose (MTD) was defined as the dose at which three or more of the six patients experienced a DLT. The RD for the next trial was defined as the dose immediately below the MTD.

Table I. Dose escalation and DLTs.

Level	Docetaxel (mg/m^2)	Cisplatin (mg/m^2)	S-1 (mg/m^2)	DLTs
1	50	60	40	0/3
2	60	60	40	0/3
3	60	60	60	0/3
4	60	60	80	0/3

DLT, dose-limiting toxicity.

Phase II study. A treatment regimen with the RD determined in the phase I study was repeated every 4 weeks for at least two cycles to evaluate the safety and effectiveness of the TPS regimen. Two or three cycles were preferred as induction chemotherapy in cases with locally advanced disease, including distant metastasis which was considered to be locally limited and treatable with radiation. Six cycles were preferred for the treatment of patients with recurrence or distant metastasis. The next course was performed for patients maintaining the eligibility criteria (white blood cell count, >3,000 mm^{-3}; absolute neutrocyte count, >1,500 mm^{-3}; platelet count, >100,000 mm^{-3}; hemoglobin >8 g/dl; AST and ALT, <2.5 times the upper normal limit; bilirubin level, <1.5 mg/dl; serum creatinine level, <1.2; creatinine clearance, >80 ml/min; and non-hematological toxicity, < grade 2). If a patient developed one of the above adverse events during S-1 administration, S-1 was discontinued during the cycle. Doses of docetaxel and S-1 were reduced if any of the above occurred during the previous cycle. If adverse events corresponding to DLT occurred during the first cycle, downstaging was achieved after the next cycle. Treatment was continued until disease progression, unacceptable toxicity, the patient's refusal or the physician's decision.

Endpoints. The endpoint in the phase I study was the determination of MTD and RD by evaluating the occurrence of DLT. The endpoint in the phase II study included the safety and efficacy of the TPS regimen. The primary endpoint was the determination of the overall and complete response rate. The secondary endpoint was the evaluation of side effects and their grades. The relative dose intensity (mg/m^2/week) was calculated as the average value of the ratio of the actual dose intensity to the planned dose intensity. Since there was a possi-

Table II. Patients and disease characteristics.

Characteristics	Phase I	Phase II
Number of patients	12	27
Gender		
Male	11	23
Female	1	4
Age (years)		
Median	60	61
Range	46-73	42-69
ECOG performance status		
0	12	27
1	0	0
2	0	0
Primary site		
Oral cavity	1	3
Maxillary sinus	2	3
Frontal sinus	0	1
Nasopharynx	1	3
Oropharynx	7	11
Hypopharynx	0	5
Larynx	1	0
Primary unknown	0	1
Disease status		
No prior treatment		
M0	9	20
M1	0	4
Recurrent	3	3
Aim of treatment		
Induction chemotherapy	10	23
Recurrent/metastasis	2	4

ECOG, Eastern Cooperative Oncology Group.

bility that several cases were treated with chemotherapy in the initial treatment, the estimated and threshold response rate were supposed as 75 and 50%, respectively. Since the required case number was calculated as 23 according to this estimation, the target case number was established as 25. Cases treated at the recommended dose in phase I were included in the phase II study.

Results

Patient and disease characteristics. Between January 2008 and February 2010, 12 patients were entered into the phase I study and 27 patients, including three patients from the level 4 group in phase I, were entered into the phase II study to confirm the efficacy and toxicity at the RD (Table II). A total of 58 courses were administered in the phase II study.

Phase I study

Dose escalation and DLT. The toxicities observed during the first course are listed in Patients and methods. DLT was not observed at any level during at the first cycle (Table I). Although no levels reached MTD, the current dose of docetaxel and S-1 reached the maximum RD. At level 4, the dose of docetaxel and S-1 reached the upper limit of the acceptable amount in Japan. Dose level 4 was therefore determined to be the RD (docetaxel, 60 mg/m^2; cisplatin, 60 mg/m^2; and S-1, 80 mg/m^2).

Phase II study. The 27 patients in the phase II study included 24 with untreated advanced disease (including 20 locally advanced cases and 4 with distant metastases) and three with recurrent or residual disease following primary treatment such as surgery or chemoradiation. Patient characteristics are shown in Table II. A total of 58 courses were administered. Among the 24 patients with previously untreated advanced disease, 23 patients received two or three courses as induction chemotherapy. Among the 4 cases with distant metastasis, three cases (metastasis to the skin, axillary node and mediastinal node) were treated with induction chemotherapy prior to radiation. Six courses were scheduled for one patient with distant metastasis to the bone and three patients with recurrence or residual disease. According to the JCOG 0706 criteria (13), there were 24 unresectable cases and three resectable cases, which consisted of T3N1M0 tongue cancer, T4aN0M0 maxillary cancer and T4aN1M0 maxillary cancer. These cases were treated with induction therapy with a TPS regimen followed by intra-arterial chemotherapy and radiation, due to the patients' wish for functional preservation.

Completion rate. Twenty-one of the 23 patients treated with induction therapy were able to complete two or three courses of the TPS regimen. Twelve of the 23 patients (52%) were able to complete the courses without dose reduction. However, dose reduction was necessary in nine cases (39%), and treatment was ceased in two cases (9%) during the second cycle due to sudden death of uncertain cause in one case and aspiration pneumonia in the other case. DLT was observed in six cases (26%). In addition, the completion rate was compared between the younger group (<66 years) and older group (≥66 years). Ten of the 16 patients in the younger group (63%) were able to complete the therapy without a dose reduction, whereas three of the seven patients (43%) in the older group were able to complete without dose reduction. The rate of DLT was 25% (4 of 16) in the younger group and 29% (2 of 7) in the older group. Among the four patients with distant metastasis and recurrent or residual disease, no patient was able to complete every course. Treatment was discontinued due to progressive disease in three patients and combination therapy was changed from three drugs to docetaxel and cisplatin due to the patient's wish in one case. Chemotherapy was performed for three cycles in one patient and two cycles in three patients. DLT was observed in one of four patients (25%).

Relative dose intensity. The relative dose intensity (RDI) was calculated by patient classification, age and drug. The mean RDI of all 27 patients was 0.83. RDI was 0.91 in 24 patients who received the TPS regimen as primary treatment and 0.35 in three patients with metastasis or recurrent/residual disease. In 24 patients treated with primary therapy, the RDI of the younger patients (<66 years) and older patients (≥66 years) were 0.93 and 0.89, respectively. The RDI of docetaxel and

Table III. Toxicities during all courses in the phase II study.

	All cases, grade %, (n=24)				Non-elderly (≤65 years), grade %, (n=17)				Elderly (≥66 years) grade %, (n=7)			
Toxicities	1	2	3	4	1	2	3	4	1	2	3	4
Hematological toxicity												
Leukopenia		8	42	50		12	47	41			29	71
Neutropenia				100				100				100
Anemia	38	54	4		41	53	6		29	57		
Thrombocytopenia	54	13	4		55	6			29	29	14	
Febrile neutopenia			46				41				57	
Non-hematological toxicity												
Anorexia	29	63	8		41	53	6			86	14	
Nausea	75	8			71	6			86	14		
Diarrhea	46	25	8		47	18	12		42	42		
Stomatitis	58	17			53	18			71	14		
AST elevation	25	8			24	12			29			
ALT elevation	17	13			18	18			14			
Creatinine elevation	17				12				29			
Low Na	75		13		76		6		71		29	
High Na												
Low K	54		13		71				14		42	
High K	42				41				42			

AST, aspartate transaminase; ALT, alanine transaminase.

Table IV. Treatment outcomes.

	n	CR	PR	SD	PD	ORR (%)
No previous treatment	23	7	13	3	0	87
M0	19	6	12	1	0	95
M1	4	1	1	2	0	50
Recurrent/residual lesion	3	0	1	0	2	33
Total	26	7	14	3	2	81

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

cisplatin was 0.93. Conversely, the RDI of S-1 tended to be lower than that of other agents (0.86). In the phase II study, S-1 administration was discontinued for less than 14 days in 13 of 58 courses (22%).

Toxicity. Toxicity was evaluated in 24 previously untreated cases (Table III). The adverse events of the 3 patients with metastasis or recurrent/residual disease were three cases of grade 4 neutropenia, one grade 1 febrile neutronenia and one diarrhea. Among these cases, treatment was ceased due to progressive diseases in 2 patients and refusal in one patient within 2 courses. Since it did not seem worthwhile to compare with previously untreated cases in which 3 courses were completed, toxicity was evaluated in the 24 previously untreated cases.

Grade 4 neutropenia was observed in all cases. Eleven patients (46%) developed febrile neutropenia, which was improved using antibiotics and G-CSF within 5 days. No DLT was observed. The incidence of febrile neutropenia was 41% in the younger group (<66 years) and 57% in the older group (≥66 years). Grade 3 thrombocytopenia was observed only in the older patients. The grade 3 or higher non-hematological toxicities observed were anorexia (8%), diarrhea (8%), hyponatremia (13%) and hypokalemia (13%). Grade 2 or higher anorexia was observed in all older patients. One patient treated for oropharyngeal cancer succumbed on day 14 of the second cycle. Although the autopsy results suggested the possibility of bleeding from the primary tumor as there was accumulated blood in the trachea, bronchi and alveoli of the lung, the exact cause of death could not be determined.

Table V. Response rate according to primary site.

	P				N				M				Total		
Primary site	n	CR	PR	ORR (%)	n	CR	PR	ORR (%)	n	CR	PR	ORR (%)	CR	PR	ORR (%)
Oral cavity	2	1	1	100	1	0	1	100	0				1	1	100
Maxillary sinus	3	1	2	100	1	1	0	100	0				1	2	100
Frontal sinus	1	1	0	100	0				0				1	0	100
Nasopharynx	3	3	0	100	3	2	1	100	0				2	1	100
Oropharynx	10	7	2	90	10	3	5	80	3	1	1	67	2	6	80
Hypopharynx	4	1	2	100	4	0	2	50	1	0	0	0	0	3	75
Total	23	14	7	91	19	6	9	79	4	1	1	50	7	13	87

P, primary site; N, cervical node metastasis; M, distant metastasis; CR, complete response; PR, partial response; ORR, overall response rate.

Treatment outcomes. The effectiveness was evaluated in 26 patients. One patient died unexpectedly from unknown causes, and response evaluation was not performed in this case (Table IV). The overall response rate was 81%. The response rate was 96% in previously untreated patients, 50% in patients with distant metastasis and 33% in patients with a recurrent or residual lesion. The complete response (CR) rate was 26% in previously untreated patients. The response rates in patients with a primary lesion, metastasis to regional lymph nodes and distant metastasis were 91 (CR, 61%), 79 (CR, 31%) and 50% (CR, 0%), respectively (Table V). In particular, a high CR (70%) was obtained for the patients with a primary lesion in the oropharynx.

Survival analysis. Twenty patients treated for locally advanced disease (M0) were included in the survival analysis. The median follow-up time was 510 days (range, 40-910 days). The median follow-up period for survivors was 617 days (range, 318-910 days). The DFS and OS were assessed by Kaplan-Meier analyses. The 1-year DFS and OS were 90 and 95%, respectively. The 2-year DFS and OS were 67 and 66%, respectively. In the seven patients with distant metastasis, recurrence and residual disease, the 1 and 2-year DFS and OS were 28.6 and 28.6% and 14.3 and 28.6%, respectively.

Discussion

Head and neck cancer (excluding thyroid cancer) accounts for approximately 5% of all cancer types and 4.7% of all cancer mortality worldwide. It occurs in approximately 640,000 people annually, of whom 360,000 will succumb to the disease (19). Among these head and neck cancer patients, 60% are diagnosed with stage III or IV localized advanced cancer, and there is a need for the development of therapies that provide a more definitive treatment for these patients. Physical and psychological after-effects such as the functional preservation of swallowing and vocalization, as well as changes in facial appearance, must also be taken into account in the treatment of head and neck cancer. In recent years, concurrent chemoradiation therapy (CCRT) has been regarded as the standard treatment for inoperable localized advanced cancer (20,21). Surgery is performed on certain patients who are not cured by CCRT, but in many cases, the reality is that a policy of best supportive care must be followed. It is anticipated that induction chemotherapy incorporating TPF therapy (22) or treatment with molecular-targeted agents (7,23) may improve survival and enable functional preservation in these patients.

Since the TAX323 (1) and TAX324 (2) studies were reported simultaneously in 2007, TPF therapy has been accepted as a standard form of induction chemotherapy. In TAX324, both OS and DFS were better for TPF compared with 5-FU/cisplatin (FP) therapy, even for long-term outcomes (3). However, TPF therapy requires prolonged infusions of 5-FU, making it inconvenient for patients and giving rise to catheter-related problems such as discomfort during therapy.

Oral preparations of 5-FU resolve this problem, enabling treatment methods that place less of a physical and psychological burden on patients (6,8,9). In the field of stomach cancer, the efficacy and safety of TPF therapy (24) and TPS therapy in which S-1 is substituted for 5-FU have been reported (25-28). In the field of head and neck cancer, Tahara *et al* reported a phase I study of combination therapy with docetaxel, cisplatin and S-1 (12). They administered docetaxel 70 mg/m^2 (day 1), cisplatin 80 mg/m^2 (day 1) and S-1 60 mg/m^2 (days 1-14) in 3-week courses. According to their study, an RDI of 0.92 was obtained, making this treatment extremely promising in view of its efficacy and safety.

We performed a separate investigation of TPS therapy, using a different administration schedule. Oral administration of S-1 for 14 days continuously was the same, but docetaxel and cisplatin were administered on day 8 instead of on day 1. In conventional TPF and TPS therapy, docetaxel is the only modulator of cisplatin, and there is no modulator of docetaxel. In our treatment method, however, because cisplatin and docetaxel were administered after the blood concentration of S-1 had reached a steady state, S-1 also acted as a modulator of cisplatin in addition to docetaxel. In addition, S-1 may also have functioned as a modulator of docetaxel. Since S-1 administration was continued after that of cisplatin, cisplatin then also functioned as a modulator of S-1 (29-31). Cisplatin, the key drug for treating squamous cell cancer, was therefore

expected to exert a stronger anti-tumor effect compared with that of conventional therapy as a result of the action of the two modulators.

The results of this phase II study found a permissible level of safety and an extremely high response rate when TPS therapy was used as induction chemotherapy. We compared our results with those of previous TPS regimens (12), TPF therapy (1,2) and C-TPF therapy (23) as induction chemotherapy for patients with localized advanced cancer and no distant metastases. The response rate for our TPS regimen with cisplatin and docetaxel administered on day 8 was 91% and the CR rate was 26%, better than the response rate of 68% and CR rate of 8.5% obtained in the TAX323 study of TPF therapy and the response rate of 72% and CR rate of 17% in the TAX324 study. The response rate was also higher than that obtained in a study of a TPS regimen with cisplatin and docetaxel administered on day 1, for which the response rate was 78% and the CR rate was 13% (12). It is not possible to make a simple comparison, however, since the study of Tahara *et al* describes a phase I study, and its therapeutic results included M1 patients and those with cancers other than squamous cell cancer. In addition, it may be associated with a different proportion of oropharyngeal cancer, which is generally considered to be chemosensitive. C-TPF therapy has been reported to achieve a 100% response rate, even higher than that for our TPS regimen, but the short follow-up period after the end of CRT means that it may be necessary to compare factors such as long-term therapeutic outcomes and medical costs (23).

It has yet to be concluded beyond doubt that the addition of TPF therapy as induction chemotherapy is superior compared with CCRT alone as treatment for unresectable localized advanced cancer. However, considering that best supportive care is the only option for the majority of patients who do not achieve CR after the end of CCRT, induction chemotherapy that offers the possibility of improving the CR rate following the conclusion of all treatment may be an attractive therapeutic option (22,32). In this context, our TPS regimen may be regarded as an extremely powerful treatment method. For patients with recurrent cancer and metastases, however, only a low treatment completion rate, RDI and response rate were obtained using our TPS regimen. Accordingly, when treating recurrent cancer or distant metastases, long-term stable disease (SD) should be the objective rather than the powerful anti-tumor effect of TPS therapy, meaning that alternative, less invasive regimes that can be administered over a longer term should be preferred.

Although our TPS regimen produced a high response rate, in terms of adverse events, the incidence of severe neutropenia and febrile neutropenia rate were greater than those reported for other studies of TPF and TPS. The fact that there was a greater incidence of severe neutropenia compared with Tahara *et al*'s TPS regimen may indicate that the timing of the administration of each drug had an effect. One possible reason for the higher rate of febrile neutropenia is that antibiotics were not administered prophylactically in our study. We are considering prophylactic use of antibiotics in future treatment (Levofloxacin 500 mg/day). However, the fact that all patients recovered within 4 days with intravenous antibiotic administration and an RDI of 0.91 was obtained suggest that this was a tolerable regimen. Although there was no occurrence of grade 4 diarrhea in the present study, adequate attention and care are needed with the occurrence of colitis associated with docetaxel-based chemotherapy (33).

When the incidence of adverse events was considered by age group, it was extremely high for dose level 4 (docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 80 mg/m^2) in elderly patients aged ≥66 years. At dose level 3 (the same doses of docetaxel and cisplatin, S-1 only reduced to 60 mg/m^2), the incidence of adverse events among elderly patients decreased to approximately the same incidence as that observed among non-elderly patients at level 4. Appropriate RDs for this regimen were therefore judged to be level 4 (docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 80 mg/m^2) for patients aged ≤65 years and level 3 (docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 60 mg/m^2) for elderly patients aged ≥66 years.

Despite the fact that the intensity of cisplatin and docetaxel was lower in our TPS regimen compared with other TPF and TPS therapies, both the response rate and incidence of adverse events tended to be higher. In elderly patients, reducing the dose of S-1 by 20 mg/m^2 was observed to decrease the incidence of adverse events. We believe that S-1 may have played a more significant role in our regimen compared with that of 5-FU in other regimens, and that this was reflected in both the therapeutic effect and adverse events.

In conclusion, TPS therapy is a promising regimen for induction chemotherapy. From the interim analysis of a phase II study, the appropriate dose was judged to be docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 80 mg/m^2 for patients aged ≤65 years and docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and S-1 60 mg/m^2 for patients aged ≥66 years. This regimen merits further studies involving larger numbers of patients.

References

1. Vermorken JB, Remenar E, van Herpen C, *et al*: Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New Eng J Med 357: 1695-1704, 2007.
2. Posner MR, Hershock DM, Blajman CR, *et al*: Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357: 1705-1715, 2007.
3. Lorch JH, Posner MR, Goloubeva KJ, *et al*: Long-term results from TAX324: a phase III trial of sequential therapy comparing TPF to PF in locally advanced (LA) squamous cell cancer of the head and neck (HNC). J Clin Oncol (Suppl) 28: 15s, 2010.
4. Baghi M, Hambek M, May A, *et al*: Adjuvant docetaxel, cisplatin and 5-fluorouracil (TPF) in locally advanced squamous cell carcinoma of the head and neck. Anticancer Res 26: 559-563, 2006.
5. Baghi M, Hambek M, Wagenblast J, *et al*: A phase II trial of docetaxel, cisplatin and 5-fluorouracil in patients with recurrent squamous cell carcinoma of the head and neck (SCCHN). Anticancer Res 26: 585-590, 2006.
6. Shirasaki T, Maruya S, Namba A, *et al*: Treatment results of chemotherapy with S-1 for head and neck cancer. Gan To Kagaku Ryoho 36: 237-240, 2009 (In Japanese).
7. Vermorken JB, Mesia R, Rivera F, *et al*: Platinum-based chemotherapy plus cetuximab in head and neck cancer. New Eng J Med 359: 1116-1127, 2008.
8. Saif MW, Syrigos KN and Katirtzoglou NA: S-1: a promising new oral fluoropyrimidine derivative. Expert Opin Investig Drugs 18: 335-348, 2009.
9. Huang J, Cao Y, Wu L, *et al*: S-1-based therapy versus 5-FU-based therapy in advanced gastric cancer: a meta-analysis. Med Oncol 28: 1004-1011, 2010.
10. Boku N, Yamamoto S, Fukuda H, *et al*: Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10: 1063-1069, 2009.

11. Koizumi W, Narahara H, Hara T, *et al*: 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.
12. Tahara M, Araki K, Okano S, *et al*: Phase I trial of combination chemotherapy with docetaxel, cisplatin and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer. Ann Oncol 22: 175-180, 2010.
13. Nakamura K, Tahara M, Kiyota N, *et al*: Phase II trial of concurrent chemoradiotherapy with S-1 plus cisplatin in patients with unresectable locally advanced squamous cell carcinoma of the head and neck: Japan Clinical Oncology Group Study (JCOG0706). Jpn J Clin Oncol 39: 460-463, 2009.
14. Fujii M, Tomita K, Nishijima W, *et al*: Phase I/II study of S-1 plus cisplatin combination chemotherapy in patients with advanced/recurrent head and neck cancer. Jpn J Clin Oncol 40: 214-221, 2010.
15. Choi YJ, Chung JS, Shin HJ, *et al*: Induction chemotherapy with S-1 plus cisplatin in patients with locally advanced squamous cell carcinoma of the head and neck. J Laryngol Otol 122: 848-853, 2008.
16. Yoon DH and Kim SB: S-1 plus cisplatin: another option in the treatment of advanced head and neck cancer? Expert Rev Anticancer Ther 10: 659-662, 2010.
17. Shirasaka T: Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. Jpn J Clin Oncol 39: 2-15, 2009.
18. Inuyama Y, Kida A, Tsukuda M, *et al*; S-1 Cooperative Study Group (Head and Neck Cancer Working Group): Late phase II study of S-1 in patients with advanced head and neck cancer. Gan To Kagaku Ryoho 28: 1381-1390, 2001 (In Japanese).
19. Ferlay J, Shin HR, Bray F, *et al*: GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr.
20. Pignon JP, le Maître A, Maillard E, *et al*: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92: 4-14, 2009.
21. Adelstein DJ, Li Y, Adams GL, *et al*: An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 21: 92-98, 2003.
22. Paccagnella A, Ghi MG, Loreggian L, *et al*: Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol 21: 1515-1522, 2010.
23. Haddad RI, Tishler RB, Norris C, *et al*: Phase I study of C-TPF in patients with locally advanced squamous cell carcinoma of the head and neck. J Clin Oncol 27: 4448-4453, 2009.
24. Van Cutsem E, Moiseyenko VM, Tjulandin S, *et al*; V325 Study Group: 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.
25. Sato Y, Takayama T, Sagawa T, *et al*: Phase II study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. Cancer Chemother Pharmacol 66: 721-728, 2010.
26. Nakayama N, Koizumi W, Sasaki T, *et al*: A multicenter, phase I dose-escalating study of docetaxel, cisplatin and S-1 for advanced gastric cancer (KDOG0601). Oncology 75: 1-7, 2008.
27. Fushida S, Fujimura T, Oyama K, *et al*: Feasibility and efficacy of preoperative chemotherapy with docetaxel, cisplatin and S-1 in gastric cancer patients with para-aortic lymph node metastases. Anticancer Drugs 20: 752-756, 2009.
28. Hironaka S, Yamazaki K, Taku K, *et al*: Phase I study of docetaxel, cisplatin and S-1 in patients with advanced gastric cancer. Jpn J Clin Oncol 40: 1014-1020, 2010.
29. Scanlon KJ, Newman EM, Lu Y, *et al*: Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci USA 83: 8923-8925, 1986.
30. Pratesi G, Gianni L, Manzotti C, *et al*: Sequence dependence of the antitumor and toxic effects of 5-fluorouracil and cis-diamminedichloroplatinum combination on primary colon rumors in mice. Cancer Chemother Pharmacol 21: 237-240, 1988.
31. Kuroki M, Nakano S, Mitsugi K, *et al*: In vivo comparative therapeutic study of optimal administration of 5-fluorouracil and cisplatin using a newly established HST-1 human squamous-carcinoma cell line. Cancer Chemother Pharmacol 29: 273-276, 1992.
32. Fury MG and Shah JP: Induction chemotherapy in the management of head and neck cancer. J Surg Oncol 101: 292-298, 2010.
33. Kreis W, Petrylak D, Savarese D and Budman D: Colitis and docetaxel-based chemotherapy. Lancet 355: 2164, 2010.