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Gastrostomy Dependence in Head and Neck Carcinoma Patient Receiving Post-operative Therapy

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Objective: Post-operative concurrent chemoradiotherapy significantly improves the rates of locoregional control and disease-free survival in high-risk patients but has significant adverse effects. Percutaneous endoscopic gastrostomy and opioid-based pain control increase treatment completion rates but can result in dysphagia.
Methods: The rate and duration of use of prophylactically placed percutaneous endoscopic gastrostomies were evaluated in 43 patients who underwent post-operative radiotherapy or chemoradiotherapy from April 2007 through March 2010. All patients completed treatment and received 60 Gy or more of radiotherapy.
Results: Thirty four of 43 patients (79.1%) used percutaneous endoscopic gastrostomies, which could later be removed in 25 of 34 patients. The median period of use was 108 days. Only one disease-free patient was permanently dependent on percutaneous endoscopic gastrostomy feeding. The frequency of percutaneous endoscopic gastrostomy use among patients with oral, oropharyngeal and hypopharyngeal cancer was 91.7, 100 and 54.5%, respectively.
Conclusions: Prolonged percutaneous endoscopic gastrostomy use is not required in patients receiving post-operative chemoradiotherapy and will not lead to dysphagia.

Key words: post-operative therapy – prophylactic PEG – nutritional management – enteral feeding – H and N-RadOncol – deglutition training

INTRODUCTION

Patients undergoing resection of head and neck cancers with positive surgical margins or extranodal spread of disease are considered to be at high risk for recurrence. Concurrent post-operative chemoradiotherapy for such patients significantly improves the rates of local and regional control and prolongs disease-free survival. However, chemoradiotherapy is associated with a substantial increase in adverse effects (1,2).

Patients with head and neck cancer receiving radiotherapy or chemoradiotherapy are at a considerable risk of malnutrition, with 75–80% of patients experiencing a weight loss during treatment (3–6) of up to 15 or 20% (7,8). Radiotherapy-related toxicities include painful mucositis, dysgeusia, xerostomia, odynophagia, thickened secretions and anorexia (7,9–14). Treatment can, therefore, decrease oral intake by physical means and by decreasing a patient's motivation to eat.

Enteral feeding refers to the delivery of nutrients directly into the stomach via a feeding tube device, such as a nasogastric feeding tube or a gastrostomy tube (15). Enteral tube feeding is used for patients who cannot obtain adequate oral intake of nutrients from food or oral nutritional supplements

or both or who cannot eat or drink safely (16). Enteral feeding can also be used during and after treatment to provide nutritional support to patients with head and neck cancers who are unable to meet their nutritional requirements because of treatment-related side effects.

In our hospital, patients receiving post-operative chemoradiotherapy undergo prophylactic percutaneous endoscopic gastrostomy (PEG). With PEG tube feeding and opioid-based pain control, the completion rate of chemoradiotherapy is increased (17).

Prophylactic PEG has been shown to significantly reduce both mean weight loss and rate of hospitalization during radiotherapy (18–21) and to result in fewer unscheduled treatment interruptions (22). Therefore, in the present study, we examined the rate and duration of use of prophylactically placed PEGs for enteral feeding during post-operative radiotherapy or chemoradiotherapy among patients with head and neck cancers.

PATIENTS AND METHODS

A chart review was performed. We evaluated the rate and duration of use of prophylactically placed PEG tubes for enteral feeding in 43 patients who underwent post-operative radiotherapy or chemoradiotherapy from April 2007 through March 2010 at the National Cancer Research Center East Hospital. Age, sex, location and stage of cancer, extent of surgery and reconstruction, radiation, chemotherapy, use of PEG and removal of PEG were evaluated.

The patients were 31 men and 12 women with a mean age of 57.4 years (range: 26–74 years). All patients completed treatment with 60 Gy or more of radiotherapy and underwent chemotherapy with cisplatin, alone or with fluorouracil or with carboplatin alone. (Table 1) All patients underwent radiation therapy within 8 weeks after definitive surgery consisting of conventionally fractionated doses of 2 Gy in 5 weekly sessions. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of >40–46 Gy. Regions that were adjacent to the high-risk area received a dose of >50–60 Gy. Regions that were at high risk for malignant dissemination or that had inadequate resection margins received a total of 66 Gy in 33 fractions over a period of 6.5 weeks.

Two patients had difficulty with oral ingestion even before radiotherapy.

RESULTS

Prophylactic PEG tubes were used for enteral feeding in 34 (79.1%) of 43 patients and were not used in 9 patients. The PEG tubes that were used were later removed in 25 of the 34 patients (73.5%). The median period of use was 108 days. Among disease-free patients, the rate of feeding tube use was 34.1% (14 of 41 patients) at 6 months, 26.3% (10 of 38 patients) at 1 year, 21.6% at 18 months (8 of 37 patients) and 18.9% (7 of 37 patients) at 2 years. Because of cancer recurrence, eight patients

Table 1. Patients

Male	31	
Female	12	
Age		
Mean, 57.4 years (range: 26–74 years)		
26–59 years	24	
≥60 years	19	
Follow-up		
Alive	24	951–2096 days (median: 1437 days)
Dead	19	132–1098 days (median: 470 days)
Primary site		
Oral cavity	24	
Hypopharynx	11	
Oropharynx	5	
Larynx	3	
T stage		
T1	4	
T2	16	
T3	9	
T4	14	
N stage		
N0	15	
N1	4	
N2	22	
N3	2	
Surgery		
Oral cancer		
Oral cavity resection without reconstruction	10	
Oral cavity resection with reconstruction	9	
Segmental mandibulectomy with reconstruction	5	
Laryngeal/hypopharyngeal cancer		
Total pharyngolaryngoesophagectomy with jejunum reconstruction	8	
Partial laryngectomy/pharyngectomy without reconstruction	6	
Oropharyngeal cancer		
Oropharynx resection without reconstruction	2	
Oropharynx resection with reconstruction	3	
Radiotherapy		
66 Gy	40	
70 Gy	3	
Chemotherapy		
Cisplatin	36	
Cisplatin + fluorouracil	2	
Carboplatin	1	
None	4	

Table 2. Rate and duration of PEG use

Tumor site	Patients	PEG not used	PEG used and removed	Alive with PEG	Used until death	Median duration of use (range), days	Rate of PEG use (%)
Oral cavity	24	2	14	1	7	96 (16–1785)	91.7
Hypopharynx	11	5	5	0	1	93 (20–731)	54.5
Oropharynx	5	0	5	0	0	55 (41–1379)	100
Larynx	3	2	1	0	0	331	33.3
Total	43	9	25	1	8	108 (16–1785)	79.1

PEG, percutaneous endoscopic gastrostomy.

Table 3. Result of analysis with PEG feeding dependence at 1 year

	Oral feeding	PEG use	Rate of PEG tube use at 1 year	
Primary site				
Oral cavity	13	6	31.6% (6 of 19)	
Larynx/hypopharynx/ oropharynx	16	3	15.8% (3 of 19)	$P = 0.445$
Surgery				
Without reconstruction	13	3	18.8% (3 of 16)	
With reconstruction	17	6	26.1% (6 of 23)	$P = 0.882$
Chemotherapy				
Concurrent chemoradiotherapy	27	9	25.0% (9 of 36)	
Radiotherapy alone	2	0	0% (0 of 2)	$P = 0.964$
Age				
<59 years	20	2	9.1% (2 of 22)	
≥60 years	9	7	43.6% (7 of 16)	$P = 0.036$*

* χ^2 test < 0.05.

used PEG tubes until their deaths. One patient, who could not ingest orally before radiotherapy because of dysphagia due to resection of the vagus and hypoglossal nerves, remains alive with a PEG tube. Only one disease-free patient was permanently dependent on PEG feeding.

The rate and duration of PEG use by disease location are shown in Table 2. The PEG was used for feeding in most patients with oral cancer (91.7%) or oropharyngeal cancer (100%) but was used at a much lower rate in patients with hypopharyngeal cancers (54.5%), particularly in those who had undergone pharyngolaryngoesophagectomy. Age >60 years was a factor predicting feeding tube dependence 1 year after (chemo-) radiotherapy (Table 3).

DISCUSSION

Nutritional management is extremely important for the completion of treatment for head and neck cancer. Although the optimal method of nutritional management has been debated, the guidelines of the American Society for Parenteral and Enteral Nutrition state that enteral nutrition is more effective than parenteral nutrition and can be used to optimally maintain the patient's general condition.

In patients receiving chemoradiotherapy for head and neck cancer, hypoalimentation can be caused by numerous complications, including nausea due to chemotherapy, opportunistic infections due to myelotoxicity, mucositis due to radiotherapy or chemotherapy and pain from eczema. Hypoalimentation leads to weight loss and deterioration of the patient's general condition, which, in turn, can lead to a cessation or reduction of treatment, extended hospitalization and a reduced quality of life. For patients with head and neck cancer, PEG is a safe and well-established procedure for delivering nutrition and drugs. On the other hand, a patient's dependence upon PEG for nutrition can lead to a subsequent inability to ingest nutrition orally. Studies, such as those by Mekhail et al. (23) and Baredes et al. (24), have found delays in the resumption of oral ingestion in patients with PEG.

Further retrospective studies have found significantly lower rates of persistent dysphagia 3 and 6 months after surgery in patients fed with nasogastric tubes than in patients fed with PEG tubes (23).

Patients who undergo nasogastric feeding have their feeding tubes removed earlier than do patients who undergo PEG feeding (23,25,26). This notion is supported by the work of Baredes et al. (24), who have reported that PEG tube use leads to a longer period of non-oral feeding because of the deconditioning of the muscles of deglutition. A PEG may also produce feeding tube dependence in patients with dysphagia (27). Kiyota et al. (28) have reported that among patients receiving adjuvant chemoradiotherapy, rates of feeding tube use at 3 months, 6 months and 1 year were 48, 40 and 20%, respectively.

In the present study, the median period of PEG use was 108 days, the rate of use at 2 years was 18.9% and only one patient was permanently dependent on PEG feeding; we consider these results to be satisfactory.

As a result of rehabilitation, there was no statistically significant difference in the rate of feeding tube use 1 year after (chemo-) radiation by primary site, reconstruction or concurrent chemotherapy.

The rate of PEG dependence after 1 year was higher in patients older than 60 years. Therefore, elderly patients have a greater need for rehabilitation than do younger patients.

PEG tubes were used by most patients with oral or oropharyngeal cancers (91.7 and 100%, respectively). On the other hand, the frequency of PEG use was much lower in patients with hypopharyngeal cancer (54.5%), particularly in patients who had undergone pharyngolaryngoesophagectomy. We speculate that a reason for this low rate of PEG use in patients with hypopharyngeal cancer is that areas of radiotherapy-induced mucositis are replaced with free jejunal grafts; because these grafts are poorly sensate, the patients feel little pain, and because the esophagus and respiratory tract are separated to prevent aspiration, oral feeding is relatively easy. Thus, we believe that PEG is unnecessary for patients who have undergone pharyngolaryngoesophagectomy.

Deglutition relies on sensory perception and the action of various organs in the head and neck region. Thus, the temporary absence of deglutition could result in functional decline. Patients being treated for head and neck cancer are likely to forgo deglutition due to either pain or lassitude, with patients using PEGs forgoing deglutition more readily and showing greater functional decline than do patients without PEGs. It is, therefore, necessary for patients with PEGs to continue ingestion and deglutition training.

At our institution, we provide the following support for patients and their families to allow early resumption of ingestion and independence from PEGs:

(1) Continuing guidance, in cooperation with a dentist, regarding oral hygiene and dryness, even after the completion of treatment.
(2) Guidance on meals to enhance appetite in cases of dysgeusia and guidance to ensure adequate nutrition intake.
(3) Guidance with regard to feelings of uneasiness after the removal of the PEG.

As a result of this support, nearly three-quarters of our patients could overcome their dependence on PEGs. In the future, we aim to study further adaptations to PEG feeding by improving the support system and accumulating a large number of cases for study.

CONCLUSION

Prolonged PEG use is not required in patients who undergo postoperative chemoradiotherapy and will not lead to dysphagia. Only one of our patients was permanently dependent on PEG feeding. We believe that our results are satisfactory. However, patients with oral or oropharyngeal cancer who are at a high risk for recurrence are more likely to require prophylactic PEG placement to maintain adequate nutritional status.

Conflict of interest statement

None declared.

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Feasibility of Cisplatin/5-Fluorouracil and Panitumumab in Japanese Patients with Squamous Cell Carcinoma of the Head and Neck

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Objective: In Japan, cisplatin/5-fluorouracil 80/800 (cisplatin 80 mg/m^2, 5-fluorouracil 800 mg/m^2) is widely used to treat recurrent/metastatic squamous cell carcinoma of the head and neck, whereas cisplatin/5-fluorouracil 100/1000 (1000 mg/m^2/24 h by continuous intravenous infusion on Days 1–4 plus cisplatin 100 mg/m^2 on Day 1 in 3-week cycles) is the standard treatment in Europe and North America.

Methods: We prospectively evaluated the feasibility of cisplatin/5-fluorouracil 100/1000 in Japanese patients enrolled in the global Phase 3 study of panitumumab 9 mg/kg combined with cisplatin/5-fluorouracil 100/1000 (Arm 1) versus cisplatin/5-fluorouracil 100/1000 alone (Arm 2).

Results: Twenty Japanese patients were enrolled and received treatment (Arm 1, $n = 13$; Arm 2, $n = 7$). Grade 3/4 adverse events included neutropenia, hypomagnesemia, stomatitis, hyponatremia, paronychia, febrile neutropenia, decreased appetite and hypokalemia. There were no fatal adverse events. Median overall survival was not estimable in Arm 1 and 15.4 months in Arm 2. Median progression-free survival was 6.9 months in Arm 1 and 5.7 months in Arm 2. The median number of infusions (cycles) of cisplatin was 5 in Arm 1 and 4 in Arm 2; the median number of infusions (cycles) of 5-fluorouracil was 6 in both arms. The mean administered dose for cisplatin was 93.6 mg/m^2 in Arm 1 and 97.2 mg/m^2 in Arm 2, and 3732.6 and 3880 mg/m^2 in Arm 1 and Arm 2, respectively, for 5-fluorouracil.

Conclusions: These results suggested that cisplatin/5-fluorouracil 100/1000 was feasible for recurrent/metastatic squamous cell carcinoma of the head and neck in Japanese patients.

Key words: head and neck – Japanese subgroup analysis – cisplatin/5-fluorouracil-100/1000

INTRODUCTION

In Japan, the incidence of squamous cell carcinoma of the head and neck (SCCHN) was reported in 16 351 people with 7021 deaths in 2006 (1). Platinum-based chemotherapy is considered a standard care for patients with recurrent and/or metastatic SCCHN (2). In Japan a combined chemotherapy regimen of cisplatin/5-fluorouracil is commonly used dose of 80/800 (cisplatin 80 mg/m^2 on Day 1 in 4-week cycles, and 5-fluorouracil 800 mg/m^2/24 h by continuous intravenous infusion on Days 1–5) (3). In contrast, in Europe and North America, the same combination chemotherapy has also been commonly used with higher dose intensity, while the standard dose of cisplatin/5-fluorouracil for patients with recurrent and/or metastatic SCCHN is higher: 5-fluorouracil 1000 mg/m^2/24 h by continuous intravenous infusion on Days 1–4 plus cisplatin 100 mg/m^2

on Day 1 in 3-week cycles (100/1000) (4–6). Therefore, little information is currently available on the efficacy and toxicity of a higher dose of cisplatin/5-fluorouracil for Japanese patients with SCCHN.

The SPECTRUM study was a randomized, two-arm, open-label, global Phase 3 trial that evaluated the efficacy and safety of panitumumab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), combined with cisplatin/5-fluorouracil 100/1000 compared with combination cisplatin/5-fluorouracil 100/1000 alone as first-line systemic treatment for recurrent/metastatic SCCHN (7). SPECTRUM enrolled 657 patients from 26 countries in Europe, North and South America and Asia. The primary endpoint of the global study was overall survival (OS); progression-free survival (PFS), objective response rate and safety were secondary endpoints.

Because SPECTRUM was the first randomized controlled study in which Japanese patients with recurrent/metastatic SCCHN received cisplatin/5-fluorouracil 100/1000 (7), it represents a unique opportunity to evaluate this chemotherapy regimen in Japanese patients. Thus, we performed a subgroup analysis of Japanese patients who participated in the global SPECTRUM trial and received the 100/1000-dose of cisplatin/5-fluorouracil either alone or in combination with panitumumab (7). Results from this subgroup analysis are compared with those from the global SPECTRUM population.

PATIENTS AND METHODS

Patients

A full description of the SPECTRUM study protocol has been published previously (7). Briefly, eligible patients had histologically or cytologically confirmed recurrent/metastatic SCCHN or locally recurrent SCCHN that was determined to be incurable by surgery or radiotherapy. All patients had Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 and satisfactory hematologic, renal, hepatic and cardiac function at screening. Exclusion criteria included prior systemic chemotherapy for recurrent/metastatic SCCHN (unless part of multimodality treatment for locoregionally advanced SCCHN completed >6 months before randomization); other primary cancer with treatment within 2 years before randomization; nasopharyngeal carcinoma; central nervous system metastases; major or minor surgery within 4 or 2 weeks, respectively; and prior anti-EGFR treatment (unless part of initial curative multimodality therapy for locally advanced SCCHN).

The study was conducted in accordance with the Declaration of Helsinki. All protocols and study procedures were approved by an independent ethics committee/institutional review board at each participating center. Written informed consent was obtained from all patients before their enrollment.

Study Design and Treatment

SPECTRUM was a randomized, open-label, Phase 3 trial conducted at 126 sites in 26 countries (including five sites in Japan). Patients enrolled in the study were randomized 1 : 1 using an interactive voice response system to receive either cisplatin/5-fluorouracil 100/1000 plus panitumumab 9 mg/kg (Arm 1) or cisplatin/5-fluorouracil 100/1000 alone (Arm 2). Cisplatin 100 mg/m^2 was administered on Day 1 of each 3-week cycle and 5-fluorouracil 1000 mg/m^2 was administered as a continuous infusion on Days 1–4 of each cycle. Randomization was stratified by prior treatment, site of primary tumor and ECOG performance status. Treatment with cisplatin/5-fluorouracil continued for a maximum of six cycles. Carboplatin (dosed to achieve an exposure area under the curve of 5 mg/ml/min) could be permanently substituted for cisplatin if patients developed decreased creatinine clearance <50 ml/min or Grade 2 or 3 neurotoxicity (including sensory/motor neuropathy or ototoxicity). All patients received cisplatin/5-fluorouracil as initial therapy. Panitumumab 9 mg/kg was given intravenously on Day 1 of each 3-week cycle, immediately before administration of chemotherapy. Patients in Arm 1 who did not have disease progression after six cycles could optionally continue to receive additional panitumumab monotherapy. Treatments were administered per protocol until disease progression, unacceptable toxicity, patient withdrawal or death.

Protocol-specified dose modifications and dose delay of study medications were permitted if toxicity occurred. Patients who experienced toxicities related to panitumumab treatment could have ≥ 1 dose of panitumumab withheld, reduced or delayed (administered at >21-day intervals). Doses of panitumumab could be delayed for skin- or nail-related toxicity requiring treatment with narcotics, systemic steroids, intravenous antibiotics, intravenous antifungal agents or surgical debridement; skin- or nail-related toxicity considered intolerable by the patient; any skin- or nail-related serious adverse event (AE); or any other Grade 3/4 toxicity (with the exception of Grade 3/4 hypomagnesemia and/or hypocalcemia manageable with magnesium/calcium replacement; Grade 3/4 nausea, diarrhea or vomiting manageable with supportive care; Grade 3/4 anemia manageable with transfusions; or Grade 4 thrombocytopenia manageable with transfusions). In the event panitumumab was held for toxicity, chemotherapy continued as scheduled. Panitumumab administration could be resumed, if the panitumumab-related toxicity was considered resolved or improved to a degree that allowed for retreatment in the case of: skin- or nail-related toxicity no longer required treatment, was no longer considered intolerable, or had improved to Grade ≤ 2; or if the non-skin- or nail-related toxicity had resolved to Grade ≤ 1.

Dosing modification guidelines for the next cycle of combination chemotherapy were based on the worst toxicity observed during the previous cycle. A new cycle of cisplatin/carboplatin and 5-fluorouracil could be administered only when patient's absolute neutrophil count was $\geq 1.5 \times 10^9$/l and the platelet count was $\geq 100 \times 10^9$/l. If chemotherapy-related toxicity did not resolve within 21 days from the first missed dose, treatment with the agent(s) believed to have caused the toxicity was discontinued. Patients who experienced chemotherapy toxicity (including Grade 4 neutropenia >5 days, febrile neutropenia,

Grade 4 thrombocytopenia [Grade 2 for carboplatin] and Grade ≥3 mucositis [5-fluorouracil only]) had their dose of cisplatin or 5-fluorouracil reduced by 20%. Dose re-escalation was not permitted. Patients with >2 dose reductions or with Grade 4 neurologic toxicity discontinued the treatment permanently. If any component of the chemotherapy regimen was discontinued for intolerability, patients could continue with the remaining component for the remaining treatments for the six planned cycles or until disease progression, intolerability, withdrawal or death.

Study Endpoints

The primary endpoint was OS, defined as the time from randomization to death. Secondary endpoints included PFS (time from randomization to disease progression or death), objective response rate, duration of response, time to response and safety.

Assessment

Clinical and laboratory assessments were performed at screening, on Day 1 of each cycle, and at the safety follow-up (30 days after the last treatment). AEs occurring during the study were defined and graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Radiographic imaging (computed tomography or magnetic resonance imaging) was performed at baseline and at 6-week intervals thereafter until disease progression occurred. Tumor response was evaluated by investigators per modified Response Evaluation Criteria in Solid Tumors version 1.0 (8). For patients meeting the criteria for tumor response, the response was confirmed ≥4 weeks after the initial response assessment. Patients were followed up for safety (30 days after the last administration of study medication) and survival (every 3 months).

Statistical Analysis

Data from Japanese patients were extracted from the full data set for the SPECTRUM study. All Japanese patients were treated at five centers Japan. The safety analysis set included all randomized patients who received ≥1 dose of panitumumab or chemotherapy. Evaluation of OS and PFS was performed using the intent-to-treat analysis set. OS was calculated from the time of randomization to death; PFS was calculated as the time from randomization to disease progression or death. OS and PFS were compared between treatment groups using the log-rank test stratified by the randomization factors. Hazard ratios and 95% CIs for OS and PFS were estimated using a Cox model stratified by the randomization factors.

RESULTS

Patients

Globally, 657 patients were enrolled and randomized in the SPECTRUM study (Arm 1, $n = 327$; Arm 2, $n = 330$). Among these, 20 Japanese patients were enrolled in the study (Arm 1, $n = 13$; Arm 2, $n = 7$), all of whom received ≥1 dose of study drug and thus composed the intent-to-treat and safety analysis sets. Demographics and baseline characteristics are summarized in Table 1. Age and tumor site of origin were generally balanced between treatment arms; however, the proportion of patients with ECOG performance status 1 was slightly greater in Arm 2 than Arm 1 (57 versus 38%), and a greater proportion of patients in Arm 1 than Arm 2 (54 versus 43%) had received prior platinum therapy. Overall, 7 of 20 patients received cisplatin for the planned six cycles (Arm 1, $n = 6$; Arm 2, $n = 1$) (Table 2). Seven patients switched to carboplatin from cisplatin, and six of seven patients who switched to carboplatin completed the planned six cycles (Arm 1, $n = 3$; Arm 2, $n = 3$). Thirteen out of 20 patients who received 5-fluorouracil completed the planned six cycles (Arm 1, $n = 9$; Arm 2, $n = 4$), consistent with the 13 patients who completed six cycles of either cisplatin or carboplatin.

Treatment Exposure

Exposure to study medication is summarized in Table 3. Among Japanese patients, the median number of infusions (cycles) of cisplatin was 5 in Arm 1 and 4 in Arm 2; the median number of infusions (cycles) of 5-fluorouracil was 6 in Arms 1 and 2. The mean dose of cisplatin was 93.6 mg/m^2 in Arm 1 and 97.2 mg/m^2 in Arm 2; the mean dose of 5-fluorouracil was 3732.6 mg/m^2 in Arm 1 and 3880.6 mg/m^2 in Arm 2. The median relative dose intensity (RDI) of cisplatin was 69.9% in Arm 1 and 75.8% in Arm 2. Seven patients (Arm 1, $n = 4$; Arm 2, $n = 3$) switched to carboplatin (primarily because of creatinine clearance <50 ml/min); the median RDI for carboplatin was 100% in Arm 1 and 91.3% in Arm 2. The median RDI of 5-fluorouracil was 75.1% in Arm 1 and 80.7% in Arm 2. The median number of panitumumab infusions administered was 8.0 and the median duration of treatment was 30.1 weeks. Of the 13 Japanese patients who received panitumumab combined with chemotherapy in Arm 1, 9 (69%) subsequently received panitumumab monotherapy. The incidence of chemotherapy cycle delays among Japanese patients was 48% (Arm 1, 29%; Arm 2, 52%), primarily because of protocol-specified laboratory values and AEs (Table 4).

Safety

Treatment-emergent AEs occurring in Japanese patients in the SPECTRUM study are summarized in Table 5. Overall, toxicities among Japanese patients were consistent with those expected for patients receiving combination cisplatin/5-fluorouracil. AEs occurring more frequently in Arm 1 than in Arm 2 were consistent with those anticipated for patients receiving anti-EGFR therapy and included hypomagnesemia, skin toxicity (rash, dermatitis acneiform, dry skin and pruritus), diarrhea and stomatitis. Four subjects discontinued chemotherapy due to chemotherapy-related toxicities (Arm 1, $n = 3$; Arm 2, $n = 1$). The AEs that led to discontinuation of

Table 1. Patient demographics and baseline characteristics of Japanese patients enrolled in the SPECTRUM study[a]

Characteristic	Arm 1 cisplatin/5-FU + panitumumab $n = 13$	Arm 2 cisplatin/5-FU $n = 7$
Sex, *n* (%)		
Men	12 (92)	6 (86)
Women	1 (8)	1 (14)
Median age, years (range)	59 (43–72)	64 (55–71)
<65, *n* (%)	8 (62)	4 (57)
≥65, *n* (%)	5 (38)	3 (43)
ECOG performance status, *n* (%)		
0	8 (62)	3 (43)
1	5 (38)	4 (57)
Median duration of disease,[b] months (range)	14.7 (1–105)	13.3 (6–40)
Involuntary weight loss in the previous 6 months, *n* (%)		
>0–5%	3 (23)	0 (0)
>5%	2 (15)	3 (43)
Primary tumor site, *n* (%)		
Oropharynx	4 (31)	2 (29)
Hypopharynx	1 (8)	2 (29)
Larynx	4 (31)	1 (14)
Oral cavity	4 (31)	2 (29)
Extent of disease, *n* (%)		
Locoregional recurrence only	3 (23)	3 (43)
Distant metastatic	5 (38)	2 (29)
Distant metastatic with locoregional recurrence	5 (38)	2 (29)
Primary tumor histologic type, *n* (%)		
Well differentiated	2 (15)	1 (14)
Moderately differentiated	6 (46)	3 (43)
Poorly differentiated	1 (8)	1 (14)
Not otherwise specified/unknown	4 (31)	2 (29)
Previous treatment,[c] *n* (%)		
Chemotherapy and/or radiotherapy	10 (77)	4 (57)
Chemotherapy		
Platinum	7 (54)	3 (43)
Fluoropyrimidine	5 (38)	2 (29)
Taxane	0 (0)	1 (14)
Other	0 (0)	1 (14)
Radiotherapy		
All patients	9 (69)	4 (57)
Patients with locally advanced disease	6 (75)	3 (60)
Surgery	13 (100)	7 (100)

5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group.
[a]Percentages are rounded to the nearest integer value and therefore may result in sums of >100% within a category.
[b]Date of randomization minus date of initial squamous cell carcinoma of the head and neck diagnosis.
[c]Previous treatment given as adjuvant or part of multimodality treatment in locally advanced disease >6 months before randomization.

Table 2. Subject disposition

Characteristic	Arm 1 cisplatin/5-FU + panitumumab $n = 13$	Arm 2 cisplatin/5-FU $n = 7$
Number of subjects ending cisplatin, *n* (%)	13 (100)	7 (100)
Reason for ending cisplatin, *n* (%)		
Completing at least six cycles	6 (46)	1 (14)
Protocol-specified criteria	4 (31)	3 (43)
Creatinine clearance <50 ml/min	3 (23)	2 (29)
Grade 2 or 3 neurologic toxicity	1 (8)	1 (14)
Disease progression	2 (15)	2 (29)
Subject request	1 (8)	0 (0)
Administrative decision	0 (0)	1 (14)
Number of subjects receiving carboplatin, *n* (%)	4 (31)	3 (43)
Number of subjects ending carboplatin, *n* (%)	4 (31)	3 (43)
Reason for ending carboplatin, *n* (%)		
Completing at least all planned cycles	3 (75)	3 (100)
Adverse event	1 (25)	0 (0)
Number of subjects ending 5-FU, *n* (%)	13 (100)	7 (100)
Reason for ending 5-FU, *n* (%)		
Completing at least six cycles	9 (69)	4 (57)
Disease progression	1 (8)	2 (29)
Adverse event	2 (15)	0 (0)
Subject request	1 (8)	0 (0)
Administrative decision	0 (0)	1 (14)

chemotherapy were Grade 2 deafness in two patients, and Grade 3 stomatitis and pneumonia in one patient each.

The incidence of treatment-emergent Grade 3 or 4 AEs was 100% in Arm 1 and 86% in Arm 2 (Table 5). Frequently occurring (in ≥15% of Japanese patients overall) treatment-emergent Grade 3 or 4 AEs included neutropenia (Arm 1, $n = 5$ [38%]; Arm 2, $n = 3$ [43%]), hypomagnesemia ($n = 4$ [31%]; $n = 0$ [0%], respectively), stomatitis ($n = 3$ [23%]; $n = 1$ [14%]), hyponatremia ($n = 3$ [23%]; $n = 0$ [0%]), paronychia ($n = 3$ [23%]; $n = 0$ [0%]), febrile neutropenia ($n = 2$ [15%]; $n = 1$ [14%]), decreased appetite ($n = 2$ [15%]; $n = 2$ [29%]) and hypokalemia ($n = 2$ [15%]; $n = 3$ [43%]). No fatal AEs were reported in Japanese patients. Serious treatment-emergent AEs occurred in 7 (35%) Japanese patients overall (Arm 1, $n = 5$ [38%]; Arm 2, $n = 2$ [29%]). Among these, treatment-related serious AEs considered by the investigators to be related to study treatment were febrile neutropenia (Arm 1, $n = 2$ [15%]; Arm 2, $n = 0$ [0%]), malaise ($n = 1$ [8%]; $n = 0$ [0%], respectively), toxic nephropathy ($n = 1$ [8%]; $n = 0$ [0%]), pneumonia aspiration ($n = 1$ [8%]; $n = 0$ [0%]), sepsis ($n = 1$ [8%]; $n = 0$ [0%]), decreased appetite ($n = 0$ [0%]; $n = 1$ [14%]) and pyrexia ($n = 0$ [0%]; $n = 1$ [14%]).

Table 3. Treatment exposure and chemotherapy switching

Characteristic	Arm 1 cisplatin/5-FU + panitumumab $n = 13$	Arm 2 cisplatin/5-FU $n = 7$
Exposure to cisplatin		
Duration of treatment, median (range), weeks	20.1 (6.3–24.6)	17.1 (3.0–23.9)
Infusions per patient, median (range), *n*	5.0 (1.0–6.0)	4.0 (1.0–6.0)
Dose delivered, mean (range), mg/m^2	93.6 (77.9–102.3)	97.2 (84.1–103.0)
Relative dose intensity,[a] median (range), %	69.9 (44.9–96.5)	75.8 (44.9–103.0)
Exposure to 5-FU		
Duration of treatment, median (range), weeks	20.1 (6.3–24.7)	18.0 (3.0–23.9)
Infusions per patient, median (range), *n*	6.0 (2.0–6.0)	6.0 (1.0–6.0)
Dose delivered, mean (range), mg/m^2	3732.6 (3266.8–4089.6)	3880.6 (3362.7–4139.0)
Relative dose intensity,[a] median (range), %	75.1 (61.8–96.9)	80.7 (58.8–103.5)
Exposure to carboplatin		
Duration of treatment, median (range), weeks	3.0 (3.0–12.0)	6.6 (3.0–19.0)
Infusions per patient, median (range), *n*	1.0 (1.0–3.0)	2.0 (1.0–5.0)
Dose delivered, mean (range), mg/m^2	339.0 (303.0–360.0)	390.0 (348.0–450.0)
Relative dose intensity,[a] median (range), %	100.0 (75.0–100.0)	91.3 (78.9–100.0)
Cisplatin to carboplatin switching		
Patients switching, *n* (%)	4 (31)	3 (43)
Reason for switching, *n* (%)		
Creatinine clearance <50 ml/min	3 (75)	2 (67)
Grade 2 or 3 neurologic toxicity	1 (25)	1 (33)

[a]Ratio of the actual dose intensity (actual cumulative dose/duration of treatment exposure period) to the planned dose intensity.

The most frequently occurring treatment-related AEs of any grade included decreased appetite (Arm 1, $n = 13$ [100%]; Arm 2, $n = 7$ [100%]), stomatitis ($n = 13$ [100%]; $n = 6$ [86%], respectively), fatigue ($n = 11$ [85%]; $n = 6$ [86%]), diarrhea ($n = 11$ [85%]; $n = 4$ [57%]), paronychia ($n = 11$ [85%]; $n = 1$ [14%]), nausea ($n = 10$ [77%]; $n = 7$ [100%]), hypomagnesemia ($n = 9$ [69%]; $n = 3$ [43%]) and vomiting ($n = 8$ [62%]; $n = 4$ [57%]).

Efficacy

At the time of this analysis (14 May 2010), 4 of 13 (31%) Japanese patients in Arm 1 and 4 of 7 (57%) Japanese patients in Arm 2 had OS events (Table 6). At the time of this analysis, median OS in Japanese patients was 15.4 months in Arm 2 and had not been reached in Arm 1; 11 (85%) Japanese patients in Arm 1 and 7 (100%) Japanese patients in Arm 2 had disease progression or had died. Median PFS in Japanese patients was 6.9 months in Arm 1 and 5.7 months in Arm 2.

DISCUSSION

This subgroup analysis of the global SPECTRUM study is the first to report the safety and feasibility of cisplatin/5-fluorouracil 100/1000 in Japanese patients with recurrent/metastatic SCCHN and suggests that the regimen has mostly acceptable toxicity in Japanese patients both alone and in combination with the anti-EGFR monoclonal antibody panitumumab in this setting.

Similar to previous report from a Japanese Phase 2 study with cetuximab (9), it is demonstrated that cisplatin/5-fluorouracil 100/1000, alone and combined with panitumumab, appears feasible and manageable for Japanese patients with recurrent/metastatic SCCHN. Although evaluation is limited by the small number of Japanese patients enrolled, the study provides us with useful information on the toxicity of cisplatin/5-fluorouracil. Overall, there were no new safety signals in Japanese patients vs. the total patient population in SPECTRUM (7). Furthermore, although some AEs (e.g., skin toxicity and hypomagnesemia) occurred more frequently in Japanese patients who received panitumumab in combination with cisplatin/5-fluorouracil versus those who received cisplatin/5-fluorouracil alone, the nature of these events and their severity was consistent with those expected for an anti-EGFR agent in combination with cisplatin/5-fluorouracil (5). However, several treatment-emergent Grade 3 or 4 AEs were more frequent among Japanese patients than in the global study population: neutropenia (Arm 1, 38 versus 32%, respectively; Arm 2, 43 versus 33%), febrile neutropenia (Arm 1, 15

Table 4. Chemotherapy cycle delays and dose changes

Characteristic	Arm 1 cisplatin/5-FU + panitumumab $n = 13$	Arm 2 cisplatin/5-FU $n = 7$
Chemotherapy cycle delays		
Cycles administered	112	31
Cycle delays,[a] *n* (%)	32 (29)	16 (52)
Number of patients with cycle delays, *n* (%)	12 (92)	4 (57)
Reasons for cycle delays,[b] *n* (%)		
Protocol-specified adverse event	8 (67)	1 (25)
Protocol-specified laboratory value	8 (67)	4 (100)
Non-protocol-specified adverse event	1 (8)	0 (0)
Other	5 (42)	0 (0)
Cisplatin dose changes		
Doses administered	62	23
Total dose changes,[c] *n* (%)	19 (31)	8 (35)
Patients with dose changes, *n* (%)	9 (69)	4 (57)
Reasons for dose changes,[b] *n* (%)		
Adverse event	4 (44)	1 (25)
Chemotherapy-related hematologic toxicity	3 (33)	1 (25)
Weight change	1 (11)	0 (0)
Other	4 (44)	2 (50)
5-FU dose changes		
Doses administered	67	31
Total dose changes,[c] *n* (%)	28 (42)	12 (39)
Patients with dose changes, *n* (%)	11 (85)	4 (57)
Reasons for dose changes,[b] *n* (%)		
Adverse event	5 (45)	1 (25)
Chemotherapy-related hematologic toxicity	3 (27)	1 (25)
Weight change	2 (18)	0 (0)
Other	6 (55)	2 (50)
Carboplatin dose changes		
Total dose changes,[c] *n* (%)	0 (0)	0 (0)

[a]The percentage is calculated relative to the total number of cycles administered.
[b]Some patients may have had ≥ 1 event. Corresponding events are displayed for each reason but are counted only once for each reason. The percentage is calculated relative to the number of patients with the event.
[c]The percentage is calculated relative to the total number of doses administered.

versus 6%; Arm 2, 14 versus 5%), stomatitis (Arm 1, 23 versus 4%; Arm 2, 14 versus 5%), hypomagnesemia (Arm 1, 31 versus 12%), hypokalemia (Arm 1, 15 versus 10%; Arm 2, 43 versus 7%), anemia (Arm 1, 15 versus 12%) and thrombocytopenia (Arm 1, 15 versus 6%). Grade 3 or 4 acute renal failure, which occurred in the total population (Arm 1, $n = 3$; Arm 2, $n = 1$), did not occur in Japanese patients. Notably, the overall incidence of serious treatment-emergent AEs in Japanese patients (Arm 1, 38%; Arm 2, 29%) was lower than in the global study population (Arm 1, 48%; Arm 2, 43%), and there were no treatment-related deaths among Japanese patients. It is important to note that the toxicity profile in Japanese patients in the SPECTRUM study was generally consistent with that previously reported in a Japanese institutional study in which patients with recurrent/metastatic SCCHN received cisplatin/fluorouracil 80/800 (3). In particular, the rates of Grade 3 or 4 nausea/vomiting (each 8% in Arm 1 and 0% in Arm 2) and weight loss (Arm 1, 0%; Arm 2, 14%) in this study are lower than the rates of Grade 3 or 4 nausea (16.6%) and anorexia (40%) reported in that study (3).

Several observations related to treatment exposure among Japanese patients are noteworthy. First, the mean cisplatin doses were relatively consistent between the treatment arms (Arm 1, 93.6 mg/m^2; Arm 2, 97.2 mg/m^2) and were delivered over a duration near the planned target of 18 weeks (Arm 1, 20.1 weeks; Arm 2, 17.1 weeks). Second, the median RDI of cisplatin among Japanese patients in both treatment arms (Arm 1, 70%; Arm 2, 76%) was lower than in the total SPECTRUM population (Arm 1, 87%; Arm 2, 85%) (7). Third, the median RDI of 5-fluorouracil among Japanese patients in both treatment arms (Arm 1, 75%; Arm 2, 81%) was lower than that in the total study population (Arm 1, 89%; Arm 2, 90%). Fourth, switching from cisplatin to carboplatin occurred more frequently in Japanese patients (Arm 1, 31%; Arm 2, 43%) than in the total population (Arm 1, 21%; Arm 2, 26%). Fifth, a high proportion of Japanese patients had chemotherapy cycle delays (Arm 1, 92%; Arm 2, 57%) and dose changes for cisplatin (Arm 1, 69%; Arm 2, 57%) and 5-fluorouracil (Arm 1, 85%; Arm 2, 57%). Finally, Japanese patients received more cycles of chemotherapy than the median for the global study population: the median number of infusions of cisplatin (Arm 1, five infusions; Arm 2, four infusions) and 5-fluorouracil (Arm 1, six infusions; Arm 2, six infusions) was slightly higher than the median number of infusions of cisplatin (Arm 1, four infusions; Arm 2, four infusions) and 5-fluorouracil (Arm 1, five infusions; Arm 2, four infusions) for the global study population. Although the reasons for the differences in the dosing of cisplatin and 5-fluorouracil between Japanese patients and the total SPECTRUM population are uncertain, there are several potential factors that may have contributed. During the study, the antiemetic aprepitant had not been approved in Japan and was therefore not available for use by Japanese patients. In contrast, aprepitant was available to patients in the other study regions (10). Although the use rate of aprepitant among the global SPECTRUM population is not known, the inability of Japanese patients to use this drug may have resulted in an increased rate of gastrointestinal toxicity (including nausea, vomiting and anorexia) with cisplatin/5-fluorouracil 100/1000, which could have contributed to the incidence of dose modifications and dose delays.

Table 5. Summary of AEs

	Arm 1 cisplatin/5-FU + panitumumab $n = 13$		Arm 2 cisplatin/5-FU $n = 7$	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Patients with any treatment-emergent AE, *n* (%)	13 (100)	13 (100)	7 (100)	6 (86)
Patients with fatal AEs, *n* (%)	0 (0)		0 (0)	
Treatment-emergent AEs of any grade occurring in ≥20% of all patients, *n* (%)				
Hematological toxicities				
Neutropenia	8 (62)	5 (38)	3 (43)	3 (43)
Anemia	6 (46)	2 (15)	0 (0)	0 (0)
Thrombocytopenia	4 (31)	2 (15)	2 (29)	0 (0)
Non-hematological toxicities				
Decreased appetite	13 (100)	2 (15)	7 (100)	2 (29)
Stomatitis	13 (100)	3 (23)	6 (86)	1 (14)
Fatigue	11 (85)	1 (8)	6 (86)	0 (0)
Diarrhea	11 (85)	1 (8)	4 (57)	0 (0)
Paronychia	11 (85)	3 (23)	1 (14)	0 (0)
Nausea	10 (77)	1 (8)	7 (100)	0 (0)
Hypomagnesemia	9 (69)	4 (31)	3 (43)	0 (0)
Rash	9 (69)	1 (8)	1 (14)	0 (0)
Constipation	8 (62)	0 (0)	5 (71)	0 (0)
Vomiting	8 (62)	1 (8)	4 (57)	0 (0)
Pruritus	8 (62)	0 (0)	3 (43)	0 (0)
Dry skin	8 (62)	1 (8)	1 (14)	0 (0)
Alopecia	7 (54)	0 (0)	3 (43)	0 (0)
Weight decreased	7 (54)	0 (0)	2 (29)	1 (14)
Hypocalcemia	7 (54)	2 (15)	1 (14)	0 (0)
Pyrexia	6 (46)	0 (0)	2 (29)	0 (0)
Dermatitis acneiform	5 (38)	0 (0)	0 (0)	0 (0)
Dysgeusia	4 (31)	0 (0)	2 (29)	0 (0)
Injection site reaction	4 (31)	0 (0)	1 (14)	0 (0)
Insomnia	3 (23)	0 (0)	3 (43)	0 (0)
Blood creatinine increased	3 (23)	0 (0)	1 (14)	0 (0)
Cheilitis	3 (23)	0 (0)	1 (14)	0 (0)
Hiccups	3 (23)	0 (0)	1 (14)	0 (0)
Peripheral neuropathy	3 (23)	2 (15)	1 (14)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	3 (23)	0 (0)	1 (14)	0 (0)
Peripheral sensory neuropathy	3 (23)	1 (8)	1 (14)	0 (0)
Hypokalemia	2 (15)	2 (15)	3 (43)	3 (43)
Edema	2 (15)	0 (0)	2 (29)	0 (0)

AE, adverse event.

Among patients who received only chemotherapy (Arm 2), median OS in Japanese patients was notably longer compared with the total SPECTRUM population (15.4 versus 9.0 months (7)). Median OS had not been reached for Japanese patients in Arm 1 because only 4 out of 13 patients had died at the time of this analysis. Survival among Japanese patients in SPECTRUM was not inferior to that of Japanese patients with SCCHN who received cisplatin/5-fluorouracil 80/800 (3).

Table 6. OS and PFS

	Arm 1 cisplatin/5-FU + panitumumab $n = 13$		Arm 2 cisplatin/5-FU $n = 7$
OS			
OS events, *n* (%)	4 (31)		4 (57)
Kaplan–Meier estimate of median OS (95% CI), months	NE (11.9–NE)		15.4 (6.4–NE)
Cox proportional hazards model HR (95% CI)		0.458 (0.114–1.837)	
P value for treatment effect		0.2702	
Log-rank test *P* value		0.2583	
PFS			
PFS events, *n* (%)	11 (85)		7 (100)
Kaplan–Meier estimate of median PFS (95% CI), months	6.9 (5.4–7.0)		5.7 (3.9–6.4)
Cox proportional hazards model HR (95% CI)		0.534 (0.202–1.409)	
P value for treatment effect		0.2050	
Log-rank test *P* value		0.2044	

HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Similarly, PFS was longer in Japanese patients versus the global study population both in Arm 1 (6.9 versus 5.8 months) and Arm 2 (5.7 versus 4.6 months). A potential explanation for improved OS and PFS among Japanese patients may be due in part to the greater proportion of Japanese patients with ECOG performance status 0 compared with that of the total population (Arm 1, 62 versus 30%; Arm 2, 43 versus 30%, respectively). ECOG performance status at study entry was among the prognostic factors identified in univariate and multivariate analyses of the total SPECTRUM population (7). It is also interesting to note that a high proportion (69%) of Japanese patients who received panitumumab combined with chemotherapy in Arm 1 continued panitumumab monotherapy with maintenance, whereas only 29% of patients in Arm 1 in the global study population received panitumumab monotherapy. In addition, a higher dose (relative to body weight) of cisplatin/5-fluorouracil received by Japanese patients vs. the other patients in SPECTRUM may also have contributed to these clinical differences. Although it is difficult to definitively explain these differences in Japanese subpopulation, the response in Japanese patients is notable given the intensity of their prior treatment; however, these data should be interpreted with caution, particularly given the small study size.

In conclusion, although chemotherapy with cisplatin/5-fluorouracil 80/800 is widely used for the treatment of Japanese patients with recurrent/metastatic SCCHN, this analysis suggests that treatment with cisplatin/5-fluorouracil 100/1000 has manageable toxicity in Japanese patients with recurrent/metastatic SCCHN. Although the number of Japanese patients in SPECTRUM was small, OS and PFS times with cisplatin/5-fluorouracil 100/1000 were longer than those in the global SPECTRUM population and were not inferior to those of Japanese patients with SCCHN receiving 80/800 dose of cisplatin/5-fluorouracil, suggesting that the treatment was not associated with unacceptable toxicity. These results suggest that initiating cisplatin/5-fluorouracil therapy with 100/1000 in Japanese patients may be feasible and that further clinical investigation of cisplatin/5-fluorouracil 100/1000, alone or combined with panitumumab, for the treatment of recurrent/metastatic SCCHN in Japanese patients would be valuable. This is the first study to report the tolerability of cisplatin/5-fluorouracil 100/1000 in Japanese patients with SCCHN in the global Phase 3 study; these findings demonstrate the feasibility of including SCCHN patients from Japan in international clinical trials investigating use of cisplatin/5-fluorouracil 100/1000 in the future. Note, however, the further clinical assessment with the full dose of cisplatin/5-fluorouracil should still be warranted in order to ensure the feasibility and safety for Japanese patients with SCCHN.

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Conflict of interest statement

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Randomized Phase II/III Trial of Post-operative Chemoradiotherapy Comparing 3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of Head and Neck: Japan Clinical Oncology Group Study (JCOG1008)

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A randomized Phase II/III study was launched in Japan to evaluate the non-inferiority of concurrent chemoradiotherapy with weekly cisplatin (40 mg/m^2) compared with concurrent chemoradiotherapy with 3-weekly cisplatin (100 mg/m^2) for post-operative high-risk patients with locally advanced squamous cell carcinoma of head and neck. This study began in October 2012, and a total of 260 patients will be accrued from 18 institutions within 5 years. The primary endpoint of the Phase II part is proportion of treatment completion and that of the Phase III part is overall survival. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during permissible treatment period and adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/].

Key words: head and neck cancer – post-operative chemoradiotherapy – high-risk patients – clinical trials – Phase II/III

INTRODUCTION

Head and neck cancer is relatively rare but increasing steadily in Japan. Squamous cell carcinoma is the most common histological type and comprises ~90% of head and neck cancer.

The prognosis of post-operative Stage III/IV locally advanced squamous cell carcinoma of head and neck (SCCHN) is still poor. Integrated analysis of RTOG95-01 (1) (Radiation Therapy Oncology Group) and EORTC22931 (2) (European Organisation for Research and Treatment of Cancer) demonstrated that microscopically positive resection margin and extracapsular nodal extension are high-risk factors for recurrence in post-operative locally advanced SCCHN. Moreover, these two trials revealed that the standard therapy for post-operative locally advanced SCCHN with high-risk factors for recurrence is surgery followed by chemoradiotherapy (CRT) with 3-weekly cisplatin (CDDP) at 100 mg/m^2 (3-weekly CDDP + RT); this adjuvant 3-weekly CDDP + RT showed 5-year survival of ~50% (1–4).

Meanwhile, concurrent CRT with weekly CDDP at 40 mg/m^2 (weekly CDDP + RT) is a promising regimen for post-operative locally advanced SCCHN with high-risk factors for recurrence. CDDP is expected to have a radiosensitizing effect when it is administered every week during radiation therapy and the dose intensity of weekly CDDP (40 mg/m^2/week) is higher than that of 3-weekly CDDP (33 mg/m^2/week). In fact, promising results of post-operative weekly CDDP + RT were reported in two prospective trials (5,6). In addition, weekly CDDP + RT has several advantages over 3-weekly CDDP + RT in terms of safety and toxicity. First, hematological toxicity tends to be milder in weekly CDDP + RT than in 3-weekly CDDP + RT. In particular, most published reports described that the incidence of Grade 3/4 neutropenia was ~30% in 3-weekly CDDP + RT compared with ~10–15% in weekly CDDP + RT (1,7–14). Second, auditory disorders are a problem associated with 3-weekly CDDP + RT, and weekly CDDP + RT is superior to the former due to the lower likelihood of neurotoxicity. In particular, CDDP-related auditory disorder is a dose-limiting toxicity; it occurs dose-dependently and is irreversible in most cases (15–18). In fact, in the RTOG95-01 study, the incidence of neurotoxicity including Grade 3 or more auditory disorders was 10% after 3-weekly CDDP + RT for head and neck cancer (1). In addition, in a feasibility study led by the National Cancer Center Hospital East, Grade 2 or more auditory disorder was observed in 8% of patients (7). On the other hand, there have been no reports on Grade 3 or more auditory disorders with weekly CDDP + RT. Hokkaido University and National Cancer Center Hospital East also reported that the incidence of Grade 2 or more auditory disorders was 0% in a retrospective study of weekly CDDP + RT in Japanese (8). Third, renal disorders rarely occur with weekly CDDP + RT, which is a major additional merit. In a retrospective overseas study reported by Uygun et al. (14), the incidence of Grade 3/4 renal disorder was lower with weekly CDDP + RT than with 3-weekly CDDP + RT. CDDP-related renal disorder is also dose-dependent and weekly CDDP + RT is superior in this regard. In fact, a Japanese study reported that, although no difference was observed in the incidence of Grade 3/4, the incidence of Grade 2 or more, for which dose reduction or discontinuation of CDDP must be considered, was 30–32% in 3-weekly CDDP + RT compared with 2–15% in weekly CDDP + RT, showing a significantly lower incidence with the latter (7–9). Finally, these potential merits of safety and toxicity for weekly CDDP + RT may lead to a shorter hospitalization period than for 3-weekly CDDP + RT. Therefore, we planned to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT.

In this randomized controlled study, we set 3-weekly CDDP + RT as the standard treatment arm and weekly CDDP + RT as the experimental treatment arm. For safety and feasibility data in Japanese post-operative high-risk patients with locally advanced SCCHN, only one feasibility study ($N = 25$) led by the National Cancer Center Hospital East is available for 3-weekly CDDP + RT. In addition, for weekly CDDP + RT, few safety and feasibility data have been accumulated in Japan, Europe and the USA Considering the above circumstances together, we evaluate the feasibility and safety of both treatment arms in the Phase II part at first and then proceed to the Phase III part to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT as a standard treatment.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2012 and the study was activated in October 2012. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/index.htm].

PROTOCOL DIGEST OF THE JCOG 1008

Purpose

The aim of this study is to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN.

Study Setting

A multi-institutional randomized Phase II/III study.

Resources

This study is supported by National Cancer Center Research and Development Funds (23-A-16 and 23-A-21).

Endpoints

The primary endpoint of the Phase II part is the proportion of treatment completion in all eligible patients. The definition of complete treatment is as follows: 3-weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of two out of three courses of 3-weekly CDDP during the radiation treatment period or within 14 days from the last day of completion of radiation; weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of five out of seven courses of weekly CDDP during the radiation treatment period.

The primary endpoint of the Phase III part is overall survival, which is defined as days from randomization to death from any cause and censored at the latest day without an event. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during the permissible treatment period and adverse events. Relapse-free survival is defined as days from randomization to any disease relapse or death from any cause and censored at the latest date when the patient is alive. Local relapse-free survival is defined as days from randomization to local and regional disease relapse or death from any cause and censored at the latest date when the patient is

evaluated as event-free. Nutrition-support-free survival denotes the percentage of surviving patients not requiring any nutrition support at the time of treatment start and then 2, 6, 12, 24, 36, 48 and 60 months after registration. The non-hospitalized treatment period during the permissible treatment period is defined as the difference between the duration of actual hospital stays and the permissible treatment period (66 days).

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill all of the following criteria:

(1) Histologically proven squamous cell carcinoma in resected specimen.
(2) Primary lesion located in the oral cavity, oropharynx, hypopharynx or larynx.
(3) Pathological Stages III, IVA or IVB (UICC seventh edition).
(4) High risk of locoregional recurrence, defined as fulfilling (i) and/or (ii):
  (i) microscopically positive resection margin;
  (ii) extracapsular nodal extension.
(5) Within 56 days of surgery.
(6) No distant metastasis in head and neck contrast CT or MRI, chest contrast CT or upper abdominal contrast CT within 28 days before registration.
(7) Aged 20–75 years old.
(8) ECOG performance status of 0 or 1.
(9) No prior radiation therapy, chemotherapy or hormonal therapy for target or non-target cancers.
(10) Adequate organ function.
(11) Normal electrocardiogram.
(12) Written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

(1) Active multiple primary cancers; synchronous or metachronous (within 5 years) double cancers except carcinoma *in situ* or intramucosal tumor.
(2) Infection requiring systemic treatment.
(3) Fever exceeding 38°C at registration.
(4) Women who are or may be pregnant, or who are nursing.
(5) Psychosis or psychiatric symptoms/signs that are judged to make participation in the study difficult.
(6) Long-term use of systemic steroidal treatment (oral/intravenous).
(7) Uncontrolled diabetes mellitus.
(8) Complication with unstable angina, or history of myocardial infarction within the last 6 months.
(9) Uncontrolled hypertension.

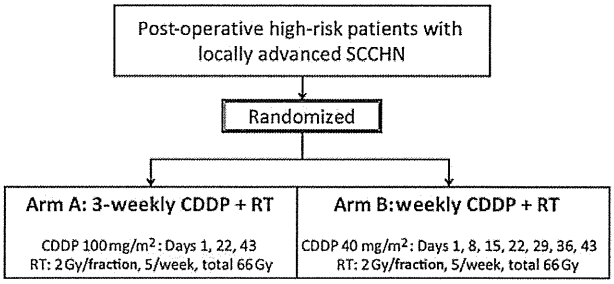

Figure 1. Schema of the study.

(10) Pleural effusion, pericardial effusion or ascites that requires drainage.
(11) Hepatitis B antigen-positive.
(12) Judged to have difficulty in abstaining from smoking or alcohol during the protocol treatment.

Treatment Methods

The protocol treatment consists of 3-weekly CDDP + RT and weekly CDDP + RT (Fig. 1).

Chemotherapy

Patients in the 3-weekly CDDP + RT arm receive concurrent CRT with CDDP at 100 mg/m^2. CDDP is administered on Days 1, 22 and 43, repeated every 3 weeks for three cycles. Patients in the weekly CDDP + RT arm receive concurrent CRT with CDDP at 40 mg/m^2. CDDP is administered on Days 1, 8, 15, 22, 29, 36 and 43, repeated every week for seven cycles.

Radiation Therapy

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 66 Gy in 33 fractions over 6.5 weeks. The gross tumor volume is not defined in this trial because macroscopic sites of the disease were resected before registration. The clinical target volume (CTV) initial includes locally resected lesion and potential lymph node metastasis area, and CTV boost is defined as a high-risk area with a positive node with extracapsular extension and/or a positive surgical margin with a 1–1.5 cm margin. The planning target volumes (PTV) for CTV initial and CTV boost (PTV initial and PTV boost) are defined as 0.5–1 cm margins around CTV initial and CTV boost to compensate for setup variations and internal organ motion. A total of 46 Gy is delivered to PTV initial, and then an additional 20 Gy is provided to PTV boost.

Follow-up

All enrolled patients are followed up for at least 5 years. The efficacy and the safety are to be evaluated at least every 3 months during the first year, at least every 4 months during

the second year, every 6 months during the third year, and every 12 months during the fourth and fifth years. Data on the use and methods of nutrition support are reported at 2, 6, 12 and then every 12 months until 60 months after registration.

Study Design and Statistical Analysis

This trial is designed to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN. The planned accrual period is 5 years, and the follow-up period is 5 years after completion of accrual.

In the Phase II part, the planned sample size is 66 patients, which was calculated based on an expected proportion of complete treatment of 80% and a threshold of 50%, with a one-sided alpha of 0.025 and a beta of 0.1.

In the Phase III part, the primary analysis is carried out at 5 years after accrual completion. The hazard ratio between the treatment arms and its confidence interval, estimated by the Cox proportional hazard model stratified by the high-risk factors for recurrence (microscopically positive resection margin and extracapsular nodal extension), is used to test the non-inferiority of the weekly CDDP + RT arm in terms of overall survival. The significance level is set at 0.05 in a one-sided test because of the non-inferiority design of the study. One hundred and sixty-one events would be required to demonstrate, with a statistical power of 75%, that the weekly CDDP + RT arm is not inferior to the 3-weekly CDDP arm in terms of overall survival, with a non-inferiority margin of 10% at 5-year overall survival. Non-inferiority will be concluded if the upper limit of the confidence interval of the hazard ratio does not exceed the limit of 1.32, which is in accord with the non-inferiority margin. According to Schoenfeld and Richter's method (19), a sample size of 260 patients is necessary to observe 161 events, considering the accrual and follow-up periods and that the estimated 5-year overall survival rates of the 3-weekly CDDP + RT arm and the weekly CDDP + RT arm are 49 and 52%, respectively.

Interim Analysis and Monitoring

In this Phase II/III trial, three interim analyses are planned. The first interim analysis is planned at the time of protocol treatment completion of all registered patients in the Phase II part to evaluate the feasibility and safety of both treatment arms and to determine the progression to the Phase III part. The second interim analysis is planned when half of the planned sample size is registered to determine whether the registration of the Phase III part should be continued. The third interim analysis is planned after the registration completion to determine the continuation to the follow-up. The trial will be terminated when the primary objective is accomplished at each interim analysis.

The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and recommend that the trial either be continued or terminated early. Central monitoring will be performed every 6 months by the JCOG Data Center to evaluate study progress and improve study quality.

Participating Institutions (from North to South)

Hokkaido University Hospital, Miyagi Cancer Center, Tohoku University Hospital, Jichi Medical University Hospital, National Cancer Center Hospital East, Tokyo Jikei Medical University Hospital, National Hospital Organization Tokyo Medical Center, Cancer Institute Hospital, Tokai University, Shizuoka Cancer Center, Aichi Cancer Center, Nagoya University Hospital, Kinki University Hospital, Osaka Prefectural Hospital Organization, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University Hospital, Hyogo Cancer Center, Nara Medical University, Shikoku Cancer Center.

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Conflict of interest statement

None declared.

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原　著

頭頸部がん患者に対する放射線併用シスプラチン分割レジメンにおける予防的制吐薬アプレピタントに関する考察

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Evaluation of Aprepitant as a Prophylactic Antiemetic in the Cisplatin Split Regimen Combined with Radiation for Patients with Head and Neck Cancer: Mikinori Yoshida[*1], Shinya Suzuki[*1], Tomohiro Enokida[*2], Hiroto Ishiki[*2], Yasuhiko Ichida[*1], Shinichiro Saitoh[*1], Kazushi Endo[*3], Keishiro Izumi[*1] and Makoto Tahara[*2] ([*1]*Division of Pharmacy, and* [*2]*Division of Head and Neck Medical Oncology, National Cancer Center Hospital East,* [*3]*Drug Safety Management, Meiji Pharmaceutical University*)

Summary

The cisplatin split regimen has not been sufficiently well investigated to validate the use of aprepitant as a prophylactic antiemetic. This study aimed to retrospectively evaluate the efficacy of repeated administrations of 3-day courses of aprepitant according to the cisplatin split regimen (20 mg/m^2/day, days 1-4, 22-25, 43-46) in combination with radiation. We compared the worst Grade of nausea between 23 patients with head and neck cancer who had been administered with aprepitant (group A: between January 2010 and June 2010) and 34-patients who were not administered with aprepitant (group B: between July 2011 and December 2012). In group A, the median age was 60 years (range, 35-73 years), the male/female ratio was 18: 5, and the Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 20 patients and 1 in 3 patients. In group B, the median age was 62 years (range, 31-71 years), the male/female ratio was 30: 4, and the ECOG PS was 0 in 31 patients and 1 in 3 patients. The worst nausea grade was 0, 1, and 2 in 21, 2, and 0 patients in group A and in 19, 9, and 6 patients in group B, respectively. The proportion of patients who developed nausea was significantly lower in group A than in group B (8% vs 44%, p<0.01). Of 6 patients who experienced Grade 2 nausea, 5 patients were administered with aprepitant during the next course of chemotherapy, and 60% of them had a lower severity of nausea. Thus, aprepitant could be effectively used as a prophylactic antiemetic in the cisplatin split regimen. Key words: Aprepitant, Cisplatin, Chemoradiotherapy, Head and neck cancer, Nausea/vomiting (*Received Oct. 7, 2013/Accepted Feb. 19, 2014*)

要旨　シスプラチン（CDDP）分割レジメンに対するアプレピタント（aprepitant: APR）の使用に関して十分な検証が行われていない。本研究は放射線療法と併用し，3週間ごとにCDDP 20 mg/m^{2}を4日間連日投与するCDDP分割レジメンにおけるAPRの使用状況と悪心の実態を調査し，APRの必要性について検討した。CDDP分割レジメンを施行した頭頸部がん患者のうち，APRを使用していた2010年1月～2010年6月までの23症例をA群，APRを使用していない2011年7月～2011年12月までの34症例をB群とした。両群で発現した悪心の最大Gradeについて診療録を用いて後方視的に調査した。対象の年齢中央値はA群60（35～73）歳，B群62（31～71）歳，男性/女性はA群（18/5），B群（30/4），PS 0/1はA群（20/3），B群（31/3）であった。発現した悪心の最大Grade（0/1/2）はA群（21/2/0），B群（19/9/6）であった。悪心が発現した頻度はA群8%（2/23），B群44%（15/34）であり，A群で有意に低かった（p<0.01）。Grade 2に至ったB群の6症例のうち5症例にAPRが追加処方され，次コースにて60%（3/5）の症例で悪心が軽減した。CDDP分割レジメンにAPRを使用することで悪心が制御できる傾向が示唆された。

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