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

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Received February 7, 2014; accepted April 17, 2014

Objective: In Japan, cisplatin/5-fluorouracil 80/800 (cisplatin 80 mg/m², 5-fluorouracil 800 mg/m²) is widely used to treat recurrent/metastatic squamous cell carcinoma of the head and neck, whereas cisplatin/5-fluorouracil 100/1000 (1000 mg/m²/24 h by continuous intravenous infusion on Days 1–4 plus cisplatin 100 mg/m² 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/m² in Arm 1 and 97.2 mg/m² in Arm 2, and 3732.6 and 3880 mg/m² 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 7,021 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/m² on Day 1 in 4-week cycles, and 5-fluorouracil 800 mg/m²/24 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/m²/24 h by continuous intravenous infusion on Days 1–4 plus cisplatin 100 mg/m².
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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/m² was administered on Day 1 of each 3-week cycle and 5-fluorouracil 1000 mg/m² 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 ≥1.5 × 10⁹/l and the platelet count was ≥100 × 10⁹/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/m² in Arm 1 and 97.2 mg/m² in Arm 2; the mean dose of 5-fluorouracil was 3732.6 mg/m² in Arm 1 and 3880.6 mg/m² 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 aceneiform, 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
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 = 1 [8%]; 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 1. Patient demographics and baseline characteristics of Japanese patients enrolled in the SPECTRUM studya

| 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.

aPercentages are rounded to the nearest integer value and therefore may result in sums of >100% within a category.

bDate of randomization minus date of initial squamous cell carcinoma of the head and neck diagnosis.

cPrevious 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) |
| 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) |
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
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Table 4. Chemotherapy cycle delays and dose changes

| Characteristic                                      | Arm 1 cisplatin/5-FU + panitumumab n = 13 | Arm 2 cisplatin/5-FU n = 7 |
|----------------------------------------------------|-------------------------------------------|---------------------------|
| Cycles administered                                | 112                                       | 31                        |
| Cycle delays, n (%)                                 | 32 (29)                                   | 16 (52)                   |
| Number of patients with cycle delays, n (%)        | 12 (92)                                   | 4 (57)                    |
| Reasons for cycle delays, 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)                     |
| Doses administered                                 |                                            |                           |
| Total dose changes, n (%)                          | 19 (31)                                   | 8 (35)                    |
| Patients with dose changes, n (%)                  | 9 (69)                                    | 4 (57)                    |
| Reasons for dose changes, 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)                    |
| Doses administered in 5-FU                        |                                            |                           |
| Total dose changes, n (%)                          | 28 (42)                                   | 12 (39)                   |
| Patients with dose changes, n (%)                  | 11 (85)                                   | 4 (57)                    |
| Reasons for dose changes, 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)                    |
| Total dose changes, 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/m²; Arm 2, 97.2 mg/m²) 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%) (7). 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.
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 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 aciform | 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.
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.

Acknowledgements

The authors would like to acknowledge all the patients and their families as well as all investigators and site staff involved in the study. The authors would also like to acknowledge Benjamin Scott, PhD and Ali Hassan, PhD (Complete Healthcare Communications, Inc., Chadds Ford, PA), whose work was funded by Takeda Bio Development Center, Ltd., for assistance in writing this manuscript, as well as Yoshiharu Yamashita (Takeda Bio Development Center, Ltd.) for assistance in coordinating activities among the authors and medical writers during the preparation of this manuscript.

Funding

This work was supported by Amgen Inc. and Takeda Bio Development Center, Ltd. Funding to pay the Open Access publication charges for this article was provided by Takeda Pharmaceutical Company Limited.
Conflict of interest statement

Makoto Tahara has received honoraria from Merk Serono Co., Ltd and Bristol-Myers Squib Co., Ltd and research funding from Eisai Co., Ltd, Boehringer Ingelheim Co., Ltd and Yakult Honsha Co., Ltd. All remaining authors have no conflict of interest. Ikuo Yana and Satoru Otani are compensated employees of Takeda Bio Development Center Limited. The study was designed under the responsibility of Amgen Inc. The study was funded by Takeda Bio Development Center Limited. Study drug was provided by Takeda Bio Development Center Limited. Amgen Inc. collected and analyzed the data and contributed to the interpretation of the study. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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