CQ-13: Duration of postoperative adjuvant chemotherapy

Recommendation: Category A

- Although no definitive conclusion regarding the duration of postoperative adjuvant chemotherapy has been reached, the current standard duration of treatment by 5-FU-based adjuvant chemotherapy is 6 months.

CQ-14: Oxaliplatin (L-OHP) in postoperative adjuvant chemotherapy

Recommendation: Category A

- In August 2009, L-OHP was approved for postoperative adjuvant chemotherapy in Japan. When selecting target patients, the indication should be determined after obtaining sufficient informed consent regarding adverse events and medical care costs as well as the expected additional benefit in terms of survival time.

CQ-15: Molecular target drugs for secondary treatment

Recommendation: Category B

- It is desirable to use bevacizumab as secondary treatment in patients who can be treated with bevacizumab and have not received it as primary treatment. There is no clear evidence supporting the optimal dose in this situation (5 or 10 mg/kg) [44, 49].

CQ-16: KRAS gene mutations and anti-EGFR antibody drugs

Recommendation: Category A

- The usefulness of anti-EGFR antibody drugs has been reported in metastatic colorectal cancer without KRAS gene mutations [38–41, 47, 53, 55, 85–90].

Side Memo 2

- Anti-EGFR antibody drugs and EGFR immunostaining

Since most clinical research on cetuximab has been conducted on EGFR-positive patients, insurance coverage is limited to EGFR-positive patients. On the other hand, most clinical research on panitumumab has also been conducted on EGFR-positive patients, and evidence in regard to EGFR-negative patients is insufficient, but insurance coverage has been restricted to EGFR-positive patients. A recent report showed that there is no relationship between the effect of anti-EGFR antibody drugs and the level of EGFR expression assessed by immunostaining [91].

- CPT-11 and UGT1A1 genetic polymorphism

SN-38 is an active metabolite of CPT-11 and the UGT1A1 gene encodes an intrahepatic metabolizing enzyme which converts the active form SN-38 to the inactive form SN-38 G. In patients who are double heterozygotes for *6 and *28 or homozygotes for *6 or *28 of the UGT1A1 gene, the glucuronic acid conjugation capacity of UGT1A1 is known to be decreased and the metabolism of SN-38 to be delayed, and serious adverse drug reactions such as neutropenia may occur as a result. It is especially desirable to test for a UGT1A1 genetic polymorphism before administering CPT-11 to patients with a high serum bilirubin level, elderly patients, patients whose general condition is poor (e.g., PS2), and patients in whom severe toxicity (especially neutropenia) developed after the last administration of CPT-11. On the other hand, because CPT-11 toxicity cannot be predicted with certainty on the basis of the presence of a UGT1A1 genetic polymorphism alone, it is essential to monitor the patient's general condition during treatment and manage adverse drug reactions carefully regardless of whether a genetic polymorphism is detected.

CQ-17: Significance of preoperative chemoradiotherapy for rectal cancer

Recommendation: Category C

- Preoperative chemoradiotherapy is standard treatment for rectal cancer in Europe and the United States. However, there is insufficient evidence in support of its efficacy and safety in Japan, and it needs to be evaluated in properly designed clinical trials.

CQ-18: Chemoradiotherapy for unresectable locally advanced and locally recurrent rectal cancer

Recommendation: Category C

- The indication for chemoradiotherapy aiming at complete cure by R0 resection will also be considered for locally advanced or locally recurrent, unresectable rectal cancer.

CQ-19: Significance of surveillance after surgery of colorectal cancer

19A: Diagnosis of recurrence
Recommendation: Category A

- Early detection of recurrence has been shown to contribute to an improvement in outcome, and

postoperative surveillance examinations should be performed regularly. However, an optimal surveillance protocol incorporating the health economical point of view has not been sufficiently established.

19B: Multiple cancer
Recommendation: Category B

- With the exception of hereditary colorectal cancer, a past medical history of colorectal cancer has not been demonstrated to be a risk factor for the development of cancer in other organs, and it is unnecessary to incorporate special surveillance for multiple cancer into the surveillance performed after curative surgery for colorectal cancer.

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PHASE II STUDIES

A multicenter phase II study of the stop-and-go modified FOLFOX6 with bevacizumab for first-line treatment of patients with metastatic colorectal cancer

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Summary Currently, no prospective data exists to support a "stop-and-go" modified FOLFOX6 regimen with bevacizumab in metastatic colorectal cancer (mCRC) patients. This study aimed to evaluate the efficacy and safety of this regimen in first-line mCRC patients. Eligible patients (age ≥20 years) had previously untreated mCRC; Eastern Cooperative Oncology Group performance status of 0–2; and adequate hematologic, hepatic, and renal function. The modified FOLFOX6 regimen and bevacizumab (5 mg/kg) was administered intravenously every 2 weeks. After 8 cycles, patients received maintenance therapy with simplified LV5FU2 and bevacizumab until completion of 8 cycles or disease progression. After maintenance therapy, patients received another 8 cycles of modified FOLFOX6 with bevacizumab until completion of 8 cycles or disease progression. We recruited 50 patients between August 2007 and January 2009. The overall response rate was 48% (80% confidence interval [CI]; 38.2–58) with outcomes as follows: complete response, n=1; partial response, n=23; stable disease, n=21; progression, n=1; and not evaluated, n=4. Median time to treatment failure was 7.7 months (80% CI: 6.2–8.0), and median progression-free survival was 12.8 months (80% CI: 10.8–14). Grade 3/4 toxicities included neutropenia (40%), nausea (4%), diarrhea (14%), thrombosis (4%), and hypertension (4%) et al. Grade 1, 2, or 3 peripheral neuropathy was reported in 38%, 40%, and 10% of patients, respectively. The stop-and-go modified FOLFOX6 and bevacizumab regimen is effective and well tolerated as first-line chemotherapy for mCRC patients.

Keywords Metastatic colorectal cancer · Stop and go · Modified FOLFOX6 · Bevacizumab

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Introduction

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab binds to VEGF and inhibits VEGF-receptor binding, thereby preventing the growth and maintenance of tumor blood vessels.

The addition of bevacizumab to a regimen consisting of bolus 5-fluorouracil (5-FU), leucovorin, and irinotecan (IFL) was shown to improve survival for first-line chemotherapy of metastatic colorectal cancer (mCRC) [1]. Second-line treatment with a regimen of oxaliplatin plus 5-FU/folinic acid (FOLFOX4) combined with bevacizumab was found to improve survival [2]. In the first-line setting, the addition of bevacizumab to oxaliplatin-based chemotherapy improved progression free survival (PFS) [3]. In that study, a large proportion of patients stopped treatment earlier than allowed by the study protocol.

FOLFOX4 often induces grade 3 neurotoxicity in previously untreated metastatic colorectal cancer patients [4]. In some case, neurotoxicity became the reason for discontinuation of oxaliplatin. Moreover, the symptom remains for several years after discontinuation of oxaliplatin [5]. There were some reports to prevent neurotoxicity of oxaliplatin [6, 7]. A stop-and-go strategy, stop oxaliplatin after a difined period of time and later reintroduction, can be an effective approach for avoiding severe neurotoxicity [8, 9]. On the other hand, modified FOLFOX6 with or without bevacizumab is effective, tolerable and less burdensome for patients as a first line treatment [10]. Therefore, in the present phase II study, we investigated the efficacy and tolerability of the stop-and-go strategy for therapy with mFOLFOX6 plus bevacizumab.

Materials and methods

This study was a multicenter, open-label, phase II study. Patients at least 20 years of age were eligible if they had: histologically-confirmed metastatic or recurrent colorectal cancer; provided written informed consent; not previously undergone chemotherapy; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; adequate hematologic, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 [7]. Patients were excluded if they had brain metastasis, hypertension, proteinurea, hemorrhage, embolism, uncontrolled diabetes mellitus, heart disease, renal failure, liver failure, intestinal obstruction or active infection. The study protocol was approved by the institutional review boards of the participating institutions. This study was registered with UMIN-CTR (number: UMIN000001233). All costs of medical treatment (drugs and tests) were paid for by Japanese health insurance.

Treatment plan and evaluation

The modified FOLFOX6 regimen consisted of oxaliplatin (85 mg/m^2) on Day 1, given as a 2-hour infusion concurrent with *l*-leucovorin (200 mg/m^2), followed by 5-FU (400 mg/m^2 by injection and 2,400 mg/m^2 by continuous infusion for 46 h) [10]. Bevacizumab (5 mg/kg) was administered intravenously on day 1 before the modified FOLFOX6 regimen, and all therapies were administered every 2 weeks. After 8 cycles or until grade 3 neurotoxicity developed, patients received maintenance therapy other than oxaliplatin (simplified LV5FU2 and bevacizumab) until completion of 8 cycles or the incidence of disease progression. After maintenance therapy, patients received another 8 cycles of modified FOLFOX6 with bevacizumab until completion of 8 cycles or the incidence of disease progression. Prophylaxis of nausea and premedication for allergy after one allergic event were recommended. We did not use prophylaxis against neurotoxicity.

Tumor response was assessed according to RECIST criteria [11] every 8 weeks. Patients were re-evaluated over 4 weeks after initial documentation of complete response or partial response to confirm the assessment. Progression-free survival (PFS) was defined as the time from the date of registration to the first confirmation of disease progression, or death from any cause, and was censored at the last tumor assessment if a patient withdrew before progression. Overall survival (OS) was defined as the time from registration to any death. Time to treatment failure (TTF) was defined as the time from registration to discontinuation of the protocol treatment. Toxicity was assessed before each 2-week cycle using the Common Terminology Criteria for Adverse Events version 3.0 [12]. Clinical report forms were sent to data managers and monitored data was sent to a statistician. We shared our experience with toxicity evaluation in our prior studies [13, 14] and decided how to evaluate neurotoxicity before planning the protocol.

Statistics

The primary objective of the trial was to estimate the response rate for this treatment protocol. We calculated that with a sample size of 45 patients, assuming that the observed response rate was approximately 50% based on past studies, the half-width of the exact 80% binomial confidence interval would be approximately equal to 10.4%. In particular, for an observed response rate of 50%, the exact 80% binomial confidence interval was 38.4% to 59.4%. If the response rate is lower than 30%, the protocol treatment should not be applied in clinical practice. Assuming 5 ineligible cases, we calculated that we would need to enroll 50 patients.

The primary endpoint of this study, the response rate, was estimated, and the exact two-sided 80% confidence interval

Table 1 Patient characteristics (n=50)

Sex	
Male/Female	28 /22
Age	
Median (Range)	61 (37–75)
ECOG performance status	
0/1/2	34/16/0
Primary tumor site	
Colon/Rectum	32/18
Histology type	
Adeno/Muc/Sig	49/0/1
Metastatic site	
Liver/Lung/Lymph node/Other	34/28/22/14
Surgery	
Yes/No	41/9
Adjuvant chemotherapy	
Yes/No	8/42

was calculated. The secondary endpoints were TTF, PFS, OS, the incidence of adverse events and the incidence of grade 3 neurotoxicity. PFS, TTF and OS were estimated according to the Kaplan-Meier method. Median PFS, TTF and OS were estimated, and 80% confidence intervals were calculated with the use of the Greenwood formula. The cumulative incidence of grade 3 neurotoxicity was estimated using competing risk analysis [15], where death was considered the competing risk. Median follow-up was computed by the reverse Kaplan-Meier method [16]. The primary endpoint, TTF, PFS and OS were analyzed in the all eligible cases (all patients excluded ineligible patients). The incidence of adverse events and the incidence of grade 3 neurotoxicity were analyzed in the all treatment cases (all patients who were received one or more the protocol treatment). The FREQ procedure with binomial option (SAS software, version 9.2 (SAS Institute)) was used to analyze categorical data and the LIFETEST procedure was used to analyze time-to-event data.

Results

Patient characteristics

A total of 50 patients from 7 different Japanese hospitals were enrolled in this study from August 2007 to January 2009. All patients were included in the efficacy and safety analysis. Baseline characteristics are summarized in Table 1. Median age was 61 years (range: 37–75), 56% of the patients were men. The primary tumor was located in the colon in 32 patients (64%) and in the rectum in 18 patients (36%).

Efficacy

All 50 patients had measurable metastatic sites. The overall response rate was 48% (80% CI: 38.2, 58) with outcomes as follows: complete response, n=1; partial response, n=23; stable disease, n=21; progression, n=1; and not evaluated, n=4. The disease control rate was 90%. Two patients underwent curative surgery because of tumor shrinkage during protocol chemotherapy. After a median follow-up of 27.8 months, median TTF and PFS were 7.7 months (80% CI: 6.2, 8.0) and 12.8 months (80% CI: 10.8, 14.0), respectively (Fig. 1). At the data cut-off date, 24 patients had died, and median OS was 30.1 months (80% CI: 25.6, –).

Safety

Table 2 summarizes hematological and non–hematological toxicities. Grade 3–4 neutropenia was observed in 40% of patients, but no patient experienced Grade 3–4 febrile neutropenia. Grade 3–4 bevacizumab-associated adverse events

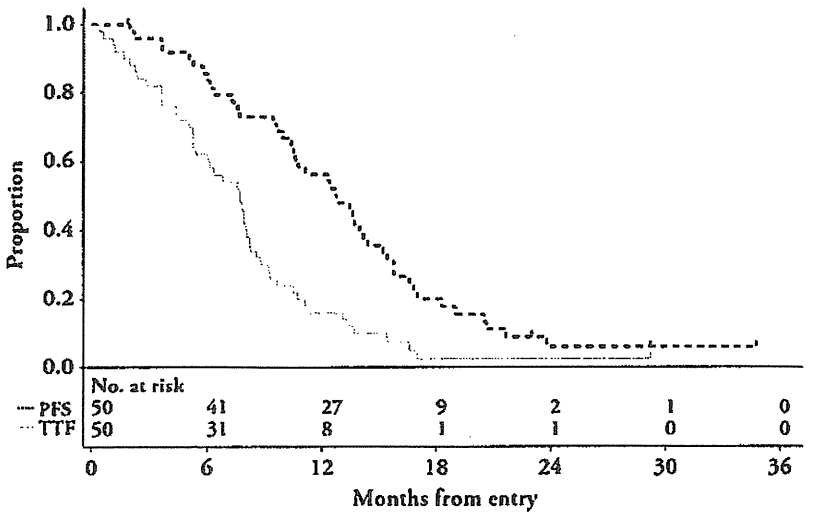

Fig. 1 The median time to treatment failure was 7.7 months (80% CI: 6.2, 8.0) and the median progression free survival time was 12.8 months (80% CI: 10.8, 14.0)

Table 2 Toxicity (n=50)

Adverse event CTC–AE v. 3.0	Grade1–2		Grade 3–4	
	No.	%	No.	%
Hematologic toxicity				
Neutropenia	24	48	20	40
Anemia	35	70	0	0
Thrombocytopenia	24	48	0	0
Bevacizumab-associated toxicity				
Thromboembolism	0	0	2	4
Hypertension	5	10	2	4
Protein urea	19	38	0	0
Bleeding	22	44	0	0
Delayed wound healing	3	6	0	0
Perforation –colon–	0	0	1	2
Non-hematologic toxicity				
Diarrhea	16	32	7	14
Sensory neurotoxicity	39	78	5	10
Nausea	34	68	2	4
Allergic reaction	9	18	0	0

were observed as follows: thrombosis 2/50, hypertension 2/50, and perforation of colon 1/50. There were no treatment-related deaths. Figure 2 shows cumulative proportion of grade 1–3 neurotoxicity. Grade 3 sensory neuropathy was observed in 5 (10%) patients during the protocol treatment. Four of five patients with Grade 3 sensory neuropathy recovered to Grade 0–2 after protocol treatment. Thirteen (26%) and fourteen (28%) patients withdrew from protocol treatment due to adverse events and doctor's decision, respectively. Protocol treatment was discontinued due to grade 2 neurotoxicity based on the doctors' decision in 7 patients, and 4 patients discontinued due to grade 3 neurotoxicity. Three patients were needed to have oxaliplatin reintroduction due to progression during maintenance and only one patient could be reintroduced.

Discontinuation during and after protocol treatment

All patients ended the protocol treatment at the data cutoff date (April 20, 2011). Fourteen (28%) patients received protocol re-introduction and only 6 patients completed 24 cycles of protocol treatment. Thirty-six patients were discontinued the protocol treatment before re-introduction because of early progression (5/36), toxicity (24/36), patients' refusal (4/36), or other reasons (3/36). The re-introduction rate in eligible patients was 53.8% (14 of 26 patients). As a post-therapy, patients received several treatments as follows: FOLFOX-based regimen, 22%; sLV5FU2-based regimen, 36%; irinotecan-based regimen, 22%; and other, 20%. Nine of twelve patients (75%) without reintroduction despite eligibility received the sLV5FU2-based regimen.

Discussion

The FOLFOX plus bevacizumab regimen is one of the standard chemotherapy for the first-line treatment of mCRC. However, oxaliplatin induces severe sensory neuropathy, and as result the stop-and-go strategy has been investigated in order to decrease toxicity. There are 2 major unresolved issues with the stop-and-go strategy: (1) whether "stop" has the same efficacy as the normal FOLFOX regimen; and (2) when is the optimal time to "go" (reintroduction)?

OPTIMOX1 [8] and OPTIMOX2 [17] studies have revealed that maintenance therapy without oxaliplatin is promising and that chemotherapy discontinuation is unfavorable. In order to increase dose intensity, a stop-and-go regimen of

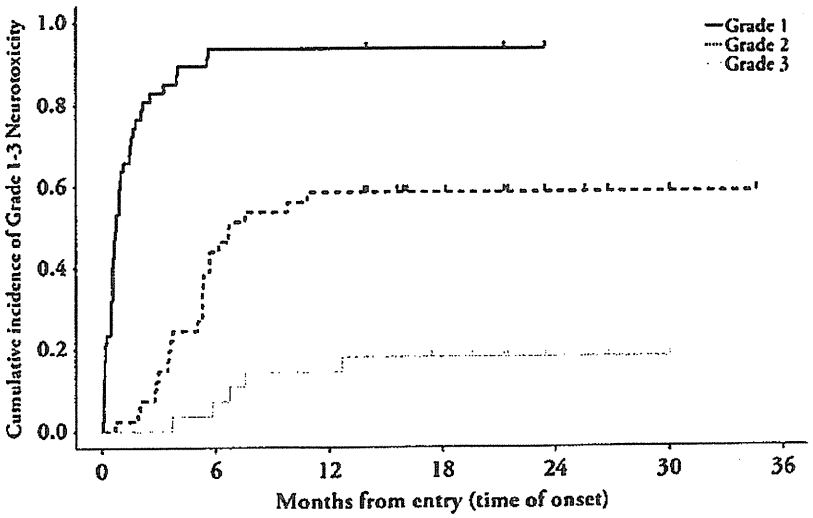

Fig. 2 Cumulative proportion of grade 1–3 neurotoxicity

OPTIMOX1 was investigated by using 6 cycles of FOLFOX7 (oxaliplatin 130 mg/m^2). On the other hand, bevacizumab added to FOLFOX4 (oxaliplatin 85 mg/m^2) in the first line study [3]. FOLFOX4 regimen requires two times hospital visit each cycle and modified FOLFOX6 (oxaliplatin 85 mg/m^2) plus bevacizumab is reported to be effective, tolerable, and less burdensome for patients as first-line treatment [10]. Thus, we added bevacizumab to mFOLFOX6 in this study. Because the dose intensity of mFOLFOX6 is lower than FOLFOX7, efficacy could be reduced if the mFOLFOX6 regimen were to be administered using a stop-and-go strategy.

Previous studies have revealed that the response rates for FOLFOX4 plus bevacizumab without a stop-and-go strategy were in the range of 45%~58.5% [3, 4, 8]. In our study, the response rate was 48% (80% CI: 28.2–56.8) as compared with the rate of 56% for stop-and-go mFOLFOX6 therapy reported in a previous retrospective study [18]. These results show that the early impact of stop-and-go mFOLFOX6 is comparable to treatment without "stop".

As for the ideal number of cycles of induction with FOLFOX, previous studies stopped at a total oxaliplatin dose of approximately 680–780 mg/m^2 [8, 9, 17–19]. The estimated incidence of grade 3 neurotoxicity was reported to be 10% after 9 cycles (oxaliplatin 765 mg/m^2) and 25% after 12 cycles (oxaliplatin 1,020 mg/m^2) [20]. In our schedule, oxaliplatin was stopped after reaching a dose of 680 mg/m^2. The total dose of oxaliplatin during the induction chemotherapy in our protocol is the same as in the CONcePT trial, investigated by using 8 cycles of modified FOLFOX7 (oxaliplatin 85 mg/m^2) [9]. Induction chemotherapy should result in a reasonably high response rate; we consider that rate to be roughly 50% and, therefore, conclude that our dosages were acceptable. Further studies are needed in order to determine the efficacy and safety of lower induction dose of oxaliplatin.

The re-introduction rate of 28% in our patients was lower than the rates of 40.1% [8] and 55.1% [17] reported in previous studies. We defined discontinuation of oxaliplatin as the time patients had grade3 neurotoxicity. But doctors and patients tended to avoid reintroduction if tumors were controlled and/or patients had sustained grade 2 neurotoxicity. Although the reintroduction rate was low, the median PFS was longer than in previous reports without bevacizumab [8, 17]. Most patients without reintroduction, for reasons other than progression, received a regimen of sLV5FU2 plus BV after protocol treatment. Bevacizumab containing intermittent oxaliplatin also revealed a long PFS (12.0 month) [9]. Bevacizumab could increase the probability of tumor control. Furthermore, all patients with grade 3 sensory neuropathy received sLV5FU2, with or without bevacizumab, after discontinuation of protocol treatment, and most of these patients recovered to grade 0–2 neurotoxicity. Consequently, our results suggest that reintroduction at the time of progression is preferable to reintroduction at the scheduled time.

It has been reported that oxaliplatin-related neurotoxicity can be treated with calcium plus magnesium [6] or pregabalin [7]. While these studies suggested that certain drugs were effective in minimizing oxaliplatin-related neurotoxicity, the impact of these drugs on survival was unclear. It remains to be determined whether drugs used to treat neurotoxicity have an acceptable risk-benefit balance in relation to oxaliplatin-based regimens for mCRC. Although our uncontrolled study data has limitations, the results indicate that the stop-and-go mFOLFOX6 plus BV regimen is an effective treatment modality for patients with mCRC.

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Conflict of interest statements The authors declare that they have no conflict of interest.

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Clinical Studies

Phase I first-in-human study of TAK-285, a novel investigational dual HER2/EGFR inhibitor, in cancer patients

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BACKGROUND: This phase I first-in-human study was conducted in Japanese patients to investigate the safety, pharmacokinetics (PKs), and determine the maximum tolerated dose (MTD) of oral TAK-285, a novel dual erbB protein kinase inhibitor that specifically targets human epidermal growth factor receptor (EGFR) and HER2.

METHODS: The TAK-285 dose was escalated until MTD was determined. A second patient cohort received TAK-285 at the MTD for at least 4 weeks.

RESULTS: In all, 26 patients received TAK-285 at doses ranging from 50 to 400 mg once daily (q.d.) or twice daily (b.i.d.); 20 patients made up the dose escalation cohort and the remaining 6 patients were the repeated administration cohort. TAK-285 was well tolerated. Dose-limiting toxicities noted in two patients who received 400 mg b.i.d. were grade 3 increases in aminotransferases and grade 3 decreased appetite. Consequently, the MTD was determined to be 300 mg b.i.d. Absorption of TAK-285 was rapid after oral dosing, and plasma exposure at steady-state increased in a dose-proportional fashion for doses ranging from 50 to 300 mg b.i.d. A partial response was observed for one patient with parotid cancer who received 300 mg b.i.d.

CONCLUSION: The toxicity profile and PK properties of oral TAK-285 warrant further evaluation.

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Keywords: first-in-human; phase I TAK-285; epidermal growth factor receptor; dual erbB protein kinase inhibitor family; receptor tyrosine kinase inhibitor

Dimerisation of the human epidermal growth factor receptor (EGFR) protein family members, including HER1/EGFR and HER2, activates intracellular kinase and initiates a phosphorylation cascade that, in tumour cells, results in enhanced cellular proliferation and survival. Especially in the case of dimers that contain HER2, such activation of signal transmission can be persistent and potent, and under these circumstances is associated with high cellular differentiation and abnormal growth (Reid *et al*, 2007).

Clinically, HER2 and EGFR overexpression and the associated increase in cellular signal transduction is a common feature of tumours such as breast cancer and gastric cancer, and is associated with aggressive disease (Yonemura *et al*, 1991; Salomon *et al*, 1995; Nicolini *et al*, 2006). The prognosis is worse for such patients than for non-overexpressing patients. This also applies to many other cancer types such as colon cancer, ovarian cancer and bladder cancer, and small molecular weight chemotherapeutic agents or antibodies that target EGFR and HER2 and inhibit their activity have been proven to be clinically effective in overexpressing cancers (Hynes and Lane, 2005; Shepherd *et al*, 2005; Thatcher *et al*, 2005; Moore *et al*, 2007; Mok *et al*, 2009).

TAK-285 is a novel low-molecular weight compound that was designed and synthesised by Takeda Pharmaceutical Company, Osaka, Japan and has been shown to selectively and potently inhibit HER2 and EGFR kinase activities. Biochemically, TAK-285 inhibits HER2 and EGFR phosphorylation, with 50% inhibition concentrations of 17 and 23 nmol l^{-1}, respectively (Aertgeerts *et al*, 2011).

The antitumour activity of TAK-285 was evaluated in several murine models employing HER2- or EGFR-overexpressing human tumour xenografts such as BT-474, 4-1 ST and A431. These studies revealed that orally administered TAK-285 effectively inhibited xenograft growth and this effect appeared to correlate with its ability to inhibit EGRF and HER2 (Iwahara *et al*, 2008). Additionally, in rodent and primate toxicity models, TAK-285 was well tolerated and induced toxicities observed with other compounds possessing a similar mechanism of action. TAK-285 also demonstrated potentially no exhibition of elevated cardiac risks whereas other tyrosine kinase inhibitors can elicit secondary effects including heart toxicity (Shell *et al*, 2008). In total, these non-clinical studies suggest that TAK-285 may possess exploitable

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antineoplastic activity and consequently a phase I first-in-human study in patients with solid tumours was conducted in Japan.

PATIENTS AND METHODS

Trial design

This was a phase I, multicentre, open-label study, conducted to investigate the safety, pharmacokinetics (PKs), and determine the maximum tolerated dose (MTD) of oral TAK-285 in patients with solid tumours. Two cohorts were planned for this study: a dose escalation cohort and a repeated administration cohort. In the dose escalation cohort, patients received a single oral dose of TAK-285, followed by 2–6 days of observation without treatment, followed by treatment with the same dose if the safety was confirmed. In this cohort, patients received TAK-285 once weekly. One cycle was 4 weeks, consisting of 3 weeks of treatment and 1 week of observation without treatment. TAK-285 was given once daily (q.d.) or twice daily (b.i.d.). The dose was escalated from a starting dose of 50 mg until the MTD was determined. In the repeated administration cohort, patients were treated with oral TAK-285 at the MTD for at least 4 weeks in order to confirm safety. Patients continued to be treated with TAK-285 at the same dose level if the treatment was well tolerated and there was no evidence of progressive disease (PD).

The study was conducted in accordance with the protocol approved by the institutional review boards of the participating institutions, and with the Harmonized Tripartite Guideline of the International Conference on Harmonization for Good Clinical Practice.

Patient eligibility

Patients with histologically/cytologically confirmed metastatic or advanced cancer that was unresponsive to standard therapy were eligible for this study, provided that the following criteria were met: Eastern Cooperative Oncology Group performance status of 0–1; age of 20–74 years; life expectancy of at least 12 weeks; adequate bone marrow and organ function; at least 1 measurable lesion based on Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse *et al*, 2000) (patients with no measurable lesion were acceptable for the dose escalation cohort only); and no previous therapy with an EGFR or HER2 inhibitor (except for trastuzumab).

Dose escalation scheme

In the dose escalation cohort, the dose of TAK-285 was decided by consideration of adverse events (AEs) observed during the first cycle. If one of three patients had a dose-limiting toxicity (DLT), another three patients were added to the cohort. If none of three patients had a DLT, the dose in subsequent patients was increased to the next level. If there remained only one patient having a DLT, the dose was also increased to the next level, however, if >1 patient had a DLT, there was no progression to the next level. Dose escalation was continued until the MTD was determined. The dose of TAK-285 was increased by 100 or 40% in accordance with accelerated titration designs reported previously (Simon *et al*, 1997). A DLT was defined as any TAK-285-related grade 4 haematological toxicity, grade 3 or worse non-haematological toxicity, grade 3 or worse neutropenia ($<1000\,mm^{-3}$) with fever of 38 °C or higher, or toxicity resulting in cessation of treatment for >21 consecutive days (including the stipulated period of observation without treatment).

Endpoints

The primary study endpoints were to determine the MTD as well as PK profiles of TAK-285 and its metabolite, M-I (data on file, Takeda Pharmaceutical Company Limited). The secondary endpoints were objective response rate (complete response (CR) and partial response (PR)), disease control rate (CR, PR and stable disease (SD), for at least 12 weeks), and time to tumour progression, defined as the time from the first dose of TAK-285 until disease progression or death. Tumour response was assessed every 4 weeks by RECIST version 1.0 (Therasse *et al*, 2000).

Safety assessments

Safety evaluations included vital signs (oxygen saturation, body temperature, breathing rate, blood pressure and pulse), clinical laboratory tests, lung function tests (pulmonary surfactant protein-A, pulmonary surfactant protein-D, Krebs von den Lunge-6 and arterial blood gas analysis), chest X-ray, and 12-lead electrocardiogram (ECG). These tests were performed weekly with the exception of chest X-rays (every 4 weeks), arterial blood gas analysis (at screening) and ECG (4 time points each at screening, on day 1 and day 8, after DLT assessment, one time point every 4 weeks). All ECG charts were submitted to the ECG evaluation committee to assess cardiac function. Adverse events were graded based on the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0 (Bethesda, MD, USA).

PK analyses

In the dose escalation cohort, plasma samples for PK analysis were collected at predose and up to 72 h after single dose administration and on day 21 after repeated administration of TAK-285. Urine samples were also collected up to 24-h postdose. In the repeated administration cohort, plasma samples for PK analysis were collected at predose and up to 12-h postdose on days 1 and 28. Urine samples were also collected up to 12-h postdose each day. Concentrations of TAK-285 and M-I in plasma and urine were determined using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods. The plasma and urine samples were treated by liquid–liquid extraction and subjected to LC-MS/MS equipped with a reversed-phase column. The lower limit of quantification for both TAK-285 and M-I was $0.2\,ng\,ml^{-1}$ in plasma and $2\,ng\,ml^{-1}$ in urine when $50\,\mu l$ of the plasma sample and $55\,\mu l$ of the urine sample (containing $5\,\mu l$ of Tween 80 solution) were analysed. Tween 80 solution was added to the urine sample to prevent the adsorption of analytes onto the sample containers. The accuracy of the plasma assay (percentage deviation from nominal) ranged from −10.8 to 11.0% for TAK-285, and from −14.0 to 13.8% for M-I. The accuracy of the urine assay ranged from −7.7 to 7.0% for TAK-285 and from −9.5 to 8.8% for M-I. Pharmacokinetic parameters of TAK-285 and M-I were estimated for each patient using noncompartmental methods with Phoenix WinNonlin Version 6.1 (Pharsight, Mountain View, CA, USA).

Pharmacodynamic analyses

At screening and on day 15 after the start of repeated administration, 20 ml of peripheral blood was obtained and divided into two 10 ml exclusive use containers (CellSave tubes) filled with $300\,\mu l$ of preservative solution (4.6% Na-ethylenediaminetetraacetate, 36% cell preservative, 0.36% polyethylene glycol and 0.4% inert ingredients). The samples were stored at room temperature and processed within 72 h after sampling. The CellSearch System (Veridex LLC, Raritan, NJ, USA) was used for the isolation and enumeration of circulating tumour cells (CTCs), which were defined as nucleated cells lacking cluster of differentiation 45 and expressing cytokeratin.

RESULTS

Patient characteristics

A total of 26 patients were enrolled between July 2007 and May 2010, and received at least one dose of TAK-285. Demographic characteristics of patients are summarised in Table 1. Safety and efficacy were analysed for all 26 patients.

Table 1 Patient characteristics

	Dose level of TAK-285 (mg)							
	50[a]	50[b]	100[b]	200[b]	300[b]	400[b]	300[c]	Total (%)
Screened	4	4	5	5	7	2	9	36
Enrolled	4	3	3	4	4	2	6	26 (100)
Completed[d]	3	3	3	3	3	0	6	21 (80.8)
Not completed	1	0	0	1	1	2	0	5 (19.2)
Owing to pre-treatment event or adverse event	1	0	0	0	1	2	0	4 (15.4)
Owing to lack of efficacy	0	0	0	1	0	0	0	1 (3.8)
Sex								
Male	3	2	1	3	3	1	4	17 (65.4)
Female	1	1	2	1	1	1	2	9 (34.6)
Age (years)								
Median	67.0	58.0	65.0	61.0	62.5	63.0	59.5	61.5
Primary tumour								
Colon/rectal	2	3	2	3	0	2	0	12 (46.2)
Gastric	1	0	0	1	0	0	2	4 (15.4)
Oesophageal	0	0	0	0	1	0	2	3 (11.5)
Other	1	0	1	0	3	0	2	7 (26.9)
Performance status								
0	1	2	2	3	2	2	4	16 (61.5)
1	3	1	1	1	2	0	2	10 (38.5)

Abbreviations: b.i.d. = twice daily; q.d. = once daily. [a]Q.d. (dose escalation cohort). [b]B.i.d. (dose escalation cohort). [c]B.i.d. (repeated administration cohort). [d]Treatment for cycle 1 or the first 28 days completed.

DLT and MTD

The 26 patients received TAK-285 at a dose ranging from 50 to 400 mg q.d. or b.i.d., 20 patients made up the dose escalation cohort and the remaining 6 patients were the repeated administration cohort. Dose-limiting toxicities observed during the study were grade 3 increased alanine aminotransferase (grade 3) and increased aspartate aminotransferase in one patient, and decreased appetite in a second patient. Both patients were treated with TAK-285 400 mg b.i.d.; hence, the MTD was determined to be 300 mg b.i.d. In the repeated administration cohort, six patients received the MTD continually for 36–169 days.

Safety

Adverse events were observed in all 26 patients who received TAK-285; 22 (84.6%) of these AEs were considered to be related to TAK-285 treatment.

The most common grade of AEs related to TAK-285 was grade 2 or lower in 17 patients (65.4%), grade 2 in 11 (42.3%), grade 3 in 5 (19.2%); there were no grade 4 AEs related to TAK-285 administration. As noted above, grade 3 AEs related to TAK-285 treatment included DLTs in two patients: increased alanine aminotransferase and increased aspartate aminotransferase in one patient, and decreased appetite in a second patient. These patients were withdrawn from the study because their DLTs resulted in permanent discontinuation of TAK-285 treatment. No other patients were withdrawn from the study because of TAK-285 treatment-related AEs. One of two patients with DLTs had myocardial ischaemia, which was the only serious AE related to TAK-285 treatment observed during the study. Two patients died during the study; in both cases, the cause of death was aggravation of the primary disease and was considered to be unrelated to TAK-285 treatment. The time period from last dose to death was 33 and 25 days, respectively.

Table 2 Frequently reported adverse events (overall incidence ⩾ 10%)

	Dose level of TAK-285 (mg)							
	50[a]	50[b]	100[b]	200[b]	300[b]	400[b]	300[c]	Total (%)
Any adverse events	4	3	3	4	4	2	6	26 (100.0)
⩾Grade 3	3	0	1	1	1	2	4	12
Alanine aminotransferase increased	3	0	0	2	1	2	4	12 (46.2)
⩾Grade 3	1	0	0	0	0	1	2	4
Aspartate aminotransferase increased	2	0	1	2	0	2	5	12 (46.2)
⩾Grade 3	1	0	0	0	0	1	1	3
Rash	0	1	1	2	1	2	4	11 (42.3)
⩾Grade 3	0	0	0	0	0	0	0	0
Blood bilirubin increased	2	0	1	2	0	2	2	9 (34.6)
⩾Grade 3	1	0	0	0	0	0	0	1
Diarrhoea	0	0	1	1	2	2	3	9 (34.6)
⩾Grade 3	0	0	0	0	0	0	0	0
Constipation	1	1	1	1	1	1	1	7 (26.9)
⩾Grade 3	0	0	0	0	0	0	0	0
Gamma-glutamyltransferase increased	2	0	1	2	0	1	1	7 (26.9)
⩾Grade 3	2	0	0	1	0	0	1	4
Decreased appetite	1	1	0	1	0	2	1	6 (23.1)
⩾Grade 3	1	0	0	0	0	1	0	2
Pyrexia	0	0	2	0	3	0	1	6 (23.1)
⩾Grade 3	0	0	0	0	0	0	0	0
Blood alkaline phosphatase increased	1	0	1	1	1	1	0	5 (19.2)
⩾Grade 3	0	0	0	0	0	0	0	0
Blood lactate dehydrogenase increased	1	1	1	2	0	0	0	5 (19.2)
⩾Grade 3	1	0	0	0	0	0	0	1
Cancer pain	1	1	1	0	0	0	2	5 (19.2)
⩾Grade 3	0	0	0	0	0	0	1	1
Nausea	0	1	1	0	0	2	1	5 (19.2)
⩾Grade 3	0	0	0	0	0	0	0	0
Dry skin	1	0	0	0	1	1	1	4 (15.4)
⩾Grade 3	0	0	0	0	0	0	0	0
Vomiting	0	1	1	0	0	1	1	4 (15.4)
⩾Grade 3	0	0	0	0	0	0	0	0
Blood creatinine increased	1	0	0	0	1	0	1	3 (11.5)
⩾Grade 3	0	0	0	0	0	0	0	0
Haemoglobin decreased	1	0	2	0	0	0	0	3 (11.5)
⩾Grade 3	1	0	0	0	0	0	0	1
Stomatitis	0	0	0	2	0	0	1	3 (11.5)
⩾Grade 3	0	0	0	0	0	0	0	0

Abbreviations: b.i.d. = twice daily; q.d. = once daily. [a]Q.d. (dose escalation cohort). [b]B.i.d. (dose escalation cohort). [c]B.i.d. (repeated administration cohort).

Table 2 shows frequently reported AEs (having an overall incidence of ⩾ 10%). The most frequently reported AEs were increased alanine aminotransferase and aspartate aminotransferase, followed

by rash, increased blood bilirubin and diarrhoea. The incidences of AEs related to TAK-285 treatment were similar to the incidences of AEs in general. A slight dose-dependent relationship was observed for these AEs. Grade 2 rash and diarrhoea were reported in the dose groups in which DLTs were observed, while only grade 1 AEs were observed in lower dose levels.

No clinically significant changes were observed in lung function tests, chest X-rays, vital signs or ECGs.

Pharmacokinetic

The PK parameters of TAK-285 and M-I are summarised in Tables 3 and 4, respectively. Plasma concentrations of TAK-285 and M-I reached the maximum (C_{max}) within 2.5 h after single oral administration. The estimated terminal-phase half-life ($t_{1/2}$) was 6–9 h for TAK-285 and 7–10 h for M-I at all doses. The time to reach the maximal plasma concentration (T_{max}) and $t_{1/2}$ were not remarkably changed after multiple dosing. On day 21, mean plasma concentrations of TAK-285 increased over a dose range of 50–300 mg b.i.d., and mean concentrations of M-I increased over the TAK-285 dose range of 50–200 mg b.i.d. (Figure 1). A dose-proportional increase in the area under the plasma concentration-time curve over the dosing interval (AUC_{0-tau}) was suggested for TAK-285 after multiple dosing at doses ranging from 50 to 300 mg b.i.d. but was not clearly indicated for M-I (Figure 2). The accumulation ratios of C_{max} were 1.2–3.6 for TAK-285 and 1.2–2.6 for M-I. The accumulation ratios of AUC were 1.4–4.6 for TAK-285 and 1.4–3.7 for M-I. The mean cumulative excretion ratios of TAK-285 and M-I in urine (up to 12- or 24-h postdose following single or multiple dosing) were below 0.02% of the dose.

Table 3 Pharmacokinetic parameters of TAK-285 after single and multiple oral dosing of TAK-285

	Dose level of TAK-285					
Parameters	**50 mg q.d.[a]**	**50 mg b.i.d.[a]**	**100 mg b.i.d.[a]**	**200 mg b.i.d.[a]**	**300 mg b.i.d.[a]**	**300 mg b.i.d.[b]**
Single dosing						
N	4	3	3	4	4	5–6
C_{max} (ng ml^{-1})	214 (30.3)	234 (55.6)	379 (91.8)	965 (194)	1350 (469)	983 (545)
$AUC_{0-\infty}$ (ng × h ml^{-1})	1730 (423)	1970 (648)	2820 (1190)	9530 (4150)	11 500 (4750)	9210 (3840)
T_{max} (h)	1.49 (1.00–2.00)	1.00 (1.00–2.02)	2.00 (1.00–4.00)	2.48 (2.00–4.00)	2.00 (2.00–2.00)	2.03 (2.00–4.00)
$t_{1/2}$ (h)	7.27 (2.58)	6.45 (0.642)	9.43 (4.85)	6.57 (1.16)	7.50 (0.968)	6.10 (2.21)
Multiple dosing[c]						
N	3	3	3	3	3	5–6
C_{max} (ng ml^{-1})	260 (57.9)	358 (51.1)	774 (344)	2420 (156)	3700 (680)	2810 (1120)
AUC_{0-tau} (ng × h ml^{-1})	2210 (973)	2720 (778)	6090 (3140)	1700 (3970)	30 900 (6750)	26 400 (9840)
T_{max} (h)	2.00 (2.00–2.02)	2.05 (2.00–2.05)	2.00 (2.00–3.00)	2.00 (1.00–2.05)	2.00 (2.00–2.02)	2.97 (0.500–6.00)
$t_{1/2}$ (h)	8.69 (2.87)	7.49 (0.738)	7.79 (0.760)	6.95 (1.21)	8.25 (1.61)	11.1 (3.65)
R (C_{max})	1.20 (0.342)	1.55 (0.205)	2.00 (0.613)	2.70 (0.829)	3.12 (1.22)	3.62 (2.05)
R (AUC)	1.35 (0.331)	1.96 (0.148)	2.79 (0.792)	3.22 (0.677)	3.92 (1.69)	4.59 (2.14)

Abbreviations: AUC = area under the plasma concentration-time curve from time zero to infinity ($_{0-\infty}$) or to dosing interval ($_{0-tau}$); b.i.d. = twice daily; C_{max} = maximal observed plasma concentration after dosing; q.d. = once daily; R = accumulation ratio of C_{max} or AUC between multiple versus single dosing; R (AUC) = $AUC_{0\ tau}$ (treatment day D)/$AUC_{0\ 12}$ (treatment day 1) (dose escalation cohort: D = 21, repeated administration cohort: D = 28); T_{max} = time to reach the maximal plasma concentration; $t_{1/2}$ = estimated terminal-phase half-life. All parameters are reported as mean (± s.d.) values, except for T_{max} that is reported as a median (range) value. [a]Dose escalation cohort. [b]Repeated administration cohort. [c]Day 21 or day 28.

Table 4 Pharmacokinetic parameters of M-I after single and multiple oral dosing of TAK-285

	Dose level of TAK-285					
Parameters	**50 mg q.d.[a]**	**50 mg b.i.d.[a]**	**100 mg b.i.d.[a]**	**200 mg b.i.d.[a]**	**300 mg b.i.d.[a]**	**300 mg b.i.d.[b]**
Single dosing						
N	4	3	3	4	4	6
C_{max} (ng ml^{-1})	57.2 (11.7)	62.6 (16.4)	165 (35.4)	313 (106)	383 (79.9)	272 (190)
$AUC_{0-\infty}$ (ng × h ml^{-1})	401 (79.3)	494 (174)	1340 (350)	2870 (242)	3230 (911)	2710 (1690)
T_{max} (h)	1.49 (1.00–2.00)	2.00 (1.00–2.02)	2.00 (2.00–4.00)	2.00 (2.00–4.05)	2.00 (2.00–2.00)	2.50 (2.00–3.00)
$t_{1/2}$ (h)	8.32 (2.83)	7.54 (1.21)	9.70 (4.51)	7.40 (1.45)	10.0 (1.96)	6.99 (2.53)
Multiple dosing[c]						
N	3	3	3	3	3	6
C_{max} (ng ml^{-1})	68.0 (12.4)	96.1 (53.2)	302 (62.9)	767 (258)	549 (123)	584 (349)
AUC_{0-tau} (ng × h ml^{-1})	523 (26.3)	786 (451)	2660 (902)	6410 (3330)	4750 (1020)	5600 (3480)
T_{max} (h)	2.00 (1.00–2.02)	2.05 (2.00–3.00)	3.00 (3.00–4.05)	2.05 (2.00–3.00)	2.00 (2.00–2.02)	2.99 (0.500–3.98)
$t_{1/2}$ (h)	11.8 (3.99)	9.57 (2.11)	10.0 (2.38)	8.53 (1.42)	14.0 (3.17)	14.3 (7.44)
R (C_{max})	1.19 (0.202)	1.49 (0.526)	1.90 (0.651)	2.73 (2.02)	1.58 (0.456)	2.64 (1.41)
R (AUC)	1.40 (0.216)	2.27 (0.896)	2.99 (0.740)	3.58 (2.23)	2.42 (0.859)	3.68 (1.99)

Abbreviations: AUC = area under the plasma concentration-time curve from time zero to infinity ($_{0-\infty}$) or to dosing interval ($_{0-tau}$); b.i.d. = twice daily; C_{max} = maximal observed plasma concentration after dosing; q.d. = once daily; R = accumulation ratio of C_{max} or AUC between multiple versus single dosing; R (AUC) = AUC_{0-tau} (treatment day D)/AUC_{0-12} (treatment day 1) (dose escalation cohort: D = 21, repeated administration cohort: D = 28); T_{max} = time to reach the maximal plasma concentration; $t_{1/2}$ = estimated terminal-phase half-life. All parameters are reported as mean (± s.d.) values, except for T_{max} that is reported as a median (range) value. [a]Dose escalation cohort. [b]Repeated administration cohort. [c]Day 21 or day 28.

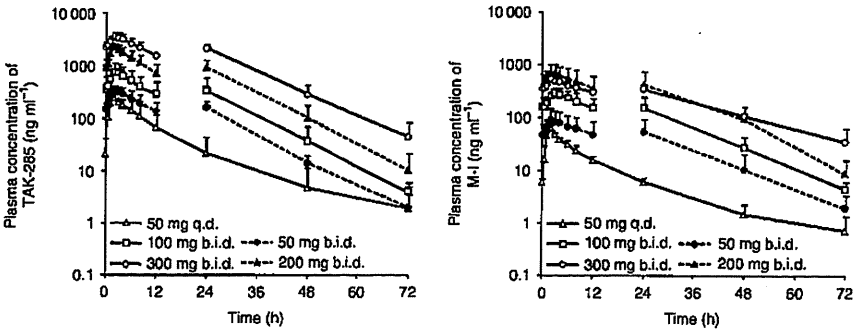

Figure 1 Mean plasma concentration-time profile of TAK-285 or M-I on day 21 in the dose escalation cohort. Mean ± s.d. ($n = 3-4$ at each dose level); TAK-285 was additionally dosed at 12 h postdose b.i.d.

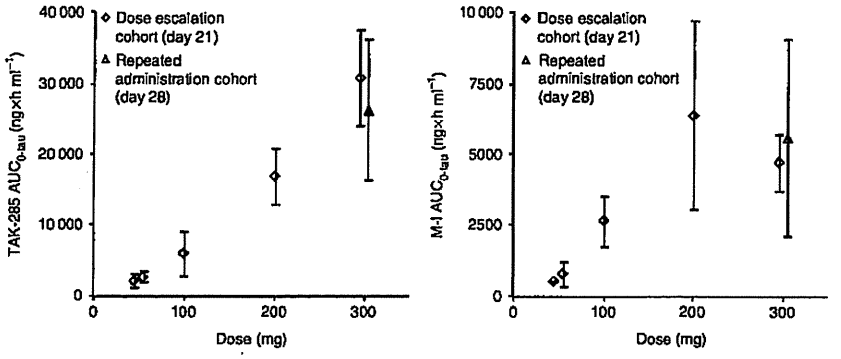

Figure 2 Relationship between dose and AUC_{0-tau} of TAK-285 or M-I after multiple oral administration of TAK-285 (day 21 or day 28). Data are mean ± s.d. ($n = 3-6$ at each dose level).

Pharmacodynamics

Circulating tumour cell samples both at screening and on cycle 1 day 15 after the start of repeated administration were obtained and evaluated in all patients except for those who were removed from study by cycle 1 day 15 and 1 patient with a coagulated blood sample on cycle 1 day 15. Overall, seven patients had unfavourable baseline counts ($\geqslant 5$ cells per 7.5 ml blood), none of which converted to a favourable count after TAK-285 treatment. Analysis of CTC data did not show significant changes after treatment with TAK-285.

Antitumour activity

One patient with parotid cancer (3.8%) achieved a PR lasting for 56 days. However, the remaining patients were reported as PD.

The maximum percentage decrease from baseline in tumour size (sum of measured lesions) was evaluated separately for all patients. Only one patient in the dose escalation cohort showed reduction in tumour size, whereas three of six patients in the repeated administration cohort showed reduction in tumour size.

The objective response rate and disease control rate were each 3.8% (1 of 26 patients), and the median time to tumour progression was 58 days.

DISCUSSION

Clinically, TAK-285 was very well tolerated in spite of the fact that AEs were observed in all patients. The most frequent AEs were increased alanine aminotransferase and increased aspartate aminotransferase, followed by rash, increased blood bilirubin and diarrhoea; these were similar to AEs seen with other inhibitors of the EGFR family of tyrosine kinases (Hidalgo *et al*, 2001; Herbst *et al*, 2002; Ranson *et al*, 2002; Arora and Scholar, 2005; Lacouture *et al*, 2006). The incidences of frequently reported AEs appeared to correlate with dose; however, because of the limited number of patients studied this relationship could not be confirmed.

Dose-limiting toxicities were observed in two patients receiving 400 mg b.i.d. in the dose escalation cohort, but were not observed in the repeated administration cohort receiving the MTD. A serious AE, myocardial ischaemia, related to TAK-285 was reported in one of two patients with DLTs (receiving 400 mg b.i.d.). This event was considered to be related to TAK-285 treatment because diarrhoea that developed after the start of treatment with TAK-285 was suspected to have aggravated pre-existing ischemic heart disease. The remaining serious AEs were regarded as unrelated to TAK-285 treatment. Two patients died during the study, and the cause of death was considered to be unrelated to TAK-285 treatment for both patients.

It was interesting that pneumonitis was not reported in this study and is in contrast to findings seen with gefitinib, another EGFR tyrosine kinase inhibitor (Inoue *et al*, 2003). In addition, no significant changes in ECG were reported despite the known expression of HER2 in cardiac myocytes (Slamon *et al*, 2001; Seidman *et al*, 2002; Negro *et al*, 2004). Similarly, rash induced by TAK-285 was relatively mild (i.e., grade 2 or lower; grade 1 in a majority of patients), compared with that seen with gefitinib and erlotinib (Shepherd *et al*, 2005; Thatcher *et al*, 2005). The correlation between the incidence of diarrhoea and dose, which was previously reported with lapatinib (Burris *et al*, 2009), was also examined in our study; a similar although smaller correlation was

observed with TAK-285. Diarrhoea was relatively mild (i.e., grade 2 or lower) in our study, and was grade 1 in a majority of patients.

In addition to evaluating the PK of TAK-285, the PK of the TAK-285 metabolite, M-I, was also evaluated. Laboratory studies revealed that M-I inhibits the kinase activities of HER2, EGFR, and HER4 with 50% inhibition concentrations of 98, 29 and 280 nmol l^{-1}, respectively (data on file, Takeda Pharmaceutical Company Limited). The C_{max} of TAK-285 and M-I was observed up to 2.5 h after single dose administration at all doses, indicating that absorption of TAK-285 was relatively rapid after oral administration. The $t_{1/2}$ values of M-I mirrored those of TAK-285 at all doses, and their concentrations in plasma declined in a similar manner. The accumulation of TAK-285 and M-I following multiple dose administration was considered to be moderate because the mean accumulation ratios for C_{max} and AUC were below 4.6 for both. A dose-proportional increase in exposure to TAK-285 at steady state was indicated over the dose range tested (50–100 mg b.i.d.), but the exposure to M-I did not increase with dose at 300 mg b.i.d. This suggests that metabolism of TAK-285 to M-I by hydroxylation may be saturated at higher doses. Urinary excretion of TAK-285 and M-I was negligible and indicated that renal excretion does not contribute significantly to the clearance of either TAK-285 or M-I.

The relationship between CTCs and prognosis has been reported for prostate and breast cancer (Cristofanilli *et al*, 2004; Danila *et al*, 2007), and the CTC test was approved by the FDA in January 2004. The association between CTCs and tumour response was not assessed sufficiently, because only one patient reported as PR, whose CTC number on day 15 was not available because of a coagulated blood sample. In this study, there were no significant changes in CTC number that might suggest therapeutic efficacy.

The antitumour response was rated as PR in one patient with parotid cancer in the repeated administration cohort. HER2 has been reported to be highly expressed in parotid cancer (Cornolti *et al*, 2007; Williams *et al*, 2010), and lapatinib was reported to be effective for the treatment of parotid cancer in a phase I study (Burris *et al*, 2009).

In summary, based upon its safety, tolerability profile, PK characteristics and potential antineoplastic activity in patients with advanced solid tumours, further evaluation of TAK-285 for the treatment of patients with solid tumours appears warranted.

Clinical Studies

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化学療法

Chemotherapy for esophageal cancer

室　圭

Key words：食道癌，化学療法，扁平上皮癌，CDDP+5FU療法，食道胃接合部癌

はじめに

食道癌は消化器領域の悪性腫瘍の中でも予後不良で根治困難な癌の一つである．2007年度の我が国の食道癌の死亡者数は11,669人であり，7番目に多い癌である．我が国の食道癌の90％以上が扁平上皮癌であり，腺癌は数％にすぎない．最近腺癌の報告が多くなっているが，少なくとも統計学的には腺癌増加傾向は明らかになっていない．一方，欧米では近年，食道扁平上皮癌が減少し腺癌が急増している．特に米国では食道癌症例の70％を腺癌が占めている状況であり，これは肥満の増加，それに伴う逆流性食道炎・バレット食道炎の増加に起因していると考えられている．このような状況ゆえに欧米では，食道癌と胃癌をesophagogastric cancerとして一括りにした治療開発が主体となってきており，扁平上皮癌である食道癌と，腺癌である胃癌を明確に区別して治療体系を構築している我が国とは大きな隔たりがある．また，基本となる手術成績は，概して日本の成績は欧米に比し良好である．

以上のように，同じ食道癌であっても我が国と欧米ではそのバックグラウンドが大きく異なっている状況である．食道癌の手術療法はもとより，化学療法，化学放射線療法に関しても，我が国と欧米のデータを同一視することは困難である．このことから，多くのエビデンスを発信している欧米の臨床試験データを十分参考にしつつも，我が国独自の臨床試験や我が国と同じ状況下にあるアジアでの臨床試験が極めて重要になってくる．

1．各Stageにおける手術，化学療法，化学放射線療法の位置づけ

図1に新しい第7版のUICC-TNM分類に基づく各Stage別の至適治療法を示した．実際には，我が国と諸外国，あるいは施設の違いによる各治療のウエイトの差や偏りはみられるものの，絶対の治療法というものは存在せず，手術療法や化学放射線療法を軸とした集学的治療が行われているのが現状である．図1で着目すべきは，すべてのStageにおいて薬物療法が入ってきていることである．食道癌全体の治療成績向上には，どういう治療法をどの場面でどういう順番で行うべきかという戦略開発が重要なポイントである．加えて，有望な全身化学療法の開発が手術不能進行・再発食道癌のみならず，手術可能食道癌の術前化学療法や根治的化学放射線療法の治療成績向上にも寄与しうること，つまり，すべてのStageにおいて，他癌種より成績の悪い予後不良の食道癌治療の成績向上のために，有望な化学療法の開発が必要不可欠であることを強く認識すべきである．

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Stage	T	N	M	treatment
0	Tis	N0	M0	✓EMR ✓surgery ✓chemoradiotherapy
IA	T1	N0	M0	
IB	T2	N0	M0	✓surgery (+chemotherapy) ✓chemo (radio) therapy+surgery ✓chemoradiotherapy (+salvage surgery)
IIA	T3	N0	M0	
IIB	T1, 2	N1	M0	
IIIA	T4a	N0	M0	
	T3	N1	M0	
	T1, 2	N2	M0	
IIIB	T3	N2	M0	
IIIC	T4a	N1, 2	M0	✓chemoradiotherapy ✓chemotherapy (+surgery)
	T4b	any N	M0	
	any T	N3	M0	
IV	any T	any N	M1	✓chemo (radio) therapy

図1 UICC-TNM分類(第7版2009年度版)に基づく治療法の選択

表1 食道癌に対する化学療法の位置づけ

①遠隔転移例に対する症状緩和，延命効果を期待
②術前・術後化学療法として用いて，無再発生存期間や生存期間の延長を期待
③放射線照射と同時併用させて，化学放射線療法の治療成績向上を期待
—根治目的化学放射線療法として行いCR率向上，生存期間延長を期待
—術前化学放射線療法として行い切除率向上，生存期間延長を期待

以上のことから，食道癌治療においては，手術，放射線，抗癌剤のどれもが重要であり，これらを組み合わせた集学的治療が必須である．つまり，外科医，放射線治療医，腫瘍内科医による集学的治療をまさに実践している，他領域にはあまりみられない癌種といえる．

食道癌に対する化学療法は，①遠隔転移を有する症例に対する症状緩和や延命を目的とした全身化学療法，②根治切除率の向上と生存成績向上を目指した術前・術後の化学療法，③切除可能例を対象にした根治目的の化学放射線療法あるいは術前の化学放射線療法，以上3つに大別される(**表1**)．食道癌は集学的治療が必須である癌種であるが，その中でも化学療法はあらゆる場面で用いられ，食道癌治療の重要な鍵を握っている．

本稿では**表1**の①，すなわち食道癌の全身化学療法に的を絞り，現在の置かれている状況や今後の展望などを含めて記述する．

2. シスプラチン(CDDP)+5-フルオロウラシル(5FU)療法

手術や化学放射線療法の適応とならない遠隔転移例および術後再発例に対しては，全身化学療法が行われる．しかし，食道癌を対象とした全身化学療法の比較試験は国内外でほとんど存在せず，確立された標準治療はない．そんな中，一般臨床において，CDDP+5FU(CF)療法[1]が遠隔転移例および術後再発例に対する標準的治療(基準治療)の位置づけである．諸家の報告をまとめると，おおむね奏効率は25-35%，生存期間中央値(MST)は5-9カ月である．現在，全身化学療法としての我が国の標準的用量は，CDDP day 1 80 mg/m^{2}点滴静注，5FU days 1-5 800 mg/m^2 5日間持続点滴静注を4週間間隔で行う方法である．プラチナ製剤+フッ化ピリミジン系薬剤の組み合わせは長年にわたり食道癌治療の中心的な役割を担っており，現在もこ

表2 JCOG 9407（CDDP+5FU療法）とJCOG 9905（NDP+5FU療法）の比較

	JCOG 9407[1]（CDDP+5FU）	JCOG 9905[2]（NDP+5FU）
血液毒性	軽度	軽度～中等度
非血液毒性	軽度	軽度
奏効率	33.3％	39.5％
50％生存期間	201.5日	267日
1年生存割合	27.8％	33.7％

れらの誘導体（ネダプラチン，オキサリプラチンなど）を用いた治療開発が行われている．

3. その他のプラチナ製剤＋フッ化ピリミジン系薬剤の組み合わせ

第2世代のプラチナ化合物であるネダプラチン（NDP）を使ったNDP+5FU療法[2]の第II相臨床試験の結果は表2に示すとおり，CF療法を凌駕するものではなかった．NDP+5FU療法は，腎臓へのダメージが少なく補液がほとんどいらないことから，実地臨床においては，腎機能低下をきたしている症例や高齢者，循環器疾患を有する症例には有利かもしれない．しかし，このような症例ではもちろん，CDDPより若干高度である骨髄抑制には十分な留意が必要である．

また，プラチナ製剤としてCDDP（C）をオキサリプラチン（O）に置き換えたFOLFOX療法[3]や，更に5FU（F）をカペシタビン（Xeloda：X）にしたXELOX療法などの食道癌に対する治療の報告も近年多く，その有用性が示唆されている．Cunninghamらは，esophagogastric cancerとして全体の約1/3の症例を食道癌，残り2/3の症例を胃癌と食道胃接合部癌が占める対象（腺癌約90％，扁平上皮癌約10％）で，エピルビシン（E）にプラチナ製剤＋フッ化ピリミジン系薬剤併用療法を加えた4レジメンの比較試験を行い，Fに対するXの，Cに対するOのそれぞれ非劣性を検証した．また，コントロールアームのECF療法よりEOX療法が，全生存期間において有意に良好な成績を示す結果を報告した[4]．

4. タキサン系抗癌剤単独，3剤併用療法

a. タキサン系抗癌剤単独療法

上記以外で食道癌に有望な薬剤として，タキサン系抗癌剤（パクリタキセル（paclitaxel）/ドセタキセル（docetaxel））が挙げられる．表3に単剤での主な治療成績を示したが，単剤であればCF療法後の2nd lineとしての有用性が期待できる．我が国でweekly paclitaxelの治験を行い，かなり良好な成績が得られた[9]（表3）が，承認が得られず，CF療法後の2nd lineとしてドセタキセルが頻用されている．我が国において，ドセタキセル70mg/m²の3週1回投与のスケジュールで第II相臨床試験が行われ，20％の奏効率を認めた[8]が，特に化学放射線療法後の症例での投与は骨髄抑制に十分な注意が必要である．

b. 3剤併用療法

最近，胃癌，頭頸部癌など複数の癌種でCF療法にタキサン系抗癌剤であるタキソテール（Taxotere）を付加させたTCF（TPF）療法の有用性に関する試験結果が相ついで報告されている．遠隔転移を有する進行胃癌を対象としたTCF（Taxotere+CDDP+5FU） vs CF（CDDP+5FU）の比較試験（TAX 325）では，奏効率，無増悪生存期間（PFS），生存期間（OS）いずれもTCF群で有意に良好な結果が得られた[10]．本試験結果から，TCF療法は毒性が強く治療対象症例は限られるものの胃癌の新たな標準治療の一つとなった．しかし，最近では欧米中心にTCF療法の各薬剤の投与量を減量し毒性を軽減させたmodified TCF療法が胃癌領域で普及しつつある．また，切除不能進行頭頸部癌の放射線療法の導入化学療法としてTPF（Taxotere+CDDP+5FU） vs PF（CDDP+5FU）の比較試験（TAX 323/EORTC 24971）[11]，局所進行型頭頸部癌に対する臓器温存を目指した化学放射線療法（CBDCA+RT）の導入化学療法としてのTPF vs PFの比較試験（TAX 324）[12]が相ついで報告され，両試験ともTPF群において，PFS，OSの有意な延長が確認された．

以上より，胃癌（腺癌），頭頸部癌（扁平上皮