A Phase II Trial of Trastuzumab Combined with Irinotecan in Patients with Advanced HER2-positive Chemo-refractory Gastric Cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group OGSG1203 (HERBIS-5)

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Irinotecan is a key drug in second- or further-line chemotherapy for patients with advanced gastric cancer. Continuous administration of trastuzumab beyond first progression is expected to contribute to the benefit of chemotherapy for human epidermal growth factor receptor 2-positive gastric cancer. The aim of this trial is to evaluate the efficacy and safety of combination chemotherapy with trastuzumab and irinotecan in Japanese patients with advanced human epidermal growth factor receptor 2-positive chemo-refractory gastric cancer. The primary endpoint is the disease control rate. The secondary endpoints are adverse events, overall response rate, time to treatment failure, progression-free survival, overall survival and response rate stratified by prior trastuzumab use. A total of 30 patients will be enrolled in this Osaka Gastrointestinal Cancer Chemotherapy Study Group trial.

Key words: chemo-GI tract HER2-positive – trastuzumab – irinotecan

INTRODUCTION

The worldwide standard of care for first-line treatment of unresectable or recurrent gastric cancer is systemic chemotherapy with platinum and fluoropyrimidine drugs. However, the standard for second-line chemotherapy after failure of the first-line regimen remains to be established. Several Phase III studies have shown a survival benefit with second-line chemotherapy in comparison with best supportive care (1–3). A Japanese trial (WJOG4007) comparing second-line irinotecan (CPT-11) with weekly paclitaxel concluded that neither regimen was superior in terms of efficacy or tolerability (4). One explanation for this may have been the high rate of crossover in subsequent treatment. CPT-11 and taxanes may be also key drugs in second- or further-line chemotherapy for gastric cancer.

Human epidermal growth factor receptor 2 (HER2; also known as ERBB2) is a member of a family of receptors associated with tumor cell proliferation, apoptosis, adhesion, migration and differentiation. HER2 is over-expressed in ~20% of gastric cancer cases (5–7). Trastuzumab, a monoclonal antibody that targets HER2, induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated
signaling and prevents cleavage of the extracellular domain of HER2. In advanced HER2-positive gastric or gastro-esophageal junction cancer, trastuzumab has shown a survival benefit in first-line combined with standard chemotherapy (8).

Many targeted drugs have shown efficacy of continuation treatment beyond progression (9–11), including bevacizumab in colorectal cancer, rituximab in malignant lymphoma and erlotinib in non-small-cell lung cancer. There is also some evidence to support the benefit of continuing anti-HER2 therapy beyond first progression in HER2-positive metastatic breast cancer (12,13). Therefore, continuous administration of trastuzumab beyond first progression is recommended in clinical practice guidelines on the treatment of breast cancer (14).

Trastuzumab showed at least an additive antitumor effect when combined with CPT-11 in preclinical models of gastric cancer (15). Moreover, the efficacy of FOLFIRI plus trastuzumab has been reported in a retrospective analysis (16). The combination of CPT-11 with trastuzumab showed promising results in the treatment of metastatic breast cancer (17).

Therefore, the goal of this study is to conduct an open-label multicenter Phase II study to evaluate the efficacy and safety of combination therapy with trastuzumab and CPT-11 in refractory gastric cancer.

The Protocol Review Committee of the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) approved the study protocol in July 2012, and the study was initiated in August 2012. This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000008626 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGESTS OF THE STUDY (OGSG1205)

OBJECTIVE

OGSG1205 is an open-label multicentre Phase II study aimed at evaluating the efficacy and safety of combination therapy with trastuzumab and CPT-11 in patients with advanced HER2-positive chemo-refractory gastric cancer.

RESOURCES

This study is supported by the OSGS.

ENDPOINTS

The primary endpoint of this study is disease control rate (DCR), defined as the proportion of patients showing a complete response, partial response or stable disease as the best overall response according to RECIST. The secondary endpoints are rates of adverse events, overall response rate, time to treatment failure, progression-free survival (PFR), overall survival (OS) and response rate stratified by prior trastuzumab use.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

For inclusion in the study, patients will be required to fulfill all of the following criteria:

(i) Pathologically confirmed unresectable or recurrent gastric adenocarcinoma or adenocarcinoma of the gastro-esophageal junction.
(ii) HER2-positive confirmed by IHC and/or FISH (IHC 3- or IHC 2- and FISH-positive).
(iii) Disease progression during or after one or more cycles of previous chemotherapy.
(iv) Measurable or nonmeasurable target lesions according to RECIST criteria version 1.1.
(v) Aged ≥20 years.
(vi) Performance status (ECOG scale) of 0 or 2.
(vii) Sufficient oral intake.
(viii) Adequate baseline organ and marrow function.
(ix) Left ventricular ejection fraction of ≥50%.
(x) Written informed consent.
(xi) Inclusion of either trastuzumab and/or taxanes in prior chemotherapy permitted.

EXCLUSION CRITERIA

Patients were excluded from the study if they met any of the following criteria:

(i) Other malignancy within previous 5 years (except carcinoma in situ of cervix or basal cell carcinoma).
(ii) A history of CPT-11 use.
(iii) Local and/or general active infectious disease.
(iv) Serious complications such as bleeding in digestive tract, ileus, intestinal paralysis, interstitial pneumonia, pulmonary fibrosis, ischemic heart disease or cardiac dysrhythmia, heart failure, renal failure, hepatic cirrhosis, glaucoma and uncontrolled diabetes mellitus.
(v) Uncontrolled diarrhea.
(vi) A history of severe drug hypersensitivity.
(vii) Middle or large volume of ascites and/or pleural fluid.
(viii) Necessity for continuous administration of steroids.
(ix) Difficulty on registration in this study due to psychological disease.
(x) Central nerve metastasis.
(xi) Need for treatment with atazanavir sulfate.
(xii) Women in pregnancy, at risk of pregnancy or hoping to become pregnant; men who wanted their partners to become pregnant.
(xiii) Patients with active hepatitis type B and/or hepatitis C.
(xiv) Judged to be unsuitable for inclusion in the study by the investigator.

REGISTRATION

After written informed consent is obtained, an eligibility report form will be sent to the OSGSG Data Center, where
eligible patients will be subsequently enrolled in the trial. Information regarding any necessary follow-up tests will be then sent out from the registration center.

**TREATMENT METHODS**

Intravenous infusion of CPT-11 every 2 weeks at a dose of 150 mg/m²; intravenous infusion of trastuzumab at a dose of 8 mg/kg on Day 1 of the first cycle, followed by 6 mg/kg every 3 weeks. Administration of CPT-11 and trastuzumab will be repeated in independent schedules. Treatment will be continued until disease progression, unacceptable toxicity or withdrawal of consent. CPT-11 dose adjustment is allowed according to toxicity. Trastuzumab toxicity is managed by treatment interruption.

**FOLLOW-UP**

Physical and safety evaluations and laboratory tests are performed prior to the initiation of treatment. Responses are evaluated every 2 months or earlier if there are indications of treatment failure due to toxicity. All eligible patients are to be included in the assessment of efficacy and safety. Non-evaluable patients will be added to the efficacy assessment dataset as ‘not evaluable. The following dates will be recorded: (i) date of treatment commenced; (ii) date of disease progression; (iii) final date of assessment of survival and (iv) date of death.

**STATISTICAL ANALYSIS**

The primary endpoint of this study is the DCR, which will be summarized in terms of percentage, with a 95% confidence interval. The DCR is calculated primarily based on the assessment of the central radiologic review. All results will be analyzed in the full analysis set (FAS), which will include all patients, except those deemed to be ineligible after registration. The DCR will be calculated in the FAS as the primary end point. The sample size of this study will be 30 eligible patients, except those deemed to be ineligible after registration. Responses are evaluated every 2 months or earlier if there are indications of treatment failure due to toxicity. All eligible patients are to be included in the assessment of efficacy and safety. Non-evaluable patients will be added to the efficacy assessment dataset as ‘not evaluable. The following dates will be recorded: (i) date of treatment commenced; (ii) date of disease progression; (iii) final date of assessment of survival and (iv) date of death.

**MONITORING**

In-house monitoring will be performed every 6 months by the OSGSG Data Center to evaluate study progress and ensure study quality.

**Conflict of interest statement**

None declared.

**References**