Meta-analysis of patient-level data on biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer with the TCOG GI-0801 BIRIP and ECRIN TRICS RCTs: protocol paper

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Abstract

This meta-analysis will be performed to evaluate the safety and efficacy of biweekly CPT-11 plus CDDP versus CPT-11 alone in patients with advanced gastric cancer (AGC) who had received S-1-based first-line chemotherapy. Individual patient-level data from two prospective randomized trials employing the same regimens in the second-line setting for advanced or recurrent gastric cancer will be collected for the study. The primary endpoint is overall survival. Subset analysis will be performed to identify differences in 1) cases with metastatic progression or early relapse after adjuvant chemotherapy, 2) previous platinum therapy, and 3) histological intestinal or diffuse type. Cumulative data from 298 patients will help define a better regimen for S-1 failure cases and might give an important information in selecting a more suitable regimen for subsets of patients.

Keywords: Meta-analysis, Gastric cancer, Second-line chemotherapy, Biweekly irinotecan plus cisplatin, Irinotecan

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Introduction

Gastric cancer is the third leading cause of cancer death worldwide¹⁾. The most commonly used first-line treatment for advanced and recurrent gastric cancer (AGC) is combination chemotherapy consisting of a fluoropyrimidine plus a platinum agent with or without docetaxel or anthracyclines²⁻⁶⁾. However, in most patients, second-line treatment will eventually become necessary, mainly as a result of tumor progression. Among patients treated with curative gastrectomy and adjuvant chemotherapy, some develop early recurrence after completion of adjuvant therapy with S-1 or capecitabine and oxali-

platin^{7,8)}.

Four randomized studies have shown that second-line chemotherapy (SLC) such as irinotecan, docetaxel monotherapy, or ramucirumab was able to provide a survival benefit in patients with advanced gastric cancer in whom first-line chemotherapy has failed⁹⁻¹²⁾. Currently, no SLC regimen has been established for patients with AGC.

Irinotecan (CPT-11) plus CDDP combination therapy or CPT-11 monotherapy has commonly been used as second-line treatment for AGC in Asia¹³⁻¹⁶⁾. In a previous phase II study of CPT-11 monotherapy as SLC, CPT-11 was reported to cause frequent diarrhea and febrile neutropenia¹⁵⁾. Consequently, CPT-11/CDDP combination therapy was developed to reduce CPT-11-associated diarrhea and febrile neutropenia by decreasing the dose of CPT-11^{13,14)}. Moreover, a phase I/II study of biweekly CPT-11/CDDP combination therapy showed promising efficacy and a manageable toxicity profile¹⁴⁾. The combination of CPT-11/CDDP might be a promising regimen

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as SLC to replace CPT-11 mono-therapy.

Recently, two randomized trials employing the same regimen of biweekly CPT-11 plus CDDP versus CPT-11 alone in the second-line setting have been reported^{17, 18}. Higuchi et al. reported ($n = 130$) that biweekly CPT-11 plus CDDP significantly prolonged progression free survival (PFS) (HR: 0.68) compared with CPT-11 alone, but did not demonstrate an overall survival (OS) benefit (HR: 1.00) in patients with metastatic or recurrent gastric cancer that progressed after S-1-based first-line chemotherapy¹⁷. Nishikawa et al. reported ($n = 168$) that CPT-11/CDDP combination therapy did not show significant benefit in terms of OS (HR: 0.83) or PFS (HR: 0.86) compared with CPT-11 alone in patients with progressive AGC previously treated with S-1 monotherapy¹⁸. In a subset analysis confined to intestinal-type tumors, CPT-11/CDDP combination therapy was associated with significantly better OS than CPT-11 monotherapy (median OS: 15.8 months vs. 14.0 months; HR: 0.569).

These findings are limited in that the two trials showed no overall survival benefit and no differences in response rate between the two regimens. This was likely because the analysis was underpowered. It still remains unclear whether biweekly CPT-11 plus CDDP is effective in patients who had already received platinum therapy. There is no confirmation that biweekly CPT-11 plus CDDP could result in better OS for intestinal-type gastric adenocarcinoma than CPT-11 monotherapy.

Based on these findings, we will be performed a meta-analysis to compare the safety and efficacy of biweekly CPT-11 plus CDDP and CPT-11 monotherapy in patients who have been enrolled in these two recent randomized trials. We have described the details of this trials as the protocol paper here.

Protocol digest of the study

Purpose

The purpose of the study is to evaluate the safety and efficacy of biweekly CPT-11 plus CDDP compared to CPT-11 monotherapy in patients with advanced gastric cancer who had received S-1-based first-line chemotherapy.

Endpoints

The primary endpoint is overall survival (OS). Secondary endpoints are progression-free survival (PFS), time to treatment failure (TTF), overall response rate (RR), disease control rate (DCR), and incidence of adverse events. These parameters are also evaluated in each subset. Subsets consist of metastatic cases with progression or cases of early relapse after adjuvant chemotherapy, previously platinum therapy, and histological intestinal or diffuse type.

Resources

This work is supported by the non-profit organization Epidemiological & Clinical Research Information Network (ECRIN) and the Tokyo Cooperative Oncology Group (TCOG).

Selection of the studies

We selected two studies, the TRICS trial¹⁸ and the TCOG GI-0801/BIRIP trial¹⁷. We selected these two trials because they were randomized phase III trials employing the same regimen of biweekly CPT-11 plus CDDP versus CPT-11 alone in a second-line setting for advanced or recurrent gastric cancer. In these two trials, eligibility criteria were equivalent and treatment methods were exactly the same.

Statistical methods

All clinical data were extracted and held centrally at the ECRIN data center. All reported P values will be two-tailed. $P < 0.05$ was chosen as the threshold for statistical significance. An academic statistician will conduct all statistical analyses using SAS version 9.3 (SAS Institute, Cary, NC, USA). Missing data will be substituted using the multiple imputation method.

Primary analysis

We will *first* verify the integrity of individual patient-level data (IPD) from the TRICS and TCOG GI-0801/BIRIP trials by comparing their descriptive statistics to the published figures. Overall survival, progression-free survival, and time to treatment failure by treatment group and trial will be described using Kaplan-Meier methods. Distributions of clinical and pathological factors, including age, sex, performance status, histologic type, disease status, gastrectomy, prior platinum agent, measurable lesion, and peritoneal metastasis will be described and compared across trials using ANOVA or Fisher's exact test. Hazard ratios for biweekly CPT-11 plus CDDP vs. CPT-11 alone will be estimated using Cox regression with adjustment for clinical and pathological factors. Tumor responses were classified using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria as complete response (CR), partial response (PR), stable disease (SD), or PD. RR is defined as the proportion of patients with CR or PR, and DCR is defined as the proportion of patients with CR, PR, or SD. Adverse events were evaluated using CTCAE version 3.0.

Identification of predictive factors of overall survival for specific regimens

We will further explore factors that predict efficacy of biweekly CPT-11 plus CDDP versus CPT-11 alone. Overall survival by treatment group and subgroups defined according to clinical and pathological factors will be described using Kaplan-Meier methods. Hazard ra-

Fig. Trial flowchart

tios, 95% confidence intervals, and *P* values of the treatment groups will be estimated using Cox regression with adjustment for clinical and pathological factors. Tests for treatment-subgroup interactions will be examined using Cox regression by including a treatment-subgroup interaction term and clinical and pathological factors as covariates. Hazard ratios, 95% confidence intervals, *P* values, and baseline survival functions of final models that include significant interactions will be estimated.

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Compliance with Ethical Standards:

Conflicts of Interest

Dr. Nishikawa has received grants and personal fees from Yakult Honsha, personal fees from Taiho Pharmaceutical, personal fees from Eli Lilly, personal fees from Chugai Pharmaceutical, outside the submitted work. T. Yamanaka S. has received personal fees from Takeda, Taiho, Chugai and Boehringer, outside the submitted work. Morita has received personal fees from Daiichi-Sankyo, outside the submitted work. T. Tsujinaka has received personal fees from Lilly, outside the submitted work. All remaining authors have declared no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Clinical trial information: UMIN 000025367

Informed consent

Informed consent was obtained from all individual participants included in the study.

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