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Original Research

A multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer (EPOC1201)☆

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KEYWORDS
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Abstract ***Aim:*** American phase I studies have reported that the recommended dose of TAS-102 (trifluridine/tipiracil) was 25 mg/m^2 twice a day (b.i.d.), although this schedule did not provide clinically relevant improvements in a phase II study of advanced gastric cancer (AGC). However, a pivotal phase III study revealed that TAS-102 at 35 mg/m^2 b.i.d. provided a clinically relevant improvement in overall survival (OS) among patients with metastatic colorectal cancer. Therefore, we re-evaluated the efficacy, safety, and pharmacokinetic parameters of TAS-102 at 35 mg/m^2 b.i.d among Japanese patients with AGC.
Methods: All patients had undergone one or two previous chemotherapy regimens that contained fluoropyrimidine, platinum agents, and taxanes or irinotecan. The primary end-point target was a disease control rate (DCR) of $\geq$50% after 8 weeks of the 35 mg/m^2 b.i.d. schedule.
Results: Twenty-nine patients were assessable after completing the 35 mg/m^2 b.i.d. schedule. The investigator-determined DCR was 65.5% (95% confidence interval [CI], 45.7–82.1%) and the independent central review's DCR was 51.9% (95% CI, 31.9–71.3%); both results exceeded the primary end-point target. The median progression-free survival and OS were 2.9 months (95% CI, 1.1–5.3 months) and 8.7 months (95% CI, 5.7–14.9 months), respectively. The grade III/IV adverse events included neutropenia (69.0%), leucopaenia (41.4%), anaemia (20.7%), and anorexia (10.3%). No AGC-specific toxicities were detected.
Conclusions: The 35 mg/m^2 b.i.d. dose of TAS-102 provided positive efficacy and an acceptable toxicity profile in patients with AGC. A randomised, double-blind, placebo-controlled, phase III study is ongoing to validate these findings.
Clinical trial registration number: UMIN000007421

1. Introduction

Gastric cancer is the third leading cause of cancer mortality, with 723,000 estimated deaths each year [1]. Fluoropyrimidine and platinum-based chemotherapies, with or without trastuzumab, are considered the global standards for first-line chemotherapy in patients with unresectable and recurrent gastric cancer [2,3]. Furthermore, taxanes, irinotecan, and ramucirumab (a novel vascular endothelial growth factor receptor-2 antibody) have recently emerged as standard second-line chemotherapy options [4–6]. However, the prognosis of patients with advanced or recurrent gastric cancer remains poor, with a median overall survival (OS) of 12 months.

TAS-102 (Taiho Pharmaceutical, Tokyo, Japan) is a novel oral nucleoside antitumour agent that comprised trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio of 1:0.5 [7]. Five independent American phase I studies have defined the recommended dose schedule for TAS-102 as a 28-day cycle, with treatment on days 1–5 and 8–12 [8,9], and the maximum tolerated dosage was defined as 25 mg/m^2 twice a day (b.i.d.) in patients with intensively pre-treated breast cancer. However, an American phase II study of 25 mg/m^2 b.i.d. in patients with advanced gastric cancer (AGC) revealed only 1 case (5.6%) of stable disease (SD) among 18 patients and that study was closed after the first stage [10]. A phase I study was subsequently conducted in Japan, which evaluated a dosage of 35 mg/m^2 b.i.d., using the 28-day cycle from the American studies. This Japanese study reported grade IV neutropenia as a dose-limiting toxicity (DLT) in the 35 mg/m^2 b.i.d. schedule, and a higher dosage (40 mg/m^2 b.i.d.) was considered intolerable [11]. Therefore, a Japanese randomised phase II study and the international randomised phase III RECOURSE (Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care [BSC] versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) study evaluated the 35 mg/m^2 b.i.d. dosage and reported clinically relevant improvements in OS and progression-free survival (PFS), compared to the placebo, among patients with metastatic colorectal cancer [12,13]. The results of the phase III study supported the approval of TAS-102 by the US Food and Drug Administration.

Because two patients with AGC did not exhibit severe toxicities at the 35 mg/m^2 dosage in the Japanese phase I study [11], we hypothesised that the 35 mg/m^2 b.i.d. dosage of TAS-102 would be feasible in patients with AGC. Therefore, we planned this open-label, single-arm, multicenter phase II study to evaluate the efficacy, safety, and pharmacokinetic (PK) profiles of TAS-102 monotherapy in patients with AGC.

2. Methods

2.1. Patient eligibility

This phase II study was conducted at six Japanese institutions and complied with the Declaration of Helsinki and the Good Clinical Practice guidelines. The study's protocol was independently prepared by the