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Original Article

Molecular Biomarker Study in a Randomised Phase III Trial of Irinotecan Plus S-1 versus S-1 for Advanced Gastric Cancer (GC0301/TOP-002)

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Abstract

Aims: Gastric cancer is a common and heterogeneous disease; however, global standard and biomarkers for selecting chemotherapy regimens have not been established. This study was designed retrospectively to identify molecular biomarkers for irinotecan plus S-1 (IRI-S) and S-1 therapy from subset analyses in GC0301/TOP-002, a randomised phase III trial for advanced gastric cancer.
Materials and methods: Paraffin-embedded primary tumour specimens were collected from 126 of 326 randomised patients in GC0301/TOP-002. The mRNA was measured for thymidylate synthase, dihydropyrimidine dehydrogenase, topoisomerase I, excision repair cross-complementing gene 1 (ERCC1) and thymidine phosphorylase; categorised into low and high to analyse their association with efficacy end points.
Results: There was no significant difference in each mRNA between S-1 and IRI-S groups, whereas there were differences among some clinical characteristics. Multivariate analyses for overall survival showed that mRNA levels were not correlated with prognosis. By comparison, between IRI-S and S-1 arms, low thymidylate synthase, low ERCC1 and high thymidine phosphorylase were associated with better prognosis for IRI-S versus S-1 (hazard ratio = 0.653, 0.702 and 0.709, respectively; $P < 0.15$ for each interaction).

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Conclusion: Low thymidylate synthase, low ERCC1 and high thymidine phosphorylase are candidates for predictive biomarkers for first-line treatment in advanced gastric cancer by IRI-S. Further study is warranted to confirm these results in other clinical trials and cohort studies.
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Key words: Excision repair cross-complementing gene 1; gastric cancer; irinotecan; predictive factor; thymidine phosphorylase; thymidylate synthase

Introduction

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer mortality [1]. Despite recent advances in systemic chemotherapy, an optimal global standard has not yet been defined in advanced gastric cancer [2]. Cisplatin and 5-fluorouracil (5-FU) was the preferred first-line chemotherapy worldwide, and oral fluoropyrimidines, S-1 or capecitabine can substitute for 5-FU [3,4]. S-1 plus cisplatin has become the standard treatment in Japan from the results of the SPIRITS trial [5]. However, toxicities of cisplatin are relatively high [6] and sometimes patients are not eligible due to low renal function or postoperative gastrointestinal sequela. Taxanes and irinotecan are other key drugs for treating advanced gastric cancer, especially in the second-line setting [7,8]. In the JCOG9912 trial, S-1 was non-inferior to 5-FU, but irinotecan plus cisplatin was not superior to 5-FU (hazard ratio 0.85, $P = 0.055$) with higher toxicities [3]. START was a randomised trial in the first-line setting to evaluate the effect of adding docetaxel to S-1 without platinum, which showed the effectiveness of docetaxel (similar to cisplatin) [9]. In GC0301/TOP-002, which was a randomised trial of irinotecan plus S-1 (IRI-S) versus S-1, the effect of adding irinotecan was not significant [10]. The median overall survival with IRI-S versus S-1 was 12.8 versus 10.5 months ($P = 0.233$) and the 1 year survival rate was 52.0 versus 44.9%, respectively. In the post-hoc subset analyses, IRI-S was significantly more effective than S-1 for patients with diffuse type histology and for those with an Eastern Cooperative Oncology Group performance status of 1 or 2. Although the efficacy of adding irinotecan was negative in both JCOG9912 and GC0301/TOP-002, the median survival prolongation suggested that some group of patients might benefit from irinotecan doublets.

Gastric cancer is a heterogeneous disease, both in terms of biology and genetics, and many biomarkers pointed out in the literature remain debatable [11]. Also, few studies have been carried out using samples from randomised trials to assist selecting the appropriate regimen for patients, except for targeted therapy. In JCOG9912's correlative study, mRNA expression levels in tumours were evaluated and excision repair cross-complementing gene 1 (ERCC1) was an independent prognostic factor, whereas no predictive marker was identified [12]. The S-1 regimen in GC0301/TOP-002 was the same as that in JCOG9912 and SPIRITS. Comparing IRI-S versus S-1 may be simple and easier to identify predictive biomarkers.

This study was designed respectively to identify potential prognostic and predictive factors for the clinical outcome after IRI-S and S-1 therapy from subset analyses in GC0301/TOP-002. We measured tumour mRNA levels related to DNA repair and the 5-FU metabolic pathway according to JCOG9912's correlative study.

Patients and Methods

Study Design and Treatment

Between June 2004 and November 2005, 326 patients (S-1 monotherapy, $n = 162$; IRI-S, $n = 164$) were enrolled in the GC0301/TOP-002 trial. They received oral S-1 (80 mg/m^2 daily for 28 days every 6 weeks) or oral S-1 (80 mg/m^2 daily for 21 days every 5 weeks) plus irinotecan (80 mg/m^2 by intravenous infusion on days 1 and 15 every 5 weeks), respectively. All patients who had at least one measurable lesion were evaluated for tumour response according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) by extramural review. Overall survival was defined as the period from randomisation until death from any cause. Progression-free survival was calculated as the time from randomisation until the first objective evidence of disease progression or death from any cause. Significant risk factors that influence overall survival of all patients accrued were performance status (hazard ratio 1.348, 95% confidence interval 1.079–1.686; $P = 0.009$), tumour histology (hazard ratio 1.720, 95% confidence interval 1.161–2.548; $P = 0.007$), target lesion (hazard ratio 1.525, 95% confidence interval 1.164–1.999; $P = 0.002$) and tumour status (hazard ratio 0.698, 95% confidence interval 0.538–0.906; $P = 0.007$).

Written informed consent for GC0301/TOP-002 was obtained before registration and the opportunity to refuse to provide tumour samples for this correlative study was open to the public through websites of the Japanese Gastric Cancer Association according to the Japanese Ethical Guidelines for Clinical Studies. The protocol for this study was approved by the institutional review board of Japanese Gastric Cancer Association and each participating hospital.

Laboratory Methods

The formalin-fixed, paraffin-embedded endoscopic biopsies or surgical specimens taken before treatment were collected from the institutes. The tumour cells on the sections of interest were selectively isolated by laser-captured or manual microdissection. mRNA for thymidylate synthase, dihydropyrimidine dehydrogenase (DPD), topoisomerase I (Topo I), ERCC1, thymidine phosphorylase and an internal reference gene (beta-actin) were

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