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Clinical Trial

Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to S-1 monotherapy: TRICS trial ☆

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KEYWORDS
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Abstract ***Aim:*** The optimal second-line regimen for treating advanced gastric cancer (AGC) remains unclear. While irinotecan (CPT-11) plus cisplatin (CDDP) combination therapy and CPT-11 monotherapy have been explored in the second-line setting, the superiority of second-line platinum-based therapies for AGC patients initially treated with S-1 monotherapy has not yet been evaluated; therefore, we aimed to examine the survival benefit of CPT-11/CDDP combination over CPT-11 monotherapy.
Methods: AGC patients showing progression after S-1 monotherapy for advanced cancer or recurrence within 6 months after completion of S-1 adjuvant therapy were randomly allocated to CPT-11/CDDP (CPT-11, 60 mg/m^2; CDDP, 30 mg/m^2, q2w) or CPT-11 (150 mg/m^2, q2w).
Results: Sixty-eight advanced and 95 recurrent cases were evaluated. The median overall survivals were 13.9 (95% confidence interval [CI]: 10.8–17.6) and 12.7 (95% CI: 10.3–17.2) months for CPT-11/CDDP and CPT-11, respectively (hazard ratio: 0.834; 95% CI: 0.596–1.167, $P = 0.288$). No significant differences were observed in the secondary end-points, including progression-free survival (4.6 [95% CI: 3.4–5.9] versus 4.1 [95% CI: 3.3–4.9] months) and response rate (16.9% [95% CI: 8.8–28.3] versus 15.4% [95% CI: 7.6–26.5]). The incidences of grade 3–4 anaemia (16% versus 4%) and elevated serum lactate dehydrogenase levels (5% versus 0%) were higher for CPT-11/CDDP than for CPT-11. Exploratory subgroup analysis revealed that CPT-11/CDDP was significantly more effective for intestinal-type AGC, compared with CPT-11 (overall survival: 15.8 versus 14.0 months; $P = 0.019$).
Conclusion: No survival benefit was observed upon adding CDDP to CPT-11 after S-1 monotherapy failure.
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1. Introduction

Gastric cancer is the third leading cause of cancer death worldwide [1]. Nearly 50% of patients with locally advanced-stage gastric cancer relapse after gastrectomy, resulting in an unfavourable long-term prognosis [2]. The survival of these patients has been demonstrated to be markedly improved upon introduction of postoperative adjuvant chemotherapy with S-1 monotherapy [3]. However, a number of patients develop early recurrence after completion of adjuvant therapy with S-1.

On the other hand, combination therapies with fluoropyrimidines and platinum have been recognised as standard regimens for the first-line treatment of advanced gastric cancer (AGC) [4]. In addition, EOX (epirubicin, oxaliplatin and capecitabine) has also become a standard regimen in Europe [5], and DCF (cisplatin [CDDP], 5-fluorouracil and docetaxel) has been developed in the US, although its application is limited because of high toxicity [6]. In contrast, when this study started, S-1 monotherapy was widely used as a standard regimen in Japan [7]. Although the result of the JCOG 9912 trial showed that S-1 monotherapy was tentatively recognised as a standard treatment, the result of the SPIRTS trial proved the superiority of S-1 plus CDDP combination therapy over S-1 monotherapy [8]. However, the S-1 monotherapy regimen showed good overall survival (OS) in both trials (11.4 and 11.0 months, respectively), and owing to its modest toxicity and the fact that intensive hydration is not required, S-1 monotherapy remains an option for frail or unfit patients in Japan.

It is common practice to offer further chemotherapy for patients with AGC after failure of first-line chemotherapies [9]. However, currently, no established second-line chemotherapy (SLC) regimen is available for AGC patients. When we designed this trial, irinotecan (CPT-11) plus CDDP combination therapy or CPT-11 monotherapy were commonly used to treat AGC in the second-line setting in Asia [10–13]. In a previous phase II study using CPT-11 monotherapy as SLC, CPT-11 was found to frequently cause diarrhoea and febrile neutropenia [10]; therefore, CPT-11/CDDP combination therapy was developed to reduce CPT-11-associated diarrhoea and febrile neutropenia by decreasing the dose of CPT-11 [12,13]. Moreover, a phase I/II study of bi-weekly CPT-11/CDDP combination therapy showed promising efficacy and a manageable toxicity profile [13].

However, the effects of platinum-based therapies in the second-line setting for AGC patients initially treated by S-1 monotherapy have not yet been examined; therefore, this trial was designed to compare the effects of combination therapy with CPT-11 and CDDP to CPT-11 monotherapy in patients who showed progression after at least one cycle of S-1 monotherapy for advanced cancer or recurrence within 6 months after completion of adjuvant therapy with S-1.

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