Randomized phase II study of irinotecan, leucovorin and 5-fluorouracil (ILF) versus cisplatin plus ILF (PILF) combination chemotherapy for advanced gastric cancer

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Background: Irinotecan, in combination with 5-fluorouracil (5-FU) or cisplatin, has demonstrated efficacy against advanced gastric cancer (AGC).

Patients and methods: Chemotherapy-naive AGC patients were randomly assigned to receive irinotecan 150 mg/m² on day 1, leucovorin 20 mg/m² and a 22-h infusion of 5-FU 1000 mg/m² on days 1 and 2 (ILF) or ILF plus cisplatin 30 mg/m² on day 2 (PILF). Treatment was repeated every 2 weeks.

Results: Of 91 registered patients, 45 patients were treated with ILF and 45 with PILF. For both arms, 687 chemotherapy cycles were delivered (median = 7 for ILF and 8 for PILF). Both ILF and PILF were generally well tolerated and there was no relevant difference in the occurrence of overall grade 3/4 toxic effects between the two arms. Four patients died during treatment: one in the ILF and three in the PILF arm. The objective response rate was 42% for both arms. There was no significant difference in therapeutic efficacy between ILF and PILF with respect to progression-free survival (4.8 versus 6.2 months; \( P = 0.523 \)) and overall survival (10.7 versus 10.5 months; \( P = 0.850 \)).

Conclusion: Both ILF and PILF are active as first-line chemotherapy for AGC. The addition of cisplatin, however, has no clear advantage over ILF.

Key words: chemotherapy, cisplatin, 5-fluorouracil, irinotecan, stomach cancer

introduction

The benefit of systemic chemotherapy for advanced gastric cancer (AGC) in the palliative setting has long been known. Several randomized trials have demonstrated that 5-fluorouracil (5-FU)-based chemotherapy is superior to best supportive care in terms of survival and preservation of quality of life (QoL) [1, 2]. To date, only two triplet combinations, namely, ECF (epirubicin, cisplatin and 5-FU) and DCF (docetaxel, cisplatin and 5-FU), have demonstrated survival benefit for patients with AGC [3, 4]. The obtained median survival times, however, were limited to within 10 months.

Irinotecan is a water-soluble camptothecin derivative and has been shown to exhibit antitumor activity against gastric cancer both as a single agent [5] and in combination with leucovorin/5-FU (ILF) [6] or cisplatin (IP) [7]. A previous randomized study of ILF regimen versus IP showed that ILF produced an overall response rate of 42% and a median survival of 10.7 months [8], which were significantly better than the results with IP regimen. However, since cisplatin is still considered to be one of the key drugs for the treatment of gastric cancer, a combination of these three active drugs (cisplatin, irinotecan and leucovorin/5-FU [PILF]) seemed to be a promising strategy to treat AGC. This three-drug combination has been reported to have promising therapeutic efficacy of 74%–85% objective response rates [9, 10], but at the cost of considerable toxicity (i.e. severe neutropenia in 90% of patients).

We previously conducted a pilot feasibility study on 17 chemotherapy-naive patients with AGC, and they were administered cisplatin 30 mg/m² combined with ILF regimen [11]. There was good adherence to treatment and the combination was found to be potentially active for AGC. On the basis of these observations, we adapted a modified regimen of biweekly administered PILF. This randomized phase II study was conducted in patients with AGC to evaluate the safety profile and antitumor activity of ILF and PILF chemotherapy regimens given as first-line therapy.

patients and methods

Patients aged 575 years with histologically confirmed, measurable AGC were enrolled for this single-center randomized phase II study. Other
inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of two or less, a life expectancy of at least 3 months and adequate major organ functions. No prior chemotherapy or only adjuvant chemotherapy that had been completed >6 months before registration and no radiotherapy within 4 weeks before study registration were allowed. This study protocol was reviewed and approved by the Gil Medical Center (Incheon, Korea) institutional review board. To obtain informed consent, the nature of the study was fully discussed with the patients before the initiation of treatment, including an explanation of the risk and possible discomfort, as well as the potential benefits.

Patients were randomly assigned to receive ILF or PILF (Figure 1). ILF consisted of irinotecan 150 mg/m² on day 1 and leucovorin 20 mg/m² plus a 22-h infusion of 5-FU 1000 mg/m² on days 1 and 2. In the PILF arm, cisplatin 30 mg/m² was administered on day 2, along with appropriate i.v. hydration before and again after cisplatin infusion. Each cycle of chemotherapy was given every 2 weeks if the patient’s blood count had returned to normal and non-hematologic toxic effects had resolved. Treatment was repeated until disease progression and/or unacceptable toxicity was detected. Dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. The use of hematopoietic growth factors was not allowed during treatment, except for patients with febrile neutropenia or grade 4 myelosuppression. No primary prophylaxis with atropine was given unless a patient experienced grade ≥2 diarrhea. Throughout the study, the dose of leucovorin was unchanged.

Follow-up history, physical examinations and toxicity assessment were carried out before each 2-week cycle of treatment. Toxicity grading was based on the National Cancer Institute criteria (National Cancer Institute—Common Terminology Criteria for Adverse Events version 3). The first evaluation with imaging was done after the completion of four cycles of chemotherapy. Response was evaluated according to the World Health Organization criteria. We also assessed QoL using the validated Korean version of the European Organization for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30), which contains 30 questions addressing various aspects of QoL [12, 13]. This self-administered questionnaire was completed by patients at baseline, at every four cycles and at the end of treatment.

The primary end point was the overall response rate. This randomized phase II trial was statistically treated as two simultaneous phase II studies and the single-stage design was applied separately for each treatment arm. The sample size estimation was on the basis of the assumption that the response rate would be ≥30% in each group of the treated population. Thirty-five patients per group were required with a significance level set at 0.05. All analyses were carried out on the intent-to-treat population, defined as all registered patients who signed an informed consent.

results

From October 2004 to November 2006, a total of 91 patients with AGC (46 patients in the ILF arm and 45 in the PILF arm) were registered. One patient assigned to the ILF arm did not receive protocol therapy because of the rapid deterioration of general condition. The clinical characteristics were available for all patients and are listed in Table 1.

treatment delivery

A total of 335 ILF (median = 7; range = 1–16) and 352 PILF (median = 8; range = 1–16) cycles were delivered. Of the 90 patients who started treatment, the main reasons for discontinuing treatment in the ILF and PILF arms were progressive disease (71% versus 47%), toxicity (9% versus 29%) and the patient’s refusal (20% versus 24%). For the patients treated with ILF, the median dose intensity of irinotecan 68 mg/m²/week corresponded to 91% of the scheduled dose, and the median duration of therapy was 4.3 months (95% confidence interval (CI) = 3.4–5.2 months). In the PILF arm, the median dose intensity of irinotecan was

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Figure 1. Flow diagram of all registered patients.
67 mg/m²/week (89% of the scheduled dose), and the median treatment duration was 5.6 months (95% CI = 4.2–7.0 months). The relative dose intensities of 5-FU were 90% for both arms. In the PILF arm, the median administered dose intensity for cisplatin was 14 mg/m²/week, which corresponded to 92% of the planned dose. One ILF patient was felt to have resectable primary lesion after 16th cycle and discontinued chemotherapy for resection with a curative intent.

### Safety outcomes

There was no relevant difference in the occurrence of overall grade 3 or 4 toxic effects between the two arms (37% versus 46%, respectively; \(P = 0.431\)). The toxicity profiles are presented in Table 2. One PILF patient developed oliguric renal failure that required a period of dialysis. There are four deaths during the treatment period. In the ILF arm, one patient died of massive upper gastrointestinal bleeding shortly after receiving the third cycle of chemotherapy. Three patients in the PILF arm died of causes possibly related to treatment: one with neutropenic sepsis complicating by diarrhea, one with pulmonary embolism and one with intracranial bleeding.

### Efficacy outcomes

There were 1 complete and 18 partial responses in each of the arms (response rate = 42%; 95% CI = 28% to 57%). Ten (22%) ILF and 17 (38%) PILF patients, respectively, had stable disease.

### Discussion

The present randomized phase II study was initiated because there is no current reference chemotherapy regimen for AGC.
chemotherapy for AGC. Oxaliplatin has significant activity against some cisplatin-resistant tumors and a favorable safety profile over cisplatin [16]. Oxaliplatin plus ILF (FOLFOXIRI) for AGC was studied in a phase II study [17]. The authors reported that FOLFOXIRI has antitumor activity, with a response rate of 67% and a median survival of 14.8 months, as well as good tolerability. FOLFOXIRI was compared with FOLFI (irinotecan 165 mg/m² on day 1, leucovorin 200 mg/ m² on day 1 and a 48-h continuous infusion 5-FU 3200 mg/m² starting on day 1, every 2 weeks) in a recently published phase III study [18]. FOLFOXIRI improved response rate, DFS and OS with an increased toxicity in patients with metastatic colorectal cancer. In contrast, FOLFOXIRI and FOLFIRI showed similar efficacy in another phase III study [19]. This discrepancy is mainly attributable to patient selection. The REAL-2 study by Cunningham et al. [20] indicated that for the first-line chemotherapy of AGC, oxaliplatin could replace cisplatin. The results of the REAL-2 study showed that there were no significant differences in response rates comparing ECF with EOF (epirubicin, oxaliplatin and 5-FU), ECX (epirubicin, cisplatin and capecitabine) and EOX (epirubicin, oxaliplatin and capecitabine) (41%, 42%, 46% and 48%, respectively). Moreover, a phase III study that compared leucovorin/5-FU and cisplatin with leucovorin/5-FU and oxaliplatin in AGC patients demonstrated that superior efficacy and safety were achieved with oxaliplatin-based chemotherapy [21].

In conclusion, the combination chemotherapy of PILF (the addition of cisplatin to ILF) was feasible and effective as the first-line treatment for AGC, but it did not prove to be superior to ILF in terms of response rate or survival. Given the comparable efficacy results, ILF could be a reasonable standard chemotherapy for untreated AGC patients. The survival results, however, reported here are by no means the best yet observed with other combination regimens for patients with AGC [3, 4]. Other active and tolerable agents are now available and it is conceivable that addition of oxaliplatin or molecularly targeted agents to ILF could improve the efficacy for treating AGC patients without compromising tolerability.

acknowledgements

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references


