Comparison of adjuvant capecitabine plus oxaliplatin (CAPOX) versus S-1 in patients with gastric cancer after gastrectomy: A nationwide cohort study based on the National Health Insurance Service (NHIS) database in Korea

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Abstract

Background

Although both capecitabine plus oxaliplatin (CAPOX) and S-1 are accepted as adjuvant chemotherapy following gastrectomy for gastric cancer, the better option between the two is still controversial.

Methods

We conducted a retrospective nationwide cohort study using data from the National Health Insurance Service of Korea. We included patients who underwent gastrectomy for a primary diagnosis of gastric cancer between January 1, 2013, and December 31, 2018. The study compared the survival outcomes of patients who received postoperative chemotherapy based on S-1 (Arm S) vs. CAPOX (Arm C), as well as other relevant clinical variables such as comorbidity and completion of planned treatment.

Results

A total of 6,602 patients were included in the analysis, with 4,199 in Arm S and 2,403 in Arm C. After propensity score matching, the final study population consisted of 2,067 patients in each arm. Arm C showed statistically inferior five-year overall survival (OS) and disease-free survival (DFS) rates compared to Arm S (84.0% vs. 90.0%; p < 0.0001; and 78.4% vs. 86.1%; p < 0.0001). Age (≥65 vs. <65) and the incomplete planned treatment also had a significant negative effect on both OS and DFS. In the multivariable analysis, Arm C still showed worse OS (hazard ratio [HR], 1.609; 95% confidence intervals [CI], 1.339–1.934; p < 0.0001) and DFS (HR, 1.552; 95% CI, 1.333–1.807; p < 0.0001) than Arm S.

Conclusion

Both S-1 and CAPOX showed excellent efficacy, but this nationwide cohort study suggests that S-1 may be a better option in certain clinical situations.

Introduction

Gastric cancer is a major type of cancer, representing a high disease burden both in incidence and mortality worldwide, including in Korea [1, 2]. In Asia, the standard of care for locally advanced gastric cancer is still upfront gastrectomy with D2 lymph node dissection followed by adjuvant chemotherapy (AC), although neoadjuvant or perioperative chemotherapy before surgery is increasingly supported by evidence [3, 4]. Both capecitabine plus oxaliplatin (CAPOX) and S-1 are accepted as standard ACs based on the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) and the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) trials, respectively. CAPOX has the advantage of a shorter treatment period of six months compared to one year for S-1, but it requires intravenous injections of oxaliplatin every three weeks and has a higher incidence of adverse events of grade III or higher compared to S-1 [5]. S-1 is an easily administered oral drug, but there are concerns that it may be less effective as a single agent than the platinum-based doublet, especially in patients with advanced-stage disease. This led to a study on the use of docetaxel in addition to S-1 in patients with stage III disease [6]. Furthermore, S-1 is mainly used in Asia and is not available in some regions, such as the United States. Accordingly, many researchers have published studies comparing these two treatments. However, these are heterogeneous and often show conflicting results. Many studies have reported similar efficacies of S-1 and CAPOX [5, 7–11]. More specifically, on the other hand, subgroup analysis in some studies has shown that CAPOX was superior compared to S-1 in patients with high-risk or more advanced stages (e.g., stage IIIB or IIIC) [9, 10]. Contrastingly, another study reported similar disease-free survival (DFS) and overall survival (OS) for S-1 and CAPOX in patients with stage III disease [5]. Another study found that CAPOX may be favorable for OS only in patients with stage II disease [8]. A recently published meta-analysis reported that the five-year OS and DFS for stage II or stage III disease were not statistically different between the two treatments [12]. All these were retrospective studies. As a prospective phase III clinical trial comparing S-1 and CAPOX is unlikely to be conducted in the future, efforts to obtain convincing evidence for these two major types of AC should continue through analyses in as diverse a patient population as possible. Therefore, to investigate these two treatments in a larger patient group, we compared S-1 and CAPOX in a patient group registered in the National Health Insurance Service (NHIS) database of Korea.

Results

Study population

During the study period, 98,556 patients were identified as having undergone both gastric cancer and gastrectomy. Among this population, patients with a history of chemotherapy prescription before surgery and those who did not receive any chemotherapy after surgery (n = 67,321), who were diagnosed with cancers other than gastric cancer (n = 23,082), who received chemotherapy after surgery but were not treated with S-1 or CAPOX (n = 1,530), and who had incomplete data (n = 21) were excluded. Consequently, 6,602 patients were included in the analysis. Of these, 4,199 patients received adjuvant S-1 (Arm S), and 2,403 were treated with CAPOX (Arm C). After PSM, the final study population consisted of 2,067 patients in each arm (Fig. 1). Table 1 summarizes the patients' demographic characteristics. The median follow-up duration was 4.47 (range, 0.1–8.0) years.

Table 1. Baseline descriptive characteristics
1.609; 95% CI, 1.339–1.934; p < 0.0001). Five-year OS rates were 90.0% and 84.0% in arms C and S, respectively (Fig. CAPOX (Fig. 2a). Deaths were confirmed in 183 and 287 of the 2,067 patients in Arm S and C, respectively. OS was also worse in Arm C than in Arm S (HR, 1.609; 95% CI, 1.339–1.934; p < 0.0001). Five-year OS rates were 90.0% and 84.0% in arms C and S, respectively (Fig. 2b).

Multivariable analysis revealed that
younger age (< 65 vs. ≥65) and completion of planned AC were associated with better DFS and OS. Contrastingly, multiple comorbidities (≥ 4 vs. 0–3) did not affect the DFS or OS. After adjusting for clinically significant variables, CAPOX remained inferior to S-1 in terms of DFS and OS (Table 2).

### Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
</tr>
<tr>
<td></td>
<td>analysis</td>
<td>analysis</td>
</tr>
<tr>
<td></td>
<td>HR, 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 (vs. &lt;65)</td>
<td>1.773</td>
<td>1.524–2.064</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male (vs. Female)</td>
<td>1.035</td>
<td>0.876–1.222</td>
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<tr>
<td>CCI group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4 (vs. 0–3)</td>
<td>1.172</td>
<td>0.724–1.896</td>
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<tr>
<td>Completion of planned adjuvant chemotherapy</td>
<td></td>
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<tr>
<td>Yes (vs. No)</td>
<td>0.343</td>
<td>0.295–0.399</td>
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<tr>
<td>Type of adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPOX (vs. S-1)</td>
<td>1.595</td>
<td>1.370–1.857</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CCI, Charlson comorbidity index; CAPOX, capecitabine plus oxaliplatin.

### Subgroup analysis

In the forest plot, a consistent trend favored S-1 over CAPOX for DFS, regardless of the subgroup (Fig. 3a). A similar pattern was observed in the subgroup analysis for OS, favoring S-1 (Fig. 3b).

### Discussion

In this retrospective nationwide cohort study, we demonstrated a difference in efficacy between S-1 and CAPOX as AC following gastrectomy in patients with gastric cancer. To the best of our knowledge, this is the only study to date indicating that adjuvant S-1 is superior to CAPOX in patients with gastric cancer. Most published reports have shown that S-1 and CAPOX are comparable to each other, especially in patients with advanced-stage disease, in contrast to our study results [9, 10]. In clinical practice, both of adjuvant S-1 and CAPOX are widely accepted and used. Some oncologists prefer CAPOX in cases of advanced-stage disease since subgroup analysis of the CLASSIC trial showed consistently favorable efficacy in patients with stages II, IIIa, and IIb disease, whereas the effect of S-1 was maintained only in stage II disease in the subgroup analysis of the ACTS-GC trial [16, 17]. Based on these results, the Korean practice guidelines for gastric cancer mention that CAPOX is the preferred choice for pathological stage II with regional lymph node metastasis or stage III disease [18]. Furthermore, based on several pivotal phase III studies, many clinicians now believe that fluoropyrimidine-based doublet chemotherapy has better efficacy than S-1 alone in these subgroups of patients [6, 19].

Why did Arm S showed better outcomes compared to Arm C in the present study? The discrepancy between our data and previous studies may be explained in some points of view. First, there is a possibility that the operational definition we used in this study could affect the capture of data on the status of disease recurrence, underestimating the actual number of recurrences. There is a subset patient who did not receive any type of palliative chemotherapy despite disease recurrence due to a number of clinical or non-clinical factors, including poor performance status, old age, or financial toxicity. As DFS was operationally defined as the period from the date of surgery to the start of first-line chemotherapy, patients whose cancer recurred but did not receive chemotherapy could not be included. Indeed, both the recurrence and mortality rates were much lower than those reported in previous studies. In the CLASSIC trial, five-year DFS and OS rates after adjuvant CAPOX were 68% and 78%, respectively [20]. The corresponding rates were 65.4% and 71.7% after adjuvant S-1 in the ACTS-GC trial [21]. In real-world data, on the other hand, the recurrence rate after gastrectomy was found to be 19.7–20.5%, which was much lower than the results of clinical trials [22, 23]. In our study, the five-year recurrence rates were 13.9% and 21.6% in Arm S and C, respectively, which were slightly lower than or similar to those from real-world data. The difference between the datasets was considered reasonable, considering that the proportion of patients who did not receive palliative first-line treatment after recurrence was approximately 13% of all patients with recurrent or metastatic unresectable gastric cancer in Korea [24]. Nevertheless, because the type of prior AC itself cannot be considered as influencing the decision not to receive chemotherapy after recurrence, it can be assumed that the magnitude of underestimation of this portion might not be significantly different between the two groups. Additionally, despite the limitations of DFS estimation, the OS rates seem to be more robust in that the mortality information of the patients in this study was based on solid data from the NHIS rather than on an operational definition.

Second, it should be considered that in our data, patients with stages II and III diseases were mixed; therefore, analyzing the outcome by stage was not possible. Given the practice pattern of more frequent use of S-1 and CAPOX in patients with stages II and III disease, respectively, improved survival outcomes in Arm S are likely to be due to the effect of an earlier stage rather than the adjuvant S-1 itself. Unfortunately, detailed information on the disease stage was
not available in the NHIS data, limiting the usefulness of these results. However, it is worth mentioning that our data suggested that both S-1 and CAPOX revealed high efficacy for patients in the adjuvant setting.

Despite this uncertainty, the following steps were taken to ensure data reliability: By performing PSM and including important variables available in the raw data, the imbalance of baseline demographic factors between the comparison groups was minimized. The superiority of S-1 over CAPOX was substantiated repeatedly, not only in the overall population but also in the subgroup analysis. These consistencies make the study results more convincing than a simple statistical coincidence. Moreover, we established strict criteria for selecting patients included in the analysis to minimize the intrinsic uncertainty in anonymized big data. For example, all patients whose diagnostic codes for gastric cancer (C16), and other cancer codes overlapped at least once were excluded, regardless of when the gastric cancer code was first generated. This is important because the current history of primary cancers other than stomach could make an accurate evaluation of AC for gastric cancer difficult.

Apart from the type of chemotherapy, completion of chemotherapy and age were important prognostic factors, which is consistent with previous reports. However, the CCI score did not have a significant effect on survival outcomes. Collectively, these results suggest that efforts should be made to complete the planned course of chemotherapy as much as possible in adjuvant settings.

In conclusion, this study found that both adjuvants S-1 and CAPOX showed excellent efficacy in patients who underwent AC after gastrectomy. As revealed in the results, it can be seen that S-1 might be better than CAPOX, or at least S-1 may not be inferior to CAPOX even considering the aforementioned limitations of the data.

Methods

Study population and data source

For this retrospective nationwide cohort study, data were obtained from the NHIS of Korea. As the NHIS is a single-payer healthcare system, it covers the entire population of the Republic of Korea [13] and provides comprehensive information on demographic data, healthcare utilization, pharmaceutical prescriptions, and death for each patient [14]. In the study population, we included patients who underwent gastrectomy [Q0251-Q0259, Q2533, Q2534, Q2536, Q2537, Q2552, Q2594, Q2598, QAS36] with a primary diagnosis of gastric cancer certified by the International Classification of Diseases (ICD) 10th codes of C16.x from January 1, 2013, to December 31, 2018. Patients who underwent a gastrectomy before 2013 were excluded. We also excluded patients who (1) received chemotherapy before surgery and did not receive any chemotherapy after surgery; (2) had a diagnosis of other cancers, which was defined as patients with an ICD code other than gastric cancer (C16); and (3) received postoperative chemotherapy other than S-1 and CAPOX. This report complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [15].

Demographic factors included age, sex, income (0–29 vs. 30–100 percentile), and the region in which the patients received AC (Seoul vs. non-Seoul). Clinical variables such as comorbidity, type of AC (S-1 and CAPOX), completion of planned treatment, the time interval between surgery and the start date of adjuvant chemotherapy, DFS, and OS were also collected. Stages (II or III) of each patient were not available. The ICD-10 codes were utilized to define the comorbidities of the study population as follows: hypertension (I10–I13, I15), diabetes mellitus (E10–E14), dyslipidemia (E78), chronic kidney disease (N18), and stroke (I63–I64).

Operational definition

Considering that the data were based on insurance claim data, the following operational definition was used to establish the predefined variables during data collection: AC was defined as the initiation of S-1 or CAPOX treatment within three months of surgery. If capecitabine and oxaliplatin were administered on the same day or at intervals of up to one week, it was defined that the adjuvant CAPOX was administered. To determine whether adjuvant S-1 was completed as planned, the reference period from the first administration start date to the last end date was estimated to be 336 days (42 days per cycle, eight cycles in total). If the administration of S-1 was finished between 30 days before and 60 days after the last day of the planned period, it was considered complete. In the case of CAPOX, if the number of oxaliplatin prescriptions was eight, the planned treatment was defined as complete, and if it was fewer than seven, it was considered incomplete. If the prescription of any chemotherapeutic agents was identified again after adjuvant S-1 or CAPOX was administered, it was defined as a recurrent case after surgery, and the patient received palliative first-line chemotherapy. Similarly, if another chemotherapy was prescribed during adjuvant S-1 or CAPOX, this was considered a case of recurrence during AC, and palliative first-line chemotherapy was initiated. DFS was defined as the period from the date of surgery to the start of first-line chemotherapy. Although we could not determine the actual date of radiologically or clinically confirmed recurrence, DFS was defined because palliative chemotherapy was initiated in cases of recurrence. OS was defined as the period from the date of surgery to the date of death. Data were not collected from patients who did not undergo chemotherapy, even if they relapsed, because they were unavailable.

Declarations

Author contributions

CHM made the study conception and design. Material preparation, data collection and analysis were performed by CHM, HK, and MK. The first draft of the manuscript was written by CHM and all authors commented on previous versions of the manuscript. HK, MK and CHM prepared figures 1-3. CHM prepared Table 1-2. All authors read and approved the final manuscript.
Acknowledgement

Disclosure of potential conflicts of interest

The authors declare that they have no conflicts of interest.

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Data availability

Data are contained within the article and is available on request.

References


Figures

![Flow Diagram of Study Population Selection](image)

**Patients with ICD 10 code of C16 and gastrectomy**

January 01, 2013-December 31, 2018 (n=98,556)

**Exclusion**
- History of chemotherapy before surgery and/or no postoperative chemotherapy (n = 67,321)
- Concomitant diagnosis of cancer other than gastric cancer (n = 23,082)
- Administration of postoperative chemotherapy other than S-1 or CAPOX (n = 1,530)
- Data incomplete (n = 21)

**Evaluable study population (n = 6,602)**

**Arm S**
Adjuvant S-1 (n = 4,199)

**Arm C**
Adjuvant CAPOX (n = 2,403)

**Propensity score matching**

**Arm S**
Adjuvant S-1 (n = 2,067)

**Arm C**
Adjuvant CAPOX (n = 2,067)

**Figure 1**

A flow diagram of study population selection
Figure 2
Survival outcomes based on the type of adjuvant chemotherapy. (a) Disease-free survival; (b) Overall survival
CAPOX, capecitabine plus oxaliplatin; HR, hazard ratio

Figure 3
Forest plots of (a) disease-free survival and (b) overall survival according to patient subgroups
HR, hazard ratio; CCI, Charlson comorbidity index; CAPOX, capecitabine plus oxaliplatin.