



# S-1 plus docetaxel combination: another adjuvant treatment option for stage III gastric cancer

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Despite decades of declining prevalence, gastric cancer (GC) still accounts for over 770,000 cancer-related mortalities worldwide (1). A common therapeutic approach for the treatment of GC involves gastric resection plus with D2 lymph node dissection. However, even following radical surgery, recurrence is typical in the case of locally advanced GC (stage II–III). Postoperative adjuvant chemotherapy trials, which were conducted mainly in Asian patients, confirmed a significant improvement in the survival rate in the adjuvant chemotherapy compared with observation only in resectable GC. Therefore, this surgery-first approach has been strengthened in Asian nations where hematogenous and peritoneal recurrences are common (2).

The Japanese ACTS-GC trial was the first positive phase III outcome to address adjuvant chemotherapy with S-1, an oral fluoropyrimidine, as being superior to the “surgery alone” (3). In this trial, 1,059 patients with stage II (excluding T1) or stage III GCs according to the Japanese classification were randomly assigned to the ‘surgery-only’ arm or ‘S-1 treatment’ arm, in which S-1 was administered for a year following D2 gastrectomy. At 3 years, recurrence-free survival (RFS) was 72% in the S-1 arm and 60% in the surgery-only arm [hazard ratio (HR) =0.62; 95% confidence interval (CI): 0.50–0.77; P<0.001], and the overall 3-year survival rates were 80% and 70%, respectively (HR =0.68; 95% CI: 0.52–0.87; P=0.003). However, subgroup analysis revealed that S-1 could only prolong survival in patients

with early disease stages (stage II or IIIA) and was unable to prevent hematogenous dissemination (3). Moreover, S-1 is also not widely available worldwide. As a result, in order to improve the clinical outcome, particularly in a more advanced stage IIIB state, it was required to look for a better alternative option, such as one based on a pharmaceutical doublet.

In this regard, JACCRO GC-07 study provided an intriguing alternative to S-1 monotherapy (4). The study’s objective was to address whether S-1 plus docetaxel doublet was superior to S-1 alone following R0 resection of pathologic stage III GC. The third English edition of the Japanese Classification of Gastric Carcinoma, which includes stage IIIA (T2N3, T3N2, T4aN1), stage IIIB (T3N3, T4aN2, T4bN0, T4bN1), or stage IIIC (T4aN3, T4bN2, T4bN3), was used to define pathologic stage III GC (5). To briefly summarize the treatment schedule, S-1 was delivered on days 1 through 14 of the first course’s 3-week cycle. After that, patients received intravenous infusions of docetaxel (40 mg/m<sup>2</sup> body surface area) on the first day of each cycle and S-1 (days 1 through 14 of a 3-week cycle) throughout the second to seventh cycle. Patients in the S-1 group received S-1 from days 1 to 28 of a 6-week up to 1 year. The investigators had planned to enroll 1,100 patients between 2013 and 2017, and the second interim analysis was published in 2019 when the number of events reached 216 among 915 enrolled patients. The research revealed that the S-1 plus docetaxel group (n=456) had

statistically better 3-year RFS to the S-1 group (n=459) (HR =0.632; 99.99% CI: 0.400–0.998; P<0.001). The enrollment was consequently prematurely stopped in September 2017 at the independent data and safety monitoring committee's advice. However, even though this met the intended hypothesis for a greater than 15% improvement in 3-year RFS, the number of deaths was modest and the number of patients at risk did not reach the necessary threshold.

The 3-year RFS results of this study were now published in *Gastric Cancer* as an extension of this study (6). The following is a summary of the key findings:

- (I) The 3-year RFS of 68% for the S-1 plus docetaxel group was significantly higher than the RFS of 57% for the S-1 group (HR =0.715; 95% CI: 0.587–0.871; P=0.0008).
- (II) Additionally, they demonstrated a 6.5% improvement in 3-year overall survival (OS) with an HR of 0.742 (95% CI: 0.596–0.925; P=0.0076). The S-1 plus docetaxel group had a 3-year OS rate of 78% as opposed to the S-1 group's 71%.
- (III) More over two thirds of patients in the S-1 plus docetaxel group successfully completed the prescribed six cycles of docetaxel, which was accompanied by a positive safety profile and treatment compliance.
- (IV) A grade 3 or higher adverse event occurred in 42% of patients taking S-1 alone and 58% of individuals receiving S-1 plus docetaxel. Neutropenia and leukopenia were the most prevalent grade 3 adverse events in the S-1 plus docetaxel group. All of the toxicities, though, were manageable and under control.

We think this trial has expanded bedside options for adjuvant chemotherapy by bridging the gap between S-1 monotherapy and more aggressive doublet therapy. For those who want to shorten treatment duration to 6 months and those who want to avoid toxicities specific to docetaxel, such as alopecia and severe neutropenia, the combination of capecitabine plus oxaliplatin, based on the CASSIC trial, would be recommended (7). However, this S-1 plus docetaxel doublet may be an effective substitute for those who do not want to experience severe peripheral neuropathy or palmar-plantar erythrodysesthesia (PPE), which can be disabling and frequently need reducing doses of oxaliplatin and capecitabine or discontinuing them altogether.

Nevertheless, we need to draw attention to several limitations on this study. First, this doublet was beneficial for stage IIIA cancer and even the stage IIIC subpopulation.

However, it was less significant for the stage IIIB patients (n=217), particularly for T3N3a, T4bN0, and T4bN1, which made up 49% of all stage IIIB cases. The authors conducted extra analyses because they were aware of this problem. However, in stage IIIB, there were no discernible alterations or variances in baseline patient characteristics or drug compliance, leaving no opportunity for logical explanations. Since JACCRO GC-07 was thought to be underpowered to assess statistical differences between subgroups, the findings of post-hoc analyses should only be taken with a grain of salt. Because 5-year RFS and OS are additional secondary goals, we will conduct a follow-up to assess the overall study's outcomes.

Second, despite having a beneficial effect on preventing nodal and hematogenous recurrence, S-1 with docetaxel had no significant effect on reducing peritoneal seeding. This finding reminded us of the CLASSIC trial, where adjuvant capecitabine plus oxaliplatin treatment had also a less effect on preventing peritoneal recurrences (7). It was still unclear what caused this discrepancy in the recurrence pattern of GC. The chemosensitivity of tumor cell clones and the sites of metastasis would differ. The peritoneum may consequently be less adversely affected by the two-drug combination. There may be options, such as a more rigorous chemotherapy regimen or intraperitoneal chemotherapy. But for now, this is only a speculation.

Third, there is still discussion over the optimal duration of adjuvant therapies. Although the majority of randomized trials carried out in Asia adopted the recommendation that adjuvant therapy should not last longer than 6 months, this study was based on a prior Japanese phase III trial in which the non-inferiority of 6-month treatment compared with 12-month treatment of S-1 monotherapy was not proven (8). Further research is still required to determine the ideal course of treatment for S-1-based chemotherapy, especially given that combinations of capecitabine plus oxaliplatin for 6 months remain a popular choice in many Asian nations.

In conclusion, despite some controversy, the adjuvant treatment with S-1 + docetaxel improved RFS and OS with a risk reduction of 29% and 26%, respectively, compared with S-1 alone, according to the trial's 3-year outcomes. This doublet deserves the attention of experts as a standard of care for patients with stage III GC after D2 dissection. These findings might be relevant in countries where chemoradiation or postoperative CT are not standard procedures.

The survival following GC surgery has steadily increased in Asian countries over the past few years since the introduction of adjuvant chemotherapy, and more improved

outcomes are anticipated in the future, in line with the many ongoing research looking into new regimens as adjuvant therapy for GC. However, Western and Asian guidelines differ in a number of ways, thus it is crucial to be aware of these differences and try to communicate with one another in order to develop better treatment plans. Unfortunately, considering the difficulty of directly comparing the findings of research conducted in Western and Asian countries in the current context, it is still premature to recommend the optimal treatment course for patients with GC. New concepts of research, such as those about ethnic or genetic differences in GC patients, global investigations to establish surgical and therapeutic standards, and research to look into the mechanisms of the carcinogenesis and progression of GC, are required for further advancements and global consensus in the adjuvant treatment of GC.

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