Editorial Commentary



# Optimal neoadjuvant chemotherapy for resectable advanced gastric cancer

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In Europe, where D2 surgery is not a standard treatment, perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) is the current standard treament for resectable gastric cancer (1). However, surgery alone often provides a favorable prognosis, and postoperative S-1 or capecitabine plus oxaliplatin is the current standard therapy in Eastern Asian countries, including Japan, South Korea, and China, where D2 surgery is the standard treatment, according to the ACTS-GC and CLASSIC trials (2,3). Thus, evidence for neoadjuvant chemotherapy has not been established. It has been suggested that neoadjuvant chemotherapy is effective only for advanced gastric cancer, which is thought to have an extremely high recurrence risk.

In recent years, S-1 + oxaliplatin (SOX regimen), which uses oxaliplatin, the same platinum medication as cisplatin, has become frequently used in daily practice as the first-line treatment for unresectable advanced or recurrent gastric cancer (4). A phase II study was conducted in South Korea to investigate the significance of performing three courses of triple therapy [docetaxel, oxaliplatin, and S-1 (DOS)] with docetaxel (DOX) in addition to these two medications (SOX) before surgery for cT3–4 or cT2N (+) gastric cancer (5). The histological complete response (pCR) rate was 19.5% (8/41), which was a very promising result. Therefore, a phase III study (PRODIGY) was conducted in which the standard treatment of postoperative S-1 therapy followed by D2 surgery (SC group) and the trial treatment of preoperative DOS + postoperative S-1 therapy followed by D2 surgery (CSC group) were randomly compared for cT2-3N (+) or cT4 gastric cancer (6).

Preoperative DOS therapy was completed in three courses in 89.9% of the CSC group, with only 2.1% experiencing tumor growth during treatment. As treatment-related adverse events of Grade 3 or higher in the CSC group, neutropenia was 12.6%, febrile neutropenia was 9.2%, diarrhea was 5.0%, and treatment-related death during preoperative treatment was 0.8%. The R0 resection rate in surgery was 96.4% in the CSC group (238 cases) and 85.8% in the SC group (246 cases) (P<0.0001), with the D2 lymph node dissection rate being 98.1% in both the CSC and SC groups. Surgery-related Grade 3 or higher adverse events were observed in 6.3% of the CSC group and 8.5% of the SC group, and one patient (0.45%) died of pulmonary embolism in the CSC group. In the CSC group, pCR was observed at 10.4% (P<0.0001). The primary endpoint of 3-year progression-free survival (PFS) was 60.2% in the SC group, and 66.3% in the CSC group, and the hazard ratio (HR) was 0.70 [95% confidence interval (CI): 0.52–0.95, P=0.023], indicating a statistically significant difference. There was no statistically significant difference in overall survival (OS) between the CSC and SC groups (HR =0.84, 95% CI: 0.60–1.19, P=0.338). The 3-year OS was 74.2% (95% CI: 67.7–79.6%) in the CSC group and 73.4% (95% CI: 67.0–78.7%) in the SC group.

Although there was no significant difference in OS, PRODIGY showed improvement in PFS, which is the primary endpoint; therefore, it can be considered a positive study. Although the preoperative DOS therapy in this study has a doubtful low rate of Grade 3 or higher neutropenia of 12.6%, it has a high completion rate of approximately 90%, pCR is obtained at about 10%, and progression

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disease is observed at only 2%. Given these factors, DOS therapy is considered a promising regimen. However, care must be taken when interpreting the findings of this study. In this study, if R0 resection was not obtained, the cases were treated as events at the time of surgery, and the difference in the PFS curve that opened at the surgery remains unchanged. From the result, patients who had R0 resection with upfront surgery may not require neoadjuvant chemotherapy (7). However, if R0 resection could not be obtained during surgery, the protocol was terminated and the post-treatment was freely selected. In this study, there was no difference in OS, and post-treatment may result in equivalent OS even if upfront surgery did not cause R0 resection. It is unclear whether neoadjuvant chemotherapy improves OS.

To perform neoadjuvant chemotherapy, treatment methods must be decided based on inaccurate preoperative staging. Even in relatively early cases that can be cured by surgery alone, harmful anticancer medications may be administered, which can result in fatal adverse events in some cases. Therefore, in clinical practice, it is preferable to limit neoadjuvant chemotherapy to highly advanced cases where R0 surgery may be impossible unless tumor shrinkage due to neoadjuvant chemotherapy is observed, such as gastric cancer with bulky lymph node metastasis or paraaortic lymph node metastasis (8,9).

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