J Gastric Cancer. 2022 Apr;22(2):79-82
https://doi.org/10.5230/jgc.2022.22.e13
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric Cancer

Editorial

Optimal Duration of Adjuvant Chemotherapy for Gastric Cancer: Might Less Be More?

Hye Sook Han

Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea

Received: Apr 15, 2022
Revised: Apr 23, 2022
Accepted: Apr 23, 2022
Published online: Apr 28, 2022

Correspondence to
Hye Sook Han
Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, 1 Chungdae-ro, Seowon-gu, Cheongju 28644, Korea.
Email: hyesukhan@chungbuk.ac.kr

ORCID iDs
Hye Sook Han
https://orcid.org/0000-0001-6729-8700

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Several large-randomized trials have indicated that adjuvant chemotherapy after curative resection with D2 lymph node dissection has a significant survival benefit in Asian patients with resectable gastric cancer. Adjuvant chemotherapy in Asian patients with resectable gastric cancer is primarily supported by the results of 2 large, randomized phase 3 trials: the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) and the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) [1,2]. Based on the results of these trials, both chemotherapy regimens (S-1 for 1 year or capecitabine plus oxaliplatin for 6 months) are currently accepted in East Asia as standard adjuvant chemotherapy regimens for pathological stage II or III gastric cancer after D2 gastrectomy [3,4]. However, as S-1 monotherapy has limited survival benefits in patients with stage III gastric cancer, oral fluoropyrimidine-based doublet regimens (capecitabine plus oxaliplatin [XELOX], S-1 plus oxaliplatin [SOX], or S-1 plus docetaxel) are recommended as adjuvant chemotherapy for these patients [2-6] (**Fig. 1A**).

Oral fluoropyrimidine-based doublet regimens as adjuvant chemotherapy have a total treatment duration of approximately 6 months and are associated with a high incidence of adverse events and a low rate of treatment completion. In the CLASSIC trial, 67% of the enrolled patients completed all eight planned cycles of XELOX, and the incidences of dose reduction for capecitabine and oxaliplatin were 48.3% and 47.1%, respectively [2]. In the Adjuvant chemoRadioTherapy In Stomach Tumors (ARTIST) 2 trial, 85% of the enrolled patients completed all eight planned cycles of SOX [5]. Adverse events were the main reasons for treatment discontinuation and dose reduction for adjuvant chemotherapy in these trials. Peripheral sensory neuropathy is a particularly troubling adverse effect of oxaliplatin that can lower the patient's quality of life and treatment compliance. Symptoms may take as long as a year to improve after the completion of chemotherapy and sometimes persist for a long time. Since the risk and severity of oxaliplatin-induced neuropathy are associated with the cumulative dose administered, 80%–90% of patients experience peripheral neuropathy and 12–34% of patients develop grade 3 or higher peripheral neuropathy when the cumulative dose of oxaliplatin is 750–850 mg/m^2 [7]. As the dose of oxaliplatin in one cycle of XELOX and SOX is 130 mg/m^2, the incidence of peripheral neuropathy increases when standard XELOX or SOX is continued for more than 6 cycles. In the CLASSIC and ARTIST 2 trials, the incidences of peripheral neuropathy of any grade were 56% and 67%, respectively, and the incidence of grade 3 and 4 peripheral neuropathy were 2% and 12%, respectively [2,5].

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Strategies to decrease the adverse effects associated with adjuvant oxaliplatin-containing chemotherapy while preserving its benefits have been investigated in patients with stage III colon cancer through the International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration [8]. However, no prospective studies have compared the standard 6-month treatment period with a shortened period of oxaliplatin-containing regimens in gastric cancer. The standard 6-month treatment period of adjuvant oxaliplatin-containing chemotherapy for gastric cancer is not based on the results of robust clinical trials, but rather than on clinical experience. In this issue of the *Journal of Gastric Cancer*, Yu et al. [9] reported that gastric cancer patients who received 6 or 8 cycles of XELOX or SOX chemotherapy over a 21-day cycle did not show significantly prolonged survival compared to those who received four cycles of the same chemotherapy. However, patients who received 6 cycles had better overall survival than those who received 4 or 8 cycles of chemotherapy. In previous retrospective studies, six cycles of oxaliplatin-containing chemotherapy led to a favorable survival outcome, and an additional two cycles did not provide additional clinical benefit [10-12]. These results are comparable to those reported by Yu et al. [9] in the *Journal of Gastric Cancer*. The results of these retrospective reports highlight the need for a prospective study examining strategies to shorten the duration of oxaliplatin-containing adjuvant chemotherapy in patients with resected gastric cancer. Two ongoing prospective phase 3 trials are examining strategies to shorten the duration of adjuvant oxaliplatin-containing chemotherapy by at least 20%–30% but less than 50% (**Fig. 1B**). The XELOX for 4 Months

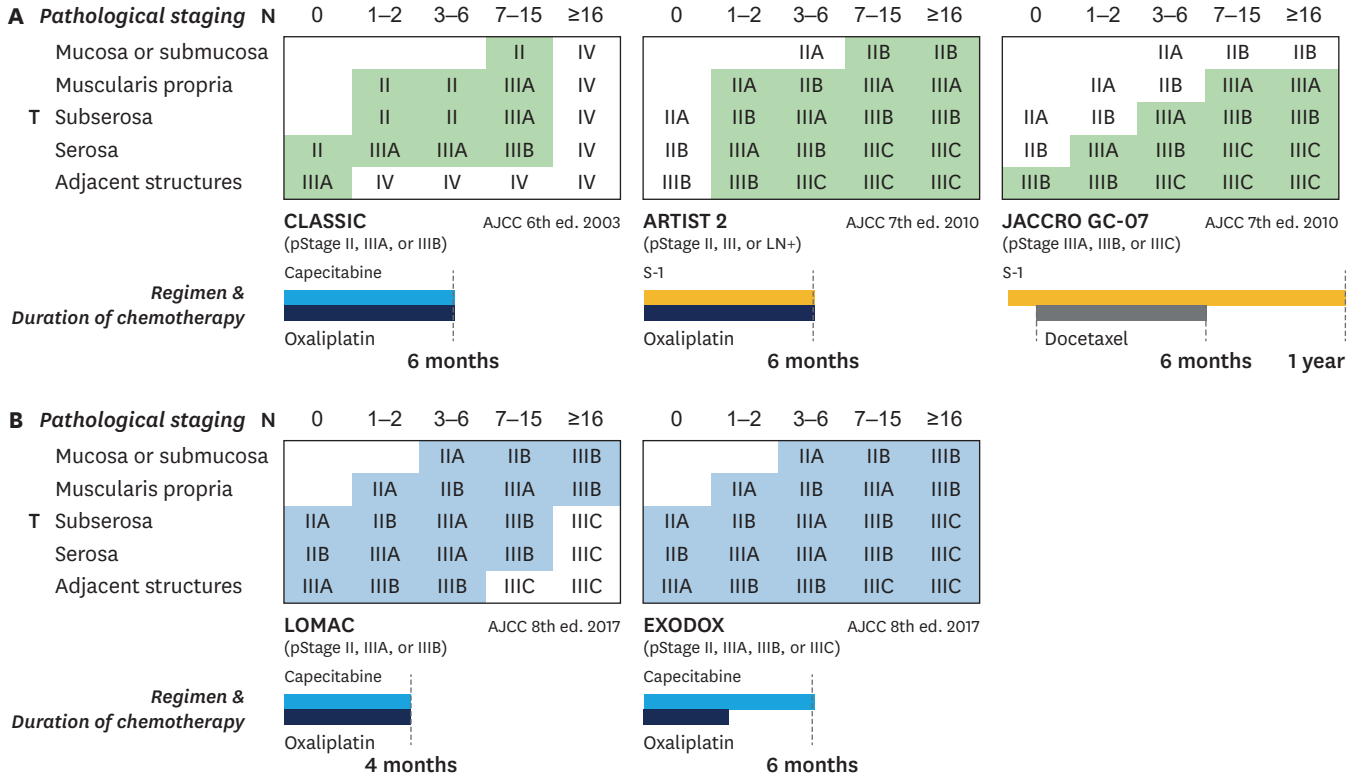

Fig. 1. Pathological staging, regimen, and duration of chemotherapy of included patients in (A) previously reported and (B) ongoing randomized phase 3 trials on adjuvant chemotherapy in patients with curatively resected gastric cancer.
T = primary tumor; N = regional lymph node; AJCC = American Joint Committee on Cancer; LN = lymph node; CLASSIC = Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer; ARTIST 2 = Adjuvant Chemoradiation Therapy in Stomach Cancer 2; JACCRO GC-07 = Japan Clinical Cancer Research Organization Gastric Cancer-07; LOMAC = XELOX for 4 Months Versus 6 Months as Adjuvant Chemotherapy in Gastric Cancer; EXODOX = Optimal Duration of Oxaliplatin in Adjuvant XELOX for Gastric Cancer Patients.

https://doi.org/10.5230/jgc.2022.22.e13

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Versus 6 Months as Adjuvant Chemotherapy in Gastric Cancer (LOMAC) trial in China [13] is comparing the efficacy and safety of XELOX for 4 months versus 6 months in gastric cancer patients with pathological stage II, IIIA, or IIIB disease. The Optimal Duration of Oxaliplatin in Adjuvant XELOX for Gastric Cancer Patients (EXODOX) trial in South Korea [14] is comparing the efficacy and safety of reduced XELOX (4 cycles of XELOX followed by 4 cycles of capecitabine alone) with those of 8 cycles of standard XELOX in gastric cancer patients with pathological stage II or III disease. The results of previously reported or ongoing phase 3 trials on adjuvant chemotherapy for gastric cancer require careful attention, as the pathological stages of the included gastric cancer patients in each trial are slightly different (**Fig. 1**). In the CLASSIC trial, gastric cancer patients with resectable disease at the most advanced stage (T4bN1-3M0/TxN3bM0, mostly IIIC) were not included [2]. Therefore, careful consideration is needed when shortening the period of adjuvant chemotherapy after surgical resection in patients with highly advanced gastric cancer.

Optimizing the application of adjuvant chemotherapy to reduce recurrence and improve overall survival in patients with gastric cancer depends primarily on a multidimensional assessment of the risk in each patient. There is a need for personalized therapy, where the weakening, shortening, intensifying, or prolonging of adjuvant chemotherapy depends on prognostic biomarkers. For this, an advanced understanding of molecular profiling is required in the future.

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