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REVIEW ARTICLE

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Recent updates in perioperative chemotherapy and recurrence pattern of gastric cancer

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Abstract

Gastrectomy with D2 lymph node dissection has become the global standard procedure for locally advanced gastric cancer to maximally reduce locoregional recurrence. In East Asia, based on the evidence of the ACTS-GC and the CLASSIC trials, postadjuvant chemotherapy with S-1 monotherapy or capecitabine and oxaliplatin after curative D2 gastrectomy is the current standard strategy. However, approximately 20% to 30% of patients still develop distant recurrence even after these postadjuvant chemotherapies, especially in those with pathological stage III disease. This review summarizes recent (2008-2018) evidence on the benefits of adjuvant therapy for locally advanced gastric cancer. JACRO GC-07, a Phase III trial, recently showed a superior 3-year recurrence-free survival of the S-1 plus docetaxel regimen in comparison to S-1 monotherapy for patients with pathological stage III gastric cancer after curative D2 gastrectomy. With regard to recent new evidence on neoadjuvant strategy, JCOG0501, a Phase III trial, did not show any superiority in 3-year overall survival (OS) of additional neoadjuvant chemotherapy with S-1/cisplatin over postadjuvant S-1 monotherapy in scirrhous type gastric cancer. Further clinical trials of neoadjuvant chemotherapy are ongoing to improve the poor prognosis for gastric cancer with extensive lymph node metastases. These trials could lead to new evidence for improved treatment of gastric cancer in the near future.

KEYWORDS

D2 lymph node dissection, gastric cancer, neoadjuvant chemotherapy, periadjuvant chemotherapy, postadjuvant chemotherapy, recurrence pattern

1 | INTRODUCTION

Although epidemiological studies demonstrated a reduction in recent years in gastric cancer incidence, gastric cancer is still the fifth most common malignancy in the world (952 000 new cases) and the third leading cause of cancer death (723 000 deaths) according to statistics from 2012.[1] Surgery remains the principal axis in the treatment of gastric cancer. However, the main role of surgery is removal of the visible tumor; surgery cannot eradicate micrometastatic cancer cells that are scattered outside of the surgical field or systemically before and during surgery. These invisible cancer cells gradually proliferate and form a visible mass that can be detected by imaging or

physical examination, a phenomenon referred to as a recurrence. The aims of adjuvant chemotherapy are "to cure" the macroscopic cancer after complete resection, whereby tumors that have grown to be macroscopically recognizable are no longer curable.[2,3]

The types of recurrence pattern after gastrectomy include locoregional recurrence, distant (lymph node or hematogenous) metastasis, and peritoneum metastasis. There are differences in the incidence of types of recurrence pattern between East Asian and Western patients with locally advanced gastric cancer. While locoregional recurrence and hematogenous metastasis are common in the United States, peritoneal, hematogenous, and lymph node metastasis are more common in East Asia.[4–6] Therefore, adjuvant chemotherapy is the standard therapeutic strategy following resection in Japan and South Korea in contrast to standard adjuvant chemoradiation in the United States. Further, it is known that there are differences in efficacy among the anticancer agents and regimens of chemotherapy for the different recurrence patterns. In this review, we summarize recent (2008–2018) evidence on the benefits of adjuvant therapy for locally advanced gastric cancer from the viewpoint of the recurrence pattern.

2 | CURATIVE SURGERY WITH D2 LYMPH NODE DISSECTION

Complete surgical resection is the essential treatment for locally advanced gastric cancer. Because pathological lymph node metastasis in gastric cancer has been reported in about 15% of early gastric cancer and 40%-70% of pathological T2-4a tumors, gastrectomy with lymphadenectomy is necessary.[7] A follow-up report from a Dutch trial showed that gastric cancer-related death was significantly less after D2 as compared to D1 gastrectomy.[8] However, D2 plus para-aortic lymph node dissection did not improve the survival rate of patients with curable gastric cancer in a Phase III trial performed in Japan.[9] Given these facts, D2 gastrectomy has become the standard surgical procedure for locally advanced gastric cancer in East Asia, particularly in Japan and South Korea.[10,11] This type of surgery is now also recommended in the United States and Europe as well.[12,13] According to the results of two Phase III studies in Japan and Korea that showed a survival benefit for adjuvant chemotherapy following D2 gastrectomy compared with surgery alone for locally advanced gastric cancer, locoregional recurrence after 5-year follow-up in the surgery alone group was still satisfactory with a low incidence (3.2% vs 10.1%, respectively).[5,6] These findings suggest that standardized D2 gastrectomy alone without adjuvant chemotherapy for locally advanced gastric cancer can adequately control locoregional recurrence. Hence, efficacy of adjuvant therapy should be discussed on the premise that locoregional recurrence can be maximally controlled by standardized D2 gastrectomy.

3 | POSTADJUVANT CHEMOTHERAPY

Since 2005, two pivotal randomized Phase III trials conducted in East Asia, the ACTS-GC and CLASSIC trials, demonstrated the efficacy of postoperative adjuvant chemotherapy in survival of patients with pathological stage III (pStage III) gastric cancer.[5,6] Although treatment with S-1 for 1 year or combination therapy with capecitabine and oxaliplatin for 6 months is effective, approximately 20%–30% of patients still develop recurrence. Comparing these two pivotal studies from the point of view of the recurrence pattern, S-1 monotherapy reduced peritoneal recurrence, with only a small effect on hematogenous metastasis (Table 1).[5] In contrast, adjuvant treatment with capecitabine plus oxaliplatin had a smaller effect on peritoneal recurrence.[6] The possible reason for these differences in recurrent pattern is that clinical effect of adjuvant treatment is highly dependent on the efficiency of the drug delivery to recurrent organ sites. Hence, adjuvant treatment should be considered according to the different pattern of recurrence in each patient.

3.1 | S-1-based doublet combination regimens

Subgroup analysis in the ACTS-GC trial showed that S-1 monotherapy reduced lymph node metastasis in both pStage II and III patients, while S-1 reduced peritoneal recurrence only in pStage II cases (Table 2).[14] Further, S-1 is less effective for pStage IIIB gastric cancer (HR: 0.791; 95% CI: 0.520-1.205), in contrast to a clear survival benefit of S-1 for pStage II and IIIA cases.[5] Therefore, S-1-based doublet combination regimens as postoperative adjuvant chemotherapy are expected to improve survival in comparison to S-1 monotherapy. Several Phase II studies have been conducted to evaluate the feasibility and safety of these doublet combination regimens. Kodera et al. evaluated the efficacy of treatment with S-1/cisplatin as postoperative adjuvant chemotherapy.[15] Subsequently, the acceptable compliance with S-1/cisplatin was shown in administration with initiating cisplatin after one course of S-1 monotherapy.[16,17] However, cisplatin has several disadvantages, including renal toxicity and the need for hospital stay. Thus, the CLASSIC trial replaced cisplatin with oxaliplatin and succeeded in reducing gastrointestinal toxicity. The Japan Clinical Cancer Research Organization (JACRO) conducted the GC-07 trial, a Phase III study, comparing S-1/docetaxel (oral S-1 at 80–120 mg/body on days 1–14 with 7 days of rest followed by six

TABLE 1 Comparison of first recurrence pattern between 5-year follow-up of ACTS-GC[5]and CLASSIC trial[6]

	ACTS-GC trial		CLASSIC trial	
	S-1 group (n = 529)	Surgery alone (n = 530)	XELOX group (n = 520)	Surgery alone (n = 515)
	Number of patients (%)			
Total number of relapses	162 (30.6)	221 (41.7)	117 (23)	186 (36)
Local	11 (2.1)	17 (3.2)	27 (5.2)	52 (10.1)
Distant	91 (17.2)	125 (23.6)	63 (12.1)	102 (19.8)
Lymph nodes	30 (5.7)	54 (10.2)	-	-
Hematogenous	61 (11.5)	71 (13.4)	-	-
Peritoneum	77 (14.6)	100 (18.9)	53 (10.2)	60 (11.7)

cycles of S-1 at the same dosage and schedule combined with docetaxel 40 mg/m^2 on day 1 of each cycle, and then four further cycles of S-1 at 80-120 mg/body on days 1–28, every 42 days) with S-1 alone (eight cycles of S-1 at 80–120 mg/body on days 1–28, every 42 days) following D2 gastrectomy for pStage III gastric cancer. The results of this trial were presented at the ASCO 2018 meeting.[18] The 3-year recurrence-free survival (RFS) of the S-1/docetaxel arm at 65.9% was significantly superior to that of S-1 alone arm at 49.6% (HR: 0.632; 99% CI: 0.400-0.998; P = 0.0007) at the planned second interim, and the independent data and safety monitoring committee recommended termination of the trial. Although S-1 monotherapy could not reduce hematogenous metastasis in all stages of cancer and peritoneal recurrence in stage III cases[5,14], S-1/docetaxel suppressed all types of recurrence including hematogenous, lymph node, and peritoneal metastases. Given these findings, S-1/docetaxel is recommended as the new standard regimen of postadjuvant chemotherapy for pStage III gastric cancer after curative D2 gastrectomy.

3.2 | Duration of postadjuvant chemotherapy

The Japan Clinical Oncology Group (JCOG) conducted the OPAS-I (JCOG1104) trial, a Phase III study, to evaluate the overall efficacy of four courses of S-1 adjuvant chemotherapy as compared to eight courses of the same regimen in patients who were diagnosed with pStage II after surgery. At the planned first interim, four courses of S-1 were inferior to eight courses of S-1 in terms of RFS, and the independent data and safety monitoring committee recommended termination of the trial.[19] The updated results of this trial were presented at the ASCO 2018 meeting.[20] The 3-year RFS was 89.8% for four courses and 93.1% for eight courses (HR: 1.84; 95% CI: 0.94–3.63), and the 3-year OS was 92.6% for the four courses and 96.1% for the eight courses (HR: 3.34; 95% CI: 1.22–9.12) of treatment. The cumulative incidence of recurrence at 3 years was 7.7% for the four courses and 5.5% for the eight courses (HR: 1.59; 95% CI: 0.75–3.39) of S-1. The 5-year follow-up report of the ACTS-GC trial showed improved survival in patients with postoperative administration of S-1 for one year compared with those who were administered for less than one year.[14] This report also showed poor 3-year survival rate in patients who were given S-1 at less than 70% dose intensity. Fujitani et al. retrospectively evaluated the duration and time to initiation of S-1 among 498 patients with pStage II/III gastric cancer.[21] They showed that patients treated for a longer duration (≥6 months) with S-1 had significantly longer survival compared with those for a shorter duration (<6 months) (74.3% vs 53.0%, respectively, in 5-year OS; HR: 0.498; 95% CI: 0.355–0.706), while time to initiation was not associated with OS. Given these results, the duration of postoperative S-1 monotherapy is recommended for one year, even with 30% reduction in dose and late initiation after surgery.

The Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) conducted two Phase II studies to evaluate the feasibility and safety of postoperative doublet chemotherapy with S-1/docetaxel (S-1 at 80–120 mg/body on days 1–14 with 7 days of rest combined with docetaxel 40 mg/m^2 on day 1 of each course, followed by S-1 at 80–120 mg/body on days 1–28, every 42 days until one year after surgery) in patients with pStage III gastric cancer.[22,23] In these two studies, they reported the feasibility and safety of four courses and eight courses of S-1/docetaxel, respectively. Comparing the results of these two studies, the 3-year OS with four and eight courses of therapy was 78.4% (95% CI: 67.9–90.6%) and 83.1% (95% CI: 74.1–93.3%), respectively, and the 3-year DFS was 66.2% (95% CI: 54.4–80.7%) and 68.5% (95% CI: 57.7–81.3%), respectively. More recently, as mentioned above, the JACRO phase III study reported that the 3-year RFS using six cycles of S-1/docetaxel followed by S-1 again was 65.9%. According to these findings, the recommended duration of postadjuvant chemotherapy after curative D2 gastrectomy is one year for S-1 monotherapy for pStage II disease and more than six cycles of S-1/docetaxel followed by S-1 for pStage III gastric cancer.

3.3 | Postadjuvant chemoradiation

Due to the lack of evidence regarding the effect of postadjuvant therapy with chemoradiation after D2 gastrectomy, postadjuvant chemotherapy is the standard strategy after D2 gastrectomy in Japan and Korea. The ARTIST trial in Korea was the first study conducted to investigate the role of postoperative chemoradiotherapy in

TABLE 2 Comparison of first recurrence pattern between each pStage in 5-year follow-up report of ACTS-GC[14]

	pStage II		pStage IIIA		pStage IIIB	
	S-1 group (n = 232)	Surgery alone (n = 233)	S-1 group (n = 194)	Surgery alone (n = 203)	S-1 group (n = 89)	Surgery alone (n = 83)
	Number of patients (%)					
Total number of relapses	38 (16.4)	67 (28.8)	67 (34.5)	94 (46.3)	53 (59.6)	51 (61.4)
Local	5 (2.2)	6 (2.6)	3 (1.5)	7 (3.4)	3 (3.4)	3 (3.6)
Lymph nodes	10 (4.3)	16 (6.9)	9 (4.6)	21 (10.3)	10 (11.2)	15 (18.1)
Hematogenous	14 (6.0)	22 (9.4)	27 (13.9)	34 (16.7)	17 (19.1)	12 (14.5)
Peritoneum	13 (5.6)	31 (13.3)	36 (18.6)	37 (18.2)	26 (29.2)	28 (33.7)

patients after curative-resected gastric cancer with D2 gastrectomy.[24] This trial was designed to investigate the OS following postoperative treatment with capecitabine plus cisplatin (XP) as compared to XP plus radiotherapy with capecitabine (XP/XRT/XP) in clinically diagnosed stage IB-IV (M0) gastric cancer patients. Consequently, the addition of XRT to XP chemotherapy did not significantly reduce recurrence after curative D2 gastrectomy in gastric cancer. Because the results of the subgroup analysis suggested a significant disease-free survival (DFS) effect of chemoradiotherapy in subsets of patients with node-positive disease, the ARTIST 2 trial (Clinical-Trials. gov identifier: NCT0176146) was established and is currently underway to evaluate adjuvant chemotherapy and chemoradiotherapy in patients with node-positive gastric cancer after D2 gastrectomy.

4 | NEOADJUVANT (PERIOPERATIVE) CHEMOTHERAPY

4.1 | Neoadjuvant chemotherapy for bulky lymph node metastasis and scirrhous type cancer in Japan

In Japan, postadjuvant chemotherapy alone could satisfactorily improve survival in locally advanced cancer after D2 gastrectomy, thus, the primary target of neoadjuvant chemotherapy is a selected population of locally advanced cancer that is either unresectable by the surgery-first approach or has a poor prognosis, such as cases with extensive lymph node metastases or a scirrhous phenotype.

It is difficult to treat local gastric cancer with advanced lymph node metastasis such as bulky metastasis in second-tier lymph nodes or metastasis in the No. 16b1/16a2 regions (Bulky N population) by surgery, even with postoperative chemotherapy. For this bulky N population, the JCOG0405 Phase II study was conducted to evaluate the safety and efficacy of neoadjuvant chemotherapy consisting of two courses of S-1/cisplatin, followed by D2 plus para-aortic lymph node dissection.[25] A combination of S-1 (S-1 at 80–120 mg/body on days 1–21, every 28 days) and cisplatin (60 mg/m^2 on day 1), which is the standard first-line treatment for advanced/metastatic gastric cancer in Japan, was the administered regimen in this study. The R0 resection rate was 82%, and the 3-year and 5-year OS were unexpectedly high at 59 and 53%, respectively. Subsequently, another Phase II trial for the bulky N population was conducted to evaluate neoadjuvant therapy using a triplet regimen with DCS (docetaxel at 40 mg/m^2 on day 1, cisplatin at 60 mg/m^2 on day 1, S-1 at 80–120 mg/body on days 1–14, every 28 days).[26] However, the response rate of this DCS regimen at 58% did not reach the expected value of 80%, thus, S-1/cisplatin remains the current standard. Neoadjuvant chemotherapy with S-1/cisplatin followed by D2 plus para-aortic lymph node dissection is now considered tentatively as the standard of care for this specific population.[27]

The scirrhous type cancer, such as type 4 or large type 3 gastric cancer with >8 cm diameter, is characterized by poorly differentiated adenocarcinoma including the histological presence of signet ring cells and by frequent peritoneal recurrence. The JCOG0501 trial, a Phase III study, was conducted to confirm the efficacy of neoadjuvant chemotherapy with S-1/cisplatin in scirrhous type gastric cancer with OS as the primary endpoint. The results of this Phase III trial were presented at the ASCO 2018 meeting.[28] Pathological response induced by neoadjuvant chemotherapy was observed in 51.0% (95% CI: 42.7–59.2) of patients. At the median follow-up at 4.5 years, the 3-year OS was 62.4% (95% CI: 54.1–69.6) in those with the postadjuvant alone arm and 60.9% (95% CI: 52.7–68.2) in the neoadjuvant plus postadjuvant arm (HR: 0.916; 95% CI: 0.679–1.236; P = 0.284). The 3-year progression-free survival (PFS) was 47.7% (95% CI: 39.4–55.4) in the postadjuvant alone arm and 47.7% (95% CI: 39.5–55.4) in the neoadjuvant plus postadjuvant arm (HR: 0.976; 95% CI: 0.738–1.292). Thus, the addition of neoadjuvant chemotherapy did not appear to affect the survival rate of the patients. Following the results of this trial, additional neoadjuvant chemotherapy with S-1/cisplatin followed by postadjuvant treatment with S-1 for gastric cancer with a scirrhous type phenotype is not recommended.

4.2 | Neoadjuvant chemotherapy for clinical stage III cancer in Japan

Upon expanding the target of neoadjuvant chemotherapy to resectable advanced gastric cancer, there was a concern of the accuracy of preoperative staging. Thus, the JCOG1302-A trial was conducted to evaluate the accuracy of preoperative staging using multidetector computerized tomography and endoscopy.[29] The optimal preoperative combination of T and N categories that had a reasonably high possibility of identifying clinical stage III (cStage III) cancer while ruling out stage I cancer was determined to be T3-T4/N+. For these cStage III (T3-T4/N+) gastric cancer patients, the NAGISA (JCOG1509) Phase III trial is currently being conducted to evaluate and compare preoperative chemotherapy with S-1/oxaliplatin (SOX) followed by surgery and postoperative chemotherapy, with surgery and postoperative chemotherapy. According to the recurrence pattern in the ACTS-GC and CLASSIC trials, SOX is also promising to reduce both hematogenous and peritoneal recurrence.

4.3 | Perioperative chemotherapy in Europe

Neoadjuvant chemotherapy consisting of three courses of ECF (epirubicin/cisplatin/infusional 5-FU) combined with surgery and three postoperative courses of ECF, has been the standard treatment for resectable gastric cancer in Europe. Recently, the German FLOT4 trial established the perioperative FLOT regimen (docetaxel/oxaliplatin/5-fluorouracil) as the new treatment standard for resectable adenocarcinoma of the gastroesophageal junction and the stomach.[30] Results of this Phase III part of the trial were reported at the ASCO 2017 meeting.[31] The FLOT regimen significantly increased rates of curative surgery and prolonged median PFS (18 vs 30 months) and median OS (35 vs 50 months) as compared to the ECF/ECX (epirubicin/cisplatin/oral capecitabine) regimen in Western countries, S-1 is licensed in advanced gastric cancer in combination with cisplatin only.[32] However, due to the pharmacogenomic

differences in Western patients, the maximum tolerated dose of S-1 with cisplatin is lower than that in Asian patients.[33] Accordingly, FLOT can be considered the new standard care in perioperative treatment for European patients with resectable gastric and gastroesophageal junction adenocarcinoma.

4.4 | Duration of neoadjuvant chemotherapy

The optimal regimen and number of courses for neoadjuvant therapy are issues to resolve. The COMPASS trial compared two and four courses of doublet neoadjuvant regimen with S-1/cisplatin and paclitaxel/cisplatin for a mixed population of patients with advanced gastric cancer (bulky N, type 4 or large type 3 cancer, and advanced junctional adenocarcinoma).[34] The 3-year OS was 60.9% for S-1/cisplatin, 64.3% for paclitaxel/cisplatin, 64.3% for the two courses, and 61.0% for the four courses of neoadjuvant therapy, while the R0 resection rate was 78.0%, 71.4%, 73.8%, and 75.6%, respectively. The COMPASS-D trial compared two and four courses of doublet neoadjuvant regimen with S-1/cisplatin and triplet neoadjuvant regimen with DCS.[32] In an early report of this trial, the rate of pathological response, defined as a complete response or <10% residual cancer remaining, was 19.4% in the S-1/cisplatin group, 15.4% in the DCS group, 15.6% in the two courses group, and 19.0% in the four courses group, while the R0 resection rate was 72.7%, 81.8%, 80.3%, and 74.2%, respectively. These two trials suggested that two cycles of doublet combination neoadjuvant regimens that include S-1 are recommended as a test arm of a future Phase III study for patients with locally advanced gastric cancer.

4.5 | Ongoing studies on molecular-targeted therapy and immunotherapy in combination with adjuvant chemotherapy for gastric cancer

When the tumor shows HER2 positivity, regimens combined with trastuzumab is promising as a neoadjuvant chemotherapy. The JCOG1301 Phase III study is currently underway to evaluate the efficacy of neoadjuvant therapy using trastuzumab in combination with S-1/cisplatin for the bulky N population.[35]

A fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody has demonstrated survival benefits for various tumors. ATTRACTION-05 Phase III study is ongoing to evaluate the efficacy of nivolumab in combination with postoperative chemotherapy (S-1 or capecitabine plus oxaliplatin) in pStage III gastric and esophagogastric junction cancer.[36] KEYNOTE-585 Phase III study is also underway to evaluate the efficacy of pembrolizumab in combination with perioperative chemotherapy (cisplatin with either oral capecitabine or intravenous5-fluorouracil) for patients with locally advanced gastric and esophagogastric junction cancer.[37]

5 | CONCLUSION

D2 gastrectomy has become a global standard procedure for locally advanced gastric cancer to maximally reduce locoregional recurrence. In East Asia, postadjuvant chemotherapy using S-1 monotherapy or capecitabine and oxaliplatin after curative D2 gastrectomy is the standard pre-emptive or facilitative strategy. The addition of S-1 and docetaxel, the current new standard regimen of postadjuvant chemotherapy, is promising to reduce even distant metastasis and improve prognosis in resected pStage III gastric cancer. Further, new Phase III studies that evaluate neoadjuvant chemotherapy using S-1-based combination regimens are expected to provide new results on the treatments that will improve survival of patients with cStage III as well as extensive lymph node metastases.

DISCLOSURE

Conflict Of Interest: Authors declare no conflict of interests for this article.

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