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ORIGINAL ARTICLE

Short-term outcomes of a phase II trial of perioperative capecitabine plus oxaliplatin therapy for advanced gastric cancer with extensive lymph node metastases (OGSG1701)

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Abstract

Background The prognosis of advanced gastric cancer (GC) with extensive lymph node (LN) metastasis treated with surgery alone remains poor. We conducted a multicenter phase II study to evaluate the efficacy and safety of perioperative capecitabine plus oxaliplatin (CapeOx) therapy in patients with advanced GC with extensive LN metastases.

Patients and Methods Patients with histologically proven HER2-negative or unknown gastric adenocarcinoma with paraaortic LN (PALN) metastases and/or bulky LN metastases located at the celiac axis, common hepatic artery, and/or splenic artery were included in the study. Patients received three cycles of preoperative CapeOx every 3 weeks, followed by five cycles of postoperative CapeOx after gastrectomy with D2 or D2 + including PALN dissection. The primary endpoint was the response rate (RR) according to the RECIST v1.0 criteria.

Results Thirty patients from 14 institutions were enrolled from September 2017 to June 2022. Complete response, partial response, stable disease, and progressive disease occurred in zero, 20, eight, and one patient, respectively. One patient was not evaluated. The RR was 66.7% (90% confidence interval, 50.1–80.7%; one-sided P = 0.049). The preoperative chemotherapy completion rate and the curative resection rate were 96.7% and 93.3%, respectively. The minor (grade ≥ 1b) pathological RR was 66.7%. Grade 3 adverse events of preoperative chemotherapy included neutropenia in 3.3%, anemia in 6.7%, and anorexia in 10.0%. One treatment-related death occurred due to postoperative complications.

Conclusion Preoperative CapeOx chemotherapy showed a favorable RR, curative resection rate, and acceptable adverse events in patients with advanced GC with extensive LN metastasis.

Registration number UMIN000028749 and jRCTs051180186.

Keywords Advanced gastric cancer · Perioperative chemotherapy · Extensive lymph node metastases · Capecitabine · Oxaliplatin

Introduction

Gastric cancer (GC) has among the poorest prognoses of all cancers worldwide [1]. Surgery alone does not provide satisfactory outcomes, and perioperative chemotherapy has accordingly become the global standard of care for patients with advanced GC [2, 3]. The FLOT4 trial, conducted in Germany, showed that fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) was associated with more favorable survival than fluorouracil or capecitabine plus cisplatin and epirubicin in patients with resectable advanced GC, and FLOT is thus considered a useful perioperative chemotherapy regimen [4].

S-1, S-1 plus docetaxel, or capecitabine plus oxaliplatin (CapeOx) is the standard of care after gastrectomy for advanced GC in Japan, while the benefits of perioperative treatment, including preoperative chemotherapy, are currently being investigated in clinical trials [5–7]. In addition, perioperative chemotherapy is being developed for GC with paraaortic (PA) lymph node (LN) or bulky LN metastasis with a poor prognosis, even if preceded by gastrectomy. Several phase II trials have investigated the efficacy of preoperative chemotherapy in patients with GC

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with a poor prognosis. Cisplatin plus S-1 therapy showed a 65% clinical response rate (RR), while preoperative chemotherapy with a triplet regimen of docetaxel and cisplatin plus S-1 showed a 58% clinical RR in patients with GC with PALN or bulky LN metastasis [8, 9]. Preoperative docetaxel, oxaliplatin, and S-1 (DOS) therapy has demonstrated a favorable major (grade ≥ 2) pathological RR (pRR) of 65% and pathological complete response (CR) rate of 24% in patients with GC with PALN and/or bulky LN metastases, but the standard of care is still unclear [10].

The doublet regimen of CapeOx therapy has shown a relatively high RR of around 50% in patients with GC, and is recommended in Japanese GC treatment guidelines as a first-line treatment regimen for unresectable or recurrent GC [11–13]. CapeOx therapy has recently become the standard of care and the baseline chemotherapy regimen in phase III trials designed to demonstrate the efficacy of immune checkpoint inhibitors or molecular targeted agents in combination with chemotherapy in patients with advanced GC, and is recognized globally as an effective chemotherapy regimen [14–16]. In addition, CapeOx therapy has become the standard of care as postoperative adjuvant chemotherapy, and eight courses or 6 months of CapeOx therapy resulted in significantly better survival than surgery alone in the CLASSIC trial including patients with stage II or III GC (hazard ratio [HR]: 0.66, 95% confidence interval [CI] 0.51–0.85; P = 0.0015) [13, 17]. Compliance with postoperative adjuvant chemotherapy, however, may be compromised due to excessive invasion and postoperative complications in patients undergoing gastrectomy for advanced GC with extensive LN metastases that are difficult to resect without preoperative treatment or have a very poor prognosis, even if curative resection is possible, and appropriate preoperative treatments are therefore needed.

Regarding cycles of preoperative treatment, most phase III clinical trials, such as the Magic and PRODIGY trials, demonstrated favorable outcomes following three cycles of preoperative chemotherapy [2, 18], while two cycles of preoperative docetaxel and cisplatin plus S-1 did not provide the expected RR [9]. In the FLOT4 trial, patients received four cycles of 8 weeks of preoperative chemotherapy, with a standard duration of 2–3 months. To maximize the effects of CapeOx therapy, which has demonstrated high anti-tumor efficacy and postoperative adjuvant chemotherapy effects, we considered that three preoperative and five postoperative cycles, rather than the original eight cycles of postoperative CapeOx therapy, might provide safe and effective adjuvant therapy. We therefore conducted a multicenter phase II study to evaluate the efficacy and safety of perioperative CapeOx therapy (three preoperative and five postoperative cycles) in patients with advanced GC with extensive LN metastases, who were difficult to resect without preoperative treatment or who had a very poor prognosis, even if curative resection could be achieved.

Patients and methods

Study design and patients

The OGSG 1701 trial was a single-arm, prospective, multicenter phase II trial. The trial was conducted in accordance with the international ethical recommendations stated in the Declaration of Helsinki. The protocol was approved by the institutional review and ethics board of each participating hospital and was registered in the University Hospital Medical Information Network (UMIN) database (UMIN000028749) and Japan Registry of Clinical Trials (jRCTs051180186). Written informed consent was obtained from all patients before enrollment. Study chemotherapy treatment was initiated within 14 days of enrollment.

The eligibility criteria were as follows: (1) histologically proven GC; (2) HER2-negative or unknown; (3) LN metastasis (> 1 cm based on enhanced computed tomography (CT)) in PALN stations (no. 16a2 or 16b1) or bulky LN metastasis (one LN > 3 cm or two LNs > 1.5 cm based on enhanced CT) in stations no. 7, 8a, 9, 11, 12a, or 14v; (4) no mediastinal LN, lung, peritoneal, liver, or other distant metastases on enhanced CT, no PALN metastasis other than no. 16a2/16b1, no pleural effusion or ascites; (5) no Borrmann type 4 or type 3 tumor > 8 cm; (6) no esophageal invasion or invasion ≤ 3 cm; (7) no gastric stump cancer; (8) no clinical signs of cervical LN or distant metastases; (9) age 20–80 years; (10) Eastern Cooperative Oncology Group performance status 0–1; (11) no prior chemotherapy, radiotherapy, or endocrine therapy for any malignancies; (12) no prior gastrectomy except bypass surgery and endoscopic resection; (13) fair oral intake with or without bypass surgery; (14) adequate organ function (Supplementary text 1); and (15) written informed consent. Patients with synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ or mucosal carcinoma, poorly controlled comorbidities, or severe medical conditions were excluded. Tumor stage and D classifications were in accordance with the Japanese Classification of Gastric Carcinoma, third English edition, and the seventh edition of the International Union Against Cancer TNM staging system [19, 20].

Treatment

Three cycles of neoadjuvant CapeOx were administered, followed by five cycles of adjuvant CapeOx after gastrectomy, based on the OGSG1601 trial [21]. Patients who met the above eligibility criteria were given 1000 mg/m^2 capecitabine orally twice daily (2000 mg/m^2/day) for 2 weeks with

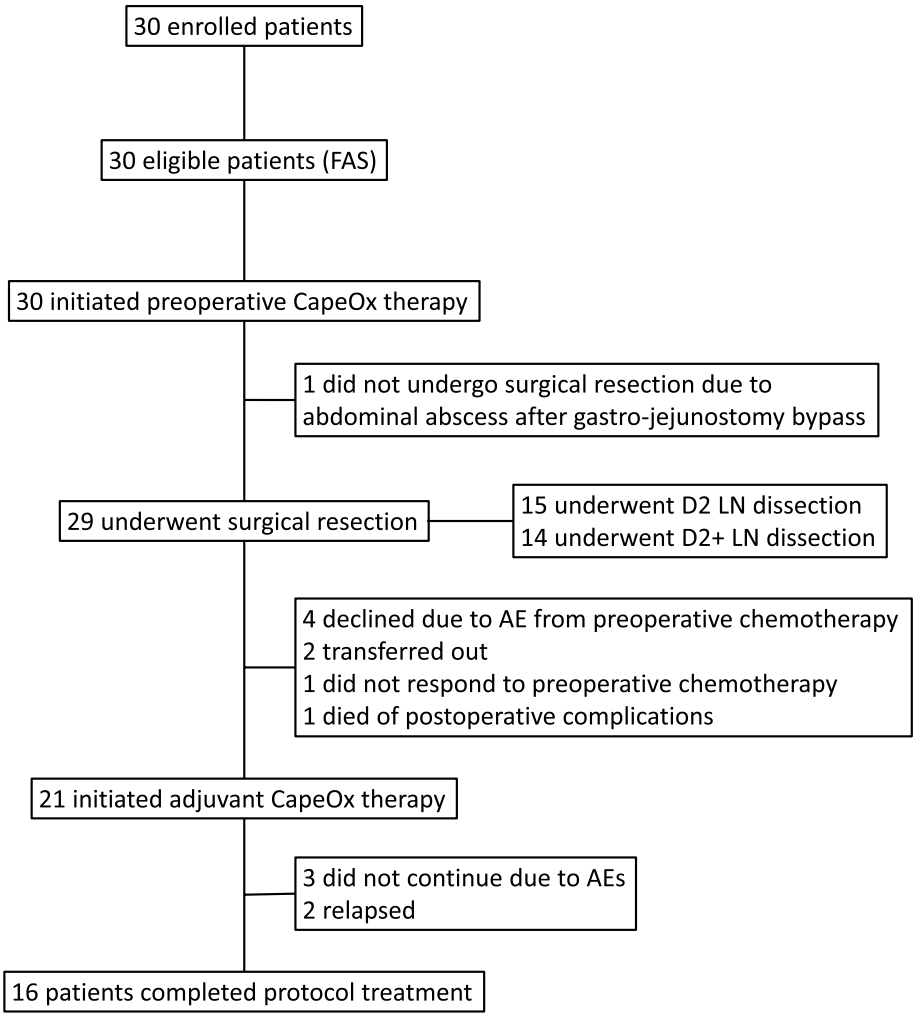

Fig. 1 Consort diagram. *FAS* full analysis set, *CapeOx* capecitabine plus oxaliplatin, *LN* lymph node, *AE* adverse event

intravenous oxaliplatin (130 mg/m^2) on day 1, repeated every 3 weeks (one cycle). Three cycles of CapeOx therapy were administered preoperatively, unless clear disease progression or unacceptable toxicity was observed. Tumor response was assessed after three cycles of preoperative chemotherapy. If judged to be resectable, surgery, involving total or partial gastrectomy, was performed between 14 and 56 days after the last administration of capecitabine. LN dissection consisted of D2 dissection plus sampling of LNs suspected of metastasis prior to treatment or paraaortic no. 16a2/b1 LN dissection. In cases with direct invasion of surrounding organs, partial or total excision of the invaded organ was performed if it could be easily combined with resection; however, left upper abdominal exenteration, pancreaticoduodenectomy, Appleby's operation, peritonectomy, and total gastrectomy plus esophageal subtotal resection were not permitted. If R0 resection was judged to be impossible, protocol treatment was discontinued. If gastrectomy with R0 was performed, five cycles of postoperative CapeOx therapy were initiated 4–6 weeks after gastrectomy. A total of eight cycles of perioperative CapeOx were administered in total. The patient was allowed to undergo surgery after two preoperative cycles followed by six cycles of postoperative adjuvant chemotherapy, at the discretion of the attending physician.

For preoperative chemotherapy, capecitabine was reduced to 1500 or 1000 mg/m^2/day and oxaliplatin was reduced to 100 mg/m^2, depending on the grade of adverse events (AEs) (Supplementary text 2).

The initial dose of postoperative chemotherapy was recalculated based on the patient's height and weight within the first week of treatment; however, if the final dose of the third and final cycle of preoperative chemotherapy was lower, the final dose of preoperative chemotherapy was used as the dose for adjuvant chemotherapy. If the patient's weight after 29 postoperative Days was > 15% below the weight at registration, or if the attending physician determined that the patient had not recovered sufficient strength after surgery, the patient was started on capecitabine alone.

Table 1 Patient characteristics

	(n = 30)
Age, years	
Median (range)	66 (40–78)
Sex	
Male	24 (80%)
Female	6 (20%)
ECOG performance status	
0	25 (83%)
1	5 (17%)
Main tumor location	
Upper third	12 (40%)
Middle third	8 (27%)
Lower third	9 (30%)
Esophagus	1 (3%)
Esophageal involvement	
Absent	26 (87%)
Present	4 (13%)
Macroscopic type	
0	3 (10%)
1	1 (3%)
2	9 (30%)
3	16 (53%)
5	1 (3%)
Histological type	
Intestinal	14 (47%)
Diffuse	16 (53%)
Depth of tumor invasion (T)	
cT2 (MP)	5 (17%)
cT3 (SS)	12 (40%)
cT4a (SE)	13 (43%)
Lymph node metastasis (N)	
cN1	10 (33%)
cN2	12 (40%)
cN3a	8 (27%)
Distant metastasis (M)	
cM0	13 (43%)
cM1	17 (57%)
cStage	
cStage IIB	4 (13%)
cStage IIIA	1 (3%)
cStage IIIB	7 (23%)
cStage IIIC	1 (3%)
cStage IV	17 (57%)
Node status	
Bulky lymph nodes only	13 (43%)
PALN only	15 (50%)
PALN and bulky lymph nodes	2 (7%)

ECOG Eastern Cooperative Oncology Group, *PALN* paraaortic lymph node

Endpoints

The primary endpoint of the study was the RR to preoperative treatment, evaluated by central peer review according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. [22] The secondary endpoints were 3-year overall survival and progression-free survival, percentage completion of preoperative adjuvant chemotherapy, R0 resection, and protocol treatment, relative dose intensities (RDIs) of capecitabine and oxaliplatin in preoperative and postoperative adjuvant chemotherapy, minor (grade ≥ 1b) pRR based on the Japanese Classification of Gastric Carcinoma criteria, AEs of preoperative and postoperative adjuvant chemotherapy, surgical complications, and RR according to the RECIST version 1.1 [23]. RDI was defined as the ratio of the delivered dose intensity to the planned dose intensity of capecitabine or oxaliplatin. AEs of chemotherapy were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and the Clavien-Dindo classification [24]. Surgical complications were evaluated according to the Clavien-Dindo classification [25]. Pathological response was evaluated and graded by the institutional pathologists, according to the Japanese classification of gastric carcinoma, third edition [19].

Follow-up

All patients were followed up for a minimum of 3 years from the start of treatment. CT scans were performed every 6 months until the third postoperative year and every year until the fifth postoperative year. Relapse was confirmed by imaging studies, including ultrasonography, CT, and gastrointestinal endoscopy.

Statistical analysis

The primary endpoint was the RR, defined as the percentage of patients who achieved CR and partial response (PR), according to RECIST v1.0. The expected RR for preoperative CapeOx therapy in this study was 65%, with reference to the results of JCOG0405 [8]. The 90% CI was set so that the lower confidence limit was ≥ 50%, assuming that the RR in this study was the same as that in JCOG0405 [8]. With these settings, 28 patients were required for the interval width of the 90% CI for the RR to be < 15% on one side. The total sample size was set at 30 patients to account for deviation.

Clopper-Pearson's exact method was used to calculate the 90% CIs for the primary endpoint of RR. Regarding the secondary endpoints, overall and progression-free survival curves were estimated using the Kaplan–Meier method, and CIs were estimated using the Greenwood formula. Binary outcomes were summarized as frequency and proportion,

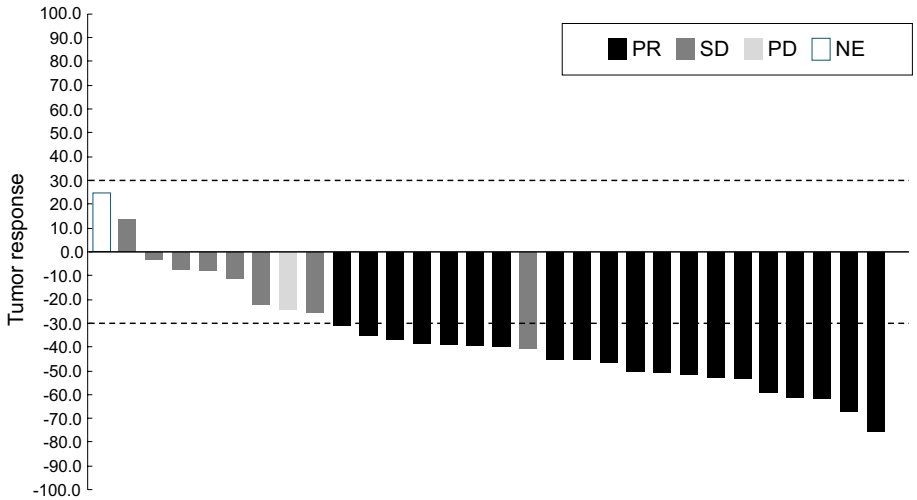

Fig. 2 Waterfall chart of clinical tumor response. *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluated

and exact 95% CIs were calculated using the Clopper-Pearson method.

The primary endpoint was based on the full analysis set and AEs of postoperative adjuvant chemotherapy were analyzed in patients who received this treatment. Statistical analysis was conducted using R version 4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Thirty patients from 14 institutions were enrolled in this study between March 2018 and June 2022 (Fig. 1). The patients' characteristics are shown in Table 1. Fifty percent of patients had bulky LN metastases, 56.7% had PALN metastases, and 6.7% had both.

There were no CRs, 20 patients had PR, eight patients had stable disease, and one patient had progressive disease (PD). One patient was not evaluated because they only received one cycle of preoperative chemotherapy due to AEs. The RR according to RECIST ver1.0 for the primary endpoint was 66.7% (90% CI, 50.1–80.7%; 95% CI, 47.2–82.7%) (Fig. 2). The null hypothesis was rejected (one-sided $P = 0.049$). The disease-control rate was 93.3% (95% CI, 77.9–99.2%). The RR for the 24 patients evaluable with RECIST ver1.1 was 83.3% (95% CI, 62.6–95.3%). The minor pRR was 66.7% (95% CI, 47.2–82.7%) and pathological CR was attained in six (20%) patients (Table 2).

Three patients with PALN metastases did not undergo PALN dissection because they had disappeared on imaging. Twenty-nine patients (96.7%) completed preoperative chemotherapy, whereas one patient enrolled after gastrojejunostomy bypass discontinued treatment after one cycle due to a grade 3 abdominal abscess.

The percentage completion of R0 resection was 93.3% (95% CI, 77.9–99.2%). One patient had peritoneal metastasis at laparotomy and one was not operated on because of abdominal abscess after gastro-jejunostomy bypass. One patient required Appleby's operation for radical resection. Postoperative adjuvant chemotherapy was administered in 21 patients (70%) and completed in 16 patients, with a continuation rate of 76.2%. The percent completion of the protocol treatment was 53.3% (95%CI, 34.3–71.7%).

The mean RDIs for preoperative adjuvant chemotherapy were 97.0% for capecitabine and 97.4% for oxaliplatin, and the mean RDIs for postoperative adjuvant chemotherapy were 88.5% for capecitabine and 72.1% for oxaliplatin.

AEs during preoperative and postoperative CapeOx chemotherapy are detailed in Table 3. Grade 3 hematological toxicities during preoperative therapy included neutropenia in one patient (3.3%) and anemia in two (6.7%). Grade 3 hematological toxicities in the 21 patients who received postoperative chemotherapy included neutropenia in five patients (23.8%). There were no treatment-related deaths (TRDs) associated with chemotherapy.

One patient died due to postoperative complications including an abdominal abscess, abdominal bleeding, and disseminated intravascular coagulation (Table 4). Grade 3 AEs in the 29 patients who underwent surgery included intestinal obstruction in two patients (6.9%), anastomotic leakage in one (3.4%), thromboembolism in one (3.4%), and ascites in one (3.4%).

Discussion

In this single-arm phase II trial, CapeOx provided a promising preoperative treatment regimen for patients with advanced GC with extensive LN metastases, with a favorable RR of 66.7% for the primary endpoint. In addition, CapeOx

Table 2 Pathological findings in resected patients

	(n = 29)
Depth of tumor invasion (T)	
ypT0	6 (21%)
ypT1a	1 (3%)
ypT1b	2 (7%)
ypT2	4 (14%)
ypT3	10 (34%)
ypT4	6 (21%)
Lymph node metastasis (N)	
ypN0	12 (41%)
ypN1	4 (14%)
ypN2	2 (7%)
ypN3	11 (38%)
Distant metastasis (M)	
ypM0	23 (79%)
ypM1	6 (21%)
Peritoneal metastasis (P)	
P0	29 (100%)
P1	0 (0%)
Peritoneal lavage cytology (CY)	
CYX	1 (3%)
CY0	27 (93%)
C Y1	1 (3%)
ypStage	
0	3 (10%)
IA	2 (7%)
IB	3 (10%)
IIA	4 (14%)
IIB	2 (7%)
IIIA	0 (0%)
IIIB	6 (21%)
IIIC	1 (3%)
IV	6 (21%)
Not stated	2 (7%)
Residual tumor (R)	
R0	28 (97%)
R1	1 (3%)
Histological evaluation criteria of tumor response* for 30 patients	
Grade 0	2 (7%)
Grade 1a	7 (23%)
Grade 1b	6 (20%)
Grade 2	8 (27%)
Grade 3	6 (20%)
Not evaluated	1 (3%)
Pathological response rate for 30 patients	
pRR (≥ Grade 1b) rate [95% CI]	66.7% [47.2%-82.7%]
pCR (Grade 3) rate [95% CI]	20.0% [7.7%-38.6%]

*According to the Japanese Classifcation of Gastric Carcinoma criteria

pRR pathological response rate, *CI* confidence interval, *pCR* pathological complete response

therapy showed a high curative resection rate (93.3%) and a favorable minor pRR (66.7%). There was one TRD due to surgical complications, but CapeOx therapy had a tolerable AE profile, both preoperatively and postoperatively.

GC cure requires radical resection, which is achieved by complete surgical resection of the primary tumor, as well as any organs invaded by the cancer and localized metastatic LNs, and the prognosis is poorer when the tumor cannot be completely resected. Even in the absence of distant metastasis, the occurrence of extensive LN metastasis is associated with a poor prognosis, because micrometastases are often present outside the surgical margin, even if the lesion is completely resected macroscopically by extended surgery with LN dissection. Adjuvant therapy is therefore considered necessary; however, compliance with adjuvant chemotherapy is poor due to postoperative complications from extensive LN dissection and the combined resection of invaded organs [26, 27]. Neoadjuvant chemotherapy is expected to be effective for the treatment of GC with extensive LN metastasis, as in the current study, due to high compliance because it is administered before surgery, the chemotherapy shrinks the LN metastasis and thus improves the curative resection rate, and it can also control micrometastases. A clinical trial in Japan of preoperative chemotherapy with cisplatin plus S-1 for patients with GC with PALN and/or bulky LN metastases reported a favorable RR of 64.7% and a curative resection rate of 82.4% [8]; however, preoperative triple therapy with docetaxcel, CDDP, and S-1, which further increased drug intensity, failed to show the expected RR of 57.7%, despite an increase in severe AEs [9]. A subsequent phase II clinical trial of DOS, in which CDDP was replaced by oxaliplatin, showed favorable results with a RR by RECIST of 65%, a major pRR of 57%, pathological CR rate of 24%, and a high R0 resection rate of 93%, suggesting that DOS therapy may be suitable for patients with GC with extensive LN metastases [10]. In contrast, FLOT has become the standard perioperative chemotherapy regimen worldwide, with a pRR of 32% for tumor regression grade (TRG) 1a or 1b by the Becker criteria, 47% for TRG 1a-2, and a pathological CR rate of 16% in the FLOT4 trial [28]. In the current phase II trial, CapeOx therapy had a high pathological CR rate of 20%, which was favorable for a doublet regimen, with no inferiority to the DOS and FLOT triplet regimens. The R0 curative resection rate for advanced GC with extensive LN metastasis was 93%, which was similar to that of DOS therapy.

The major grade 3 and 4 preoperative AEs were neutropenia in 24% and 52% and febrile neutropenia in 9% and 5% for the triplet regimens of DOS and FLOT, respectively [4, 10], while only 3% of patients had grade 3 or higher neutropenia following CapeOx therapy. As a result, the mean preoperative RDI of capecitabine was 97.0% (median 100%) and the mean RDI of oxaliplatin was 97.4% (median 100%), and the

Table 3 Adverse events during chemotherapy

	Preoperative chemotherapy (n = 30)					Postperative chemotherapy (n = 21)				
	Grade 1	Grade 2	Grade 3	Grade 4	%Grade 3–4	Grade 1	Grade 2	Grade 3	Grade 4	%Grade 3–4
Neutropenia	7	2	1	0	3.3	2	6	5	0	23.8
Anemia	14	4	2	0	6.7	12	4	0	0	0
Hypoalbuminemia	11	0	2	0	6.7	10	0	0	0	0
ALT increase	9	1	2	0	6.7	5	0	0	0	0
Hyperkalemia	1	0	0	0	0	0	1	0	0	0
Hypokalemia	3	0	1	0	3.3	4	0	0	1	4.8
Hypernatremia	1	0	0	0	0	2	0	0	0	0
Hyponatremia	2	0	1	0	3.3	0	0	0	0	0
Hypocalcemia	2	2	0	0	0	3	0	0	0	0
Nausea	8	2	1	–	3.3	5	4	0	–	0
Diarrhea	5	2	1	0	3.3	7	5	2	0	9.5
Anorexia	10	3	3	0	10	6	5	1	0	4.8
Fatigue	14	2	2	–	6.7	10	2	0	–	0
Hand-foot syndrome	4	0	1	0	3.3	2	1	0	0	0
Thromboembolism	0	0	1	0	3.3	0	0	0	0	0
Abdominal abscess	0	0	1	0	3.3	0	0	0	0	0
Anastomotic leakage	0	0	1	0	3.3	0	0	0	0	0

ALT alanine aminotransferase

preoperative treatment completion rate was 93.3%, which was considered to lead to the high response rate. There was no chemotherapy-induced TRD, but one patient died due to postoperative complications and this was considered a protocol TRD. This patient originally had advanced LN metastasis, indicating that, even if the LNs are reduced by preoperative chemotherapy, surgery should be carried out with extreme care.

The response rate for preoperative CapeOx therapy was higher than in previous studies because it was the best response. CapeOx has a similar clinical response rate to CS but a better R0 resection rate, and has the advantage of being administered on an outpatient basis, without the hydration required with CDDP [8]. CapeOx also had similar clinical and pathologic response rates and R0 resection rates to DOS, but could be administered safely, with a pre-treatment neutrophil count of $\geq 1500/m^2$ with 3% ≥ grade 3 neutropenia [10]. CapeOx therapy may be a candidate for preoperative chemotherapy because of its minor AEs and high RDI, which may have resulted in a higher pathological CR rate than previous reports; however, randomized controlled trials, such as those conducted for DOS, are needed before CapeOx can be recognized as a standard of care.

The incidence of grade 3 neutropenia during postoperative chemotherapy was 24%, which was markedly increased compared with preoperative chemotherapy, while the median RDIs for capecitabine and oxaliplatin were 82.7% and 75.4%, respectively, which were lower than for preoperative chemotherapy. Possible reasons for the low RDI of CapeOx included the high level of surgical invasiveness and the doublet regimen. Postoperative adjuvant chemotherapy in the PRODIGY trial comparing preoperative DOS to S-1 plus oxaliplatin was S-1 alone, with a median RDI of about 85% for S-1 [18]. The median postoperative RDIs for capecitabine and oxaliplatin were 85% and 98% after eight courses of adjuvant chemotherapy in the CLASSIC trial [6]; however, compared with the patients in the current study, patients in the CLASSIC study had less advanced disease and no preoperative treatment. In addition, the RDI for oxaliplatin may have been particularly low in this study (72.1%) because the protocol allowed postoperative adjuvant chemotherapy to be started at a reduced preoperative dose due to AEs during preoperative treatment, and the first postoperative course to be started with capecitabine alone, depending on the patient's condition after surgery. The completion rate of protocol treatment of 53%, or the percentage of patients who were able to continue postoperative adjuvant chemotherapy, was not lower than the 47% for the FLOT regimen [4]. Perioperative CapeOx therapy is expected to have a good prognosis, especially in patients with good compliance to preoperative chemotherapy.

This study had some limitations. It was a single arm phase II trial with a small number of patients (30), and the results must therefore be interpreted with caution. In addition, GC with extensive LN metastasis is not common, and the patients were thus enrolled over a prolonged period. Despite these limitations, this study showed that the double CapeOx regimen was not clearly inferior to

Table 4 Surgical outcomes for 29 patients

(a) Operative procedure	
Operation time, min	
Median (range)	320 (147–632)
Blood loss, ml	
Median (range)	390 (25–2884)
Blood transfusion	
Absent	24 (83%)
Present	5 (17%)
Approach	
Open	24 (83%)
Laparoscopic	4 (14%)
Robbotic	1 (3%)
Type of gastrectomy	
Distal gastrectomy	13 (45%)
Total gastrectomy	15 (52%)
Proximal gastrectomy	1 (3%)
Lymph node dissection (D)	
D2	15 (52%)
D2 +	14 (48%)

(b) Perioperative complications (Clavien-Dindo classification)

	I	II	IIIa	IIIb	IVa	IVb	V	III–V (%)
Thromboembolism		1						
Pneumonia		1						
Delirium	1							
Hypetension		1						
Diarrhea		1						
Ascites	1	1	1					1 (3.4%)
Paralytic ileus	1	1						
Occlusive ileus			2					2 (6.9%)
Anastomotic leakage							1	1 (3.4%)
Pancreatic fistula	1	1						
Abdominal Absecc		1					1	1 (3.4%)
Abdominal bleeding							1	1 (3.4%)
DIC							1	1 (3.4%)

DIC disseminated intravascular coagulation

triplet regimens such as DOS and FLOT. In addition, the development of combination chemotherapy with immune checkpoint inhibitors as preoperative chemotherapy suggests that CapeOx therapy may be a promising chemotherapy candidate, with fewer AEs than triplet regimens and with an expected antitumor effect.

Conclusions

CapeOx therapy is considered to be a promising preoperative chemotherapeutic regimen for the treatment of advanced GC with extensive LN metastasis, with a good RR and a high curative resection rate. In addition, both preoperative and postoperative AEs were mild compared with triplet regimens; however, low postoperative compliance was a problem. If survival outcomes are favorable, this regimen may prove to be a promising perioperative chemotherapeutic regimen for patients with advanced GC with extensive LN metastases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10120-024-01564-9.

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Author contributions Study concept: Y. Ki., N. S., and T. Sa.; study design: Y. Ki., N. S., H. K., Y. Ku., and T. Sa.; acquisition of data: Y. Ki., N. S., S. E., J. M., A. T., R. K., M. N., H. T., and H. S.; statistical analysis of data: T. Sh.; analysis and/or interpretation of data: Y. Ki., N. S., D. S., H. K., Y. Ku., and T. Sa.; drafting the manuscript: Y. Ki.; revising the manuscript critically for important intellectual content: Y. Ki., N. S., D. S., H. K., Y. Ku., and T. Sa. All authors approved the final version of the manuscript.

Declarations

Conflict of interest The authors declare the financial interests/personal relationships, which may be considered as potential competing interests. Y.Ki., N.S., S. E., M. N., H. T., H. S., D. S., H. K., Y. Ku., and T. Sa had a conflict of interest to disclose. Disclosures are included in Supplementary text 3.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. All patients provided written informed consent.

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