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ORIGINAL RESEARCH

Antibiotic Treatment Improves the Efficacy of Oxaliplatin-Based Therapy as First-Line Chemotherapy for Patients with Advanced Gastric Cancer: A Retrospective Study

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Purpose: One of the first-line treatment for gastric cancer patients is oxaliplatin, and the efficacy of this chemotherapeutic can be attenuated by the microbiome. In this study, we retrospectively evaluated whether treatment with antibiotics improved the efficacy of oxaliplatin-based chemotherapy in patients with advanced gastric cancer.

Patients and Methods: Fifty-four patients were assigned to the antibiotic-treated group and 35 to the antibiotic-untreated group.

Results: The response rate of oxaliplatin-based chemotherapy in the antibiotic-treated and antibiotic-untreated groups was 66.7% and 41.4%, respectively (p = 0.038). The median progression-free survival after oxaliplatin-based chemotherapy in the antibiotic-treated and antibiotic-untreated groups was 8.8 and 5.2 months, respectively (hazard ratio = 0.456, 95% confidence interval = 0.254–0.819; p = 0.007, Log rank test). Univariate and multivariate analyses revealed that antibiotic treatment was the only clinical parameter that correlated with the response to oxaliplatin.

Conclusion: Antibiotic treatment could be used therapeutically to enhance the efficacy of oxaliplatin-based chemotherapy in patients with advanced gastric cancer.

Keywords: gastric cancer, chemotherapy, oxaliplatin, antibiotics

Introduction

Gastric cancer ranks fifth in terms of overall frequency common cancer and is the malignancy that causes the most deaths worldwide after lung cancer.[1] Fluoropyrimidine plus oxaliplatin combination chemotherapy is often used as first-line chemotherapy for patients with unresectable or metastatic gastric cancer.[2,3] Fluoropyrimidine (eg, 5-fluorouracil [5-FU], capecitabine, or S-1) plus oxaliplatin combination chemotherapy in patients with advanced gastric cancer elicits the following clinical responses: 44.6–65.0% response rate (RR), progression-free survival (PFS) of 5.5–6.8 months, and overall survival (OS) of 8.0–14.1 months.[4–6] Although the efficacy of chemotherapy in patients with advanced gastric cancer is improving,[7,8] there is a need to develop yet more effective treatment regimens.

The presence of bacteria is associated with resistance to chemotherapy. Geller et al reported that bacteria can impair the cytotoxicity of gemcitabine in a pancreatic cancer cell line and of oxaliplatin in a colorectal cancer cell line.[9] Based on this finding, we hypothesized that antibiotic treatment would improve the efficacy of gemcitabine or oxaliplatin in patients with pancreatic or colorectal cancer; our hypothesis was validated in two published studies.[10,11]

In this retrospective study, we determined whether oxaliplatin efficacy was improved by antibiotic treatment in patients with advanced gastric cancer.

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Materials and Methods

Patients

We reviewed the medical records (2015–2020) of patients diagnosed with gastric cancer in the Clinical Oncology Department of Tohoku University Hospital in Japan. The inclusion criteria were: (1) patients with histologically diagnosed human epidermal growth receptor 2 (HER2)-negative gastric cancer, (2) patients with unresectable or metastatic lesions, (3) patients who were treated with oxaliplatin as first-line chemotherapy, and (4) patients where the efficacy of oxaliplatin-centered chemotherapy had been determined at least once using computed tomography (CT).

There were 157 patients who were treated with oxaliplatin-based first-line chemotherapy. Of these, 68 patients did not meet the inclusion criteria and were thus excluded from the analysis. The remaining 89 patients were eligible and were further analyzed.

Treatment Methods

The type of antibiotics used in the present study was selected by the each attending physician on the condition of patients. All antibiotics were used at the standard doses. The type of antibiotics administered and the reason for the antibiotics administration have been described in Supplemental Table 1.

Oxaliplatin-centered first-line chemotherapy was as below:

- S-1 plus oxaliplatin (SOX): 40 mg/m^2 of S-1 was given orally twice a day on days 1–14, and 130 mg/m^2 of oxaliplatin was administered intravenously on day 1.
- Capecitabine plus oxaliplatin (CapeOX): 1000 mg/m^2 of capecitabine was given orally twice daily on days 1–14, and oxaliplatin (130 mg/m^2) was administered intravenously on day 1.
- Leucovorin and 5-FU plus oxaliplatin (FOLFOX): oxaliplatin (85 mg/m^2) and 200 mg/m^2 of leucovorin were administered intravenously for a period of 2 h, after which 400 mg/m^2 of 5-FU intravenous bolus infusion was given. Then, 5-FU (2400 mg/m^2) was given as a 46-h continuous infusion.
- Other therapies after first-line chemotherapy were as follows:
- Ramucirumab plus paclitaxel (PTX): 8 mg/kg of ramucirumab was given intravenously on days 1 and 15, and 80 mg/m^2 of PTX was given intravenously on days 1, 8, and 15 of each 28-day cycle.
- Nivolumab: 240 mg of nivolumab was given intravenously every 2 weeks.
- Irinotecan (CPT-11): 150 mg/m^2 of CPT-11 was given intravenously every 2 weeks.
- PTX: 80 mg/m^2 of PTX was given intravenously on days 1, 8, and 15 of each 28-day cycle.
- Ramucirumab plus nanoparticle albumin-binding PTX (nab-PTX): 8 mg/kg of ramucirumab was given intravenously on days 1 and 15, and 100 mg/m^2 of nab-PTX was given intravenously on days 1, 8, and 15 of each 28-day cycle.

Evaluation

Treatment response was assessed using the Response Evaluation Criteria in Solid Tumors version 1.0.[12] RR was defined as the combination of complete response (CR; no evidence of cancer after oxaliplatin-based chemotherapy) and partial response (PR; ≥30% reduction in the diameter of measurable lesions on CT). The CR, PR, and stable disease rate (<30% decrease and <20% increase in the diameter of measurable lesions on CT) were used together to produce the disease control rate (DCR). Hematological toxicity was determined by examining the patients' medical records and evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.[13]

Statistical Analysis

The Kaplan–Meier method was used to determine median PFS and OS. The p-values of the RR and the DCR between the antibiotic-treated and the antibiotic-untreated group were derived from Fisher's exact test. Univariate and multivariate analyses were employed to evaluate relationships between the response to oxaliplatin-based chemotherapy and the patients' backgrounds and occurrence of severe neutropenia. All statistical analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

Patient characteristics are presented in Table 1. Of the 89 patients, 54 were assigned to the antibiotic-treated group and 35 to the antibiotic-untreated group. Seven patients in the antibiotic-treated group and five in the antibiotic-untreated group had an intestinal type of gastric cancer (as assessed by histological examination). Almost all patients (93.2%) were treated with SOX as first-line chemotherapy. Ramucirumab plus PTX or ramucirumab plus nab-PTX combination therapy, nivolumab, CPT-11, or PTX monotherapy were administered as second-line chemotherapies. The majority of the patients had tumors of a histologically diffuse/mixed subtype. The reasons for using antibiotics are also described in Table 1. In the antibiotic-treated group, 50 patients (94.3%) were treated with antibiotics for reasons unrelated to infection, including surgery such as exploratory laparotomy (35.2%), resection of the stomach (27.8%), bypass surgery (27.8%), or construction of a subcutaneous port (1.9%), while four patients (7.6%) were treated with antibiotics because of an infection (one patient for atheroma and three patients for fever with elevation of both white blood cells and C-reactive protein [CRP]).

Table 1 Summary of the Patients' Treatments

Group	Antibiotics-Treated (%)	Antibiotics-Untreated (%)	P-value
Number	54	35	
Treated oxaliplatin regimen			
SOX	51(94.4)	32(91.4)	0.490
CapeOX	0(0.0)	3(8.6)	0.265
FOLFOX	3(5.6)	0(0.0)	0.161
Second line therapy			
Ramucirumab plus PTX (or nabPTX)	24(44.4)	24(68.6)	0.048
Nivolumab	3(5.6)	1(2.9)	0.542
CPT-11	1(1.9)	1(2.9)	0.761
PTX	3(5.6)	1(2.9)	0.542
After the third line therapy			
Nivolumab	13(2.4)	10(28.6)	0.645
Paclitaxel	5(9.3)	2(5.7)	0.541
CPT-11	1(1.9)	1(2.9)	0.761
Ramucirumab plus PTX(nabPTX)	4(7.4)	2(5.7)	0.754
Resection of primary site			
+	19(35.2)	10(28.6)	0.514
-	36(66.7)	25(71.4)	0.636
Adjuvant chemotherapy			
S-1	5(9.3)	4(11.4)	0.740
CapeOX	0(0.0)	1(2.9)	0.212
S-1+DTX	1(1.9)	1(2.9)	0.761
S-1+CDDP	0(0.0)	2(2.9)	0.199
Histology			
Diffuse/mixed type	43(79.6)	28((80.0)	0.446
Intestinal type	7(13.0)	5(14.3)	0.126
Not assessed	4(7.4)	2(5.7)	0.754
Reason for using antibiotics			
Operation (including open biopsy, exploratory laparotomy, construction of port, etc.)	50(92.6)		
Infection	4(7.4)		

Abbreviations: SOX, S-1 plus oxaliplatin therapy; CapeOX, capecitabine plus oxaliplatin therapy; FOLFOX, 5-FU plus oxaliplatin therapy; CPT-11, irinotecan; PTX, paclitaxel; nabPTX, nanoparticle albumin binding PTX; DTX, docetaxel; CDDP, cisplatin.

Treatment Efficacy of Oxaliplatin-Based Chemotherapy

The RR elicited by oxaliplatin-based chemotherapy is reported in Table 2. RR was significantly higher in the antibiotic-treated group than in the antibiotic-untreated group (66.7% vs 41.4%; p = 0.038). The DCR in the antibiotic-treated and antibiotic-untreated groups was 89.7% and 75.9%, respectively.

Figure 1A shows that the median PFS after oxaliplatin-based chemotherapy in the antibiotic-treated group was significantly longer than that in the antibiotic-untreated group (8.8 vs 5.2 months; hazard ratio [HR] = 0.456, 95% confidence interval [CI] = 0.254–0.819; p = 0.007, Log rank test). As shown in Figure 1B, the OS after oxaliplatin-based was not significantly different between the two groups (11.1 and 12.0 months, respectively; HR = 1.043, 95% CI = 0.634–0.1.717, p = 0.9726).

Adverse Events

The adverse events due to oxaliplatin-based chemotherapy in the antibiotic-treated and antibiotic-untreated groups are described in Table 3. Leukopenia was observed in one patient (1.9%) in the antibiotic-treated group and two patients (5.7%) in the antibiotic-untreated group. Neutropenia was observed in six patients (11.1%) in the antibiotic-treated group and five patients (14.3%) in the antibiotic-untreated group; the number of neutrocytes in these five patients was more than 900/μL, so they were not administered antibiotics. The incidental rates of other adverse events were similar between both groups.

Univariate and Multivariate Analyses

Of the 89 patients, 68 had a measurable cancer lesion. Therefore, we carried out univariate and multivariate analyses to assess the correlation between tumor shrinkage and patient backgrounds in these 68 patients (Table 4). The only statistically significant relationship was the positive correlation between antibiotic treatment and an improved response to oxaliplatin-based chemotherapy. None of the other five factors had a significant impact on the response to oxaliplatin.

Discussion

In this study, we demonstrated that antibiotic treatment improves the RR and PFS of patients with advanced gastric cancer who receive oxaliplatin-based chemotherapy. Previously, we showed that treatment with antibiotics improved the effectiveness of oxaliplatin-based chemotherapy in patients with advanced colorectal cancer.[11] Thus, improved efficacy driven by antibiotic treatment seems to be a common phenomenon in the oncology setting.

Several reports describe the relationship between the microbiome and the efficacy of chemotherapy in patients with advanced gastric cancer.[14,15] One microbial strain, *Streptomyces WAC04685*, can reduce the anticancer activity of doxorubicin via a deglycosylation mechanism.[14] *Fusobacterium nucleatum* colonization is significantly related to 5-FU resistance in patients with advanced colorectal cancer.[16] Moreover, the reductive activities of bacteria attenuate the efficacy of several anticancer drugs (including cladribine, vidarabine, doxorubicin, gemcitabine, and etoposide) in vitro and in vivo.[15,17] We did not determine the mechanisms by which antibiotics enhanced oxaliplatin-based chemotherapy in

Table 2 The Response by the Oxaliplatin-Based Regimen in Each Group

Group	Antibiotics-Treated (n=54)	Antibiotics-Untreated(n=35)	p-value
CR	0	0	
PR	26	12	
SD	9	10	
PD	4	7	
NE	15	6	
RR	66.7	41.4	0.038
DCR	89.7	75.9	0.654

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, cannot be evaluated; RR, response rate; DCR, disease control rate.

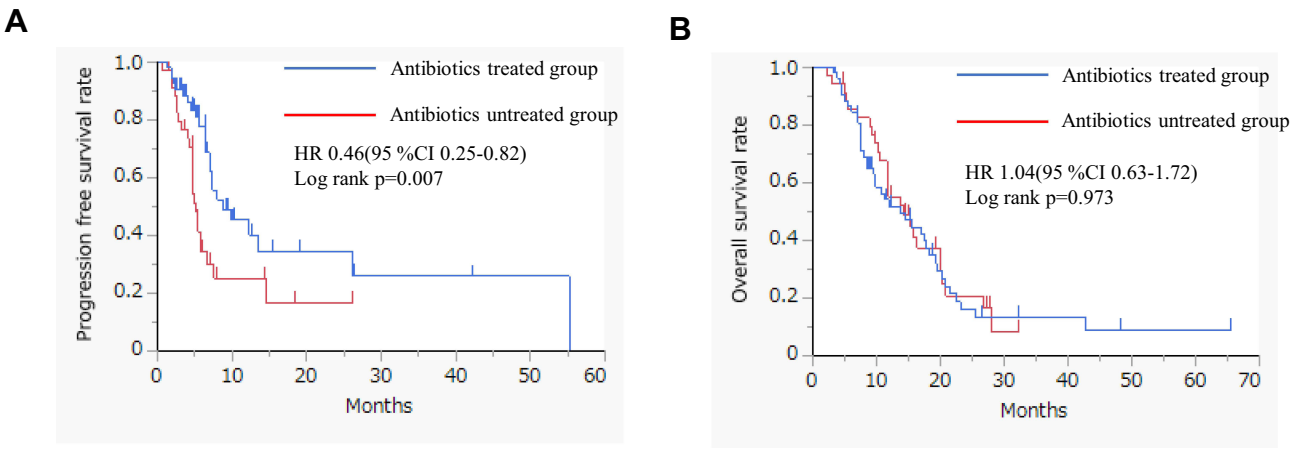

Figure 1 Kaplan–Meier curve of the (**A**) PFS and (**B**) OS of the group treated with antibiotics and the group that did not receive antibiotics.
Abbreviations: PFS, progression-free survival; OS, overall survival.

the current study. However, based on previous reports, we believe that antibiotic-dependent changes in the microbiomes of patients is the most likely explanation.

In contrast to the above data, antibiotic-dependent reduction of the microbiota led to reduced reactive oxygen species production and attenuated the efficacy of platinum chemotherapy in an in vivo xenograft model.[18] The number of bacteria in a subcutaneously injected tumor is presumably small. However, a large number of bacteria were found in human cancer tissue.[19] We therefore suggest that the discrepancy in the results might be due to differences in the number of bacteria in cancer versus xenograft tissue. However, further investigation is needed to address this point.

In this study, we used three types of oxaliplatin-based first-line chemotherapy (SOX, CapeOX, or FOLFOX). Their efficacies are similar when used as first-line chemotherapy in patients with advanced gastric cancer.[3,6,20,21] The RRs of SOX, CapeOX, and FOLFOX therapies were similar between the two groups (SOX: p = 0.490; CapeOX: p = 0.265; FOLFOX: p = 0.161). Thus, we could compare the two balanced groups for chemotherapeutic intensity.

Median OS was not improved in the antibiotic-treated group compared with the antibiotic-untreated group. However, antibiotic treatment did significantly improve PFS. Second-line chemotherapy for advanced gastric cancer significantly contributes to extending PFS following first-line chemotherapy.[22] In our current study, the RR of patients treated with ramucirumab plus PTX (or nab-PTX) combination therapy as second-line chemotherapy was significantly higher in the antibiotic-untreated group compared with the antibiotic-treated group (69.8% vs 44.4%). Thus, antibiotic treatment appears to significantly extend OS in the antibiotics-untreated group. Therefore, there was no significant difference in the OS between the two groups in the present study.

The incidence of severe myelosuppression and elevation of aspartate transaminase, alanine transaminase (ALT), or creatinine were similar between the two groups, indicating that antibiotic treatment does not have an impact on the toxicity of oxaliplatin-based chemotherapy.

Table 3 Severe (Grade 3 or 4) Adverse Events in Each Group

	Antibiotics-Treated (n=54)	Antibiotics-Untreated (n=35)	p-value
Leukopenia	1(1.9)	2(5.7)	0.324
Neutropenia	6(11.1)	5(14.3)	0.657
Anemia	1(1.9)	1(2.9)	0.761
Thrombocytopenia	2(3.7)	1(2.9)	0.835
Elevation of AST or ALT	1(1.9)	0(0.0)	0.322
Elevation of creatinine	1(1.9)	1(2.9)	0.761

Abbreviations: AST, alanine aminotransferase; ALT, aspartate aminotransferase.

Table 4 Univariate and Multivariate Analyses for the Response by the Treatment of Oxaliplatin-Containing Regimen

	n	Univariate Analysis p-value	ORR	Multivariate Analysis p-value	ORR
Gender					
Male	41	0.565	1.761(0.559–3.459)	0.347	1.566(0.665–2.549)
Female	27				
Age					
<70	38	0.995	1.052(0.385–2.883)	0.854	1.025(0.255–2.224)
≥70	30				
Antibiotics					
Treated	37	0.029	3.151(1.137–8.812)	0.029	4.595(1.526–7.619)
untreated	28				
Resection of primary site					
Y	19	0.298	1.822(0.589–5.622)	0.216	2.947(0.479–18.113)
N	46				
Adjuvant chemotherapy					
Y	9	0.849	0.871(0.211–3.599)	0.364	0.361(0.038–3.394)
N	56				
Histology					
Intestinal type	12	0.202	0.433(0.121–1.549)	0.163	0.378(0.094–1.523)
Diffuse/mixed type	53				

This study has some limitations. First, it was retrospective in nature. Second, it was comprised of a small number of patients. Third, the possibility that S-1 efficacy was improved by antibiotic treatment could not be excluded. Almost all patients (93.3%) in this study were treated with SOX as first-line chemotherapy. RR, PFS, and OS were all similar between patients treated with FOLFOX therapy (n = 3) and CapeOX therapy (n = 3): RR: 0% vs 0%; PFS: 6.5 vs 5.6 months (p = 0.658, Log rank test); and OS: 11.4 vs 11.5 months (p = 0.946, Log rank test). Although the presence of bacteria does not appear to impair the cytotoxicity of 5-FU in several cancer cell lines,[9] it is possible that antibiotic treatment might improve the efficacy of S-1 therapy. Other clinical studies will be needed to address this open point. Finally, we did not elucidate the molecular mechanisms underlying the enhanced response to oxaliplatin-based chemotherapy that was elicited by antibiotic treatment. Further basic and clinical studies are needed to address these points.

Conclusion

The addition of antibiotics to treatment regimens for advanced gastric cancer patients could improve the effectiveness of oxaliplatin-centered therapy in these individuals.

Institutional Review Board Statement

This study protocol was approved by the ethics committee of Tohoku University Hospital. The ethics committee of Tohoku University Hospital gave permission to conduct retrospective studies without the receipt of consent statements from patients (opt-out system). All data in the current study had no personal identifiers and were kept confidential.

The present research complies with the Declaration of Helsinki.

Data Sharing Statement

Data supporting the findings are the Tables and Figures that accompany the manuscript. Reasonable requests for access to the detailed retrospective observational data that support the study conclusions, please contact the first author (Hiroo Imai, e-mail: pj.ca.ukohot@8d.iami.oorih). There were no personal identifiers associated with the data, as they were kept confidential.

Author Contributions

Hiroo Imai designed the study and drafted the initial manuscript. Chikashi Ishioka is the corresponding author, analyzed and interpreted data, and helped prepare the manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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