# Docetaxel plus oxaliplatin (DOCOX) as a second-line treatment after failure of fluoropyrimidine and platinum in Chinese patients with advanced gastric cancer

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**The fluoropyrimidine and platinum-based combination chemotherapy is now widely used as first-line therapy for advanced gastric cancer (AGC). Unfortunately, about half of all patients do not respond to the current first-line chemotherapy and furthermore, most patients who achieve response to first-line chemotherapy eventually experience disease progression. Although there is a need for effective salvage treatment after the failure of first-line chemotherapy, data on the safety and efficacy of second-line treatment in AGC is limited. The current study evaluated an experimental combination regimen of docetaxel (60 mg/m$^2$) as an intravenous infusion of less than 1 h, followed by oxaliplatin (130 mg/m$^2$) intravenously for less than 2 h. Both drugs were administered on day 1 of a 21-day cycle, in pretreated Chinese patients with AGC. The trial enrolled 48 patients of whom 46 (95.8%) were assessable for response. The median time to progression was 4.4 months (95% confidence interval (CI): 3.4–5.4 months) and the median overall survival was 7.2 months (95% CI: 6.6–12.1 months). Partial response was confirmed in 11 of 48 cases (22.9%; 95% CI: 10.9–34.9%) and no complete responses were seen. Significant hematologic toxicity was noted with grade 3 and grade 4 neutropenia occurring in 21.7 and 4.3% of patients, respectively, as well as grade 3 thrombocytopenia occurring in 4.3% of patients. Grade 3 febrile neutropenia occurred in 6.5% of the patients. There were no treatment-related deaths during on the study. In summary, docetaxel and oxaliplatin have modest activity with predictable hematologic toxicity when given as salvage therapy for Chinese patients treated earlier for AGC. Given the short duration of response more focus should be given to newer biologic agents and triplet regimens.** *Anti-Cancer Drugs* **19:1013–1018 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Although the incidence of gastric carcinoma has fallen in most Western countries, it remains a significant problem in terms of global health and is the second most common cause of cancer mortality worldwide [1]. Gastric cancer is often diagnosed at an advanced stage, with approximately half of all patients presenting with unresectable, locally advanced, or metastatic disease. Combination chemotherapy remains the standard of care for advanced gastric cancer and four randomized studies comparing best supportive care and chemotherapy versus best supportive care alone have shown that chemotherapy improves survival and quality of life [2–5].

Numerous classical chemotherapy agents including 5-fluorouracil (5-FU), methotrexate (MTX), mitomycin-C, doxorubicin, cisplatinum, etoposide, and epirubicin, have all shown clinical activity in advanced gastric cancer (AGC). Among them, 5-FU and cisplatinum have been widely used as a component of combination therapy such as in the widely used ECF regimen (epirubicin, cisplatinum, and 5-FU). Therapy with ECF is associated with significant benefits in terms of response rate (RR) and survival in patients with AGC compared with FAMTX (5-FU, adriamycin, and high-dose MTX) chemotherapy in randomized phase III studies [6,7]. In addition, randomized trials have shown that the combination of 5-FU and cisplatinum is associated with improved RR and time to progression (TTP) compared with FAM (5-FU, doxorubicin, and mitomycin) or 5-FU monotherapy [8]. On the basis of these studies, the first-line standard of care in Chinese patients with AGC is fluoropyrimidine and platinum-based combination chemotherapy.

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Unfortunately, nearly half of all AGC patients will not respond to cisplatinum-based first-line chemotherapy. Furthermore, most patients who achieve response to the first-line chemotherapy will ultimately experience clinical disease progression and require second-line treatment. There is a pressing need for effective salvage treatment after the failure of first-line chemotherapy in AGC. In addition, there are few data on the safety and efficacy of second-line treatments in Chinese patients with AGC.

Recently, newer agents such as docetaxel (DOC, Taxotere; Sanofi-Aventis, New York, NY, USA), and oxaliplatin (OXA, Eloxatin) have shown activity both as single agents and in combinations for AGC. DOC is a novel semisynthetic taxane with broad significant antitumor activity and a predictable toxicity profile consisting primarily of hematologic and neuropathic events. Results of a DOC -containing regimen in the treatment of gastric cancer are encouraging and a combination with cisplatinum has been reported to yield an overall RR of 37–56%. [9,10] OXA is novel alkylating agent that inhibits DNA replication by forming adducts between two adjacent guanines or guanine and adenine molecules. The adducts of OXA seem to be more effective than those of cisplatinum with regard to the inhibition of DNA synthesis [11–13]. OXA also has a more favorable clinical safety profile compared with cisplatinum including lack of ototoxicity or renal toxicity. The dose-limiting toxicity of OXA, however, is a cumulative sensory peripheral neuropathy [14].

It has recently been shown that the combination of taxanes and OXA may be synergistic *in vitro*, when DOC is administered before OXA [15]; the same conclusion was reached in a phase I study [16]. Several potential advantages support the rationale for testing the combination of DOC and OXA (DOCOX) in the treatment of AGC. Both agents have a significant activity in AGC. Furthermore, OXA has similar efficacy to cisplatinum with less hematological toxicity and OXA is less emetogenic than cisplatinum eliminating the need for intravenous hydration. In Chinese patients accustomed to inpatient therapy this translates into practical patient convenience. The regimen can be administered as an outpatient using a single infusion room visit without the need for ambulatory infusion devices. On the basis of this information, we decided to evaluate a regimen that combined OXA and DOC in Chinese patients with AGC who had received a cisplatinum-based first-line therapy earlier. The primary endpoint of this study was a RR.

## Patients and methods

### Eligibility criteria

Eligible patients were 18 years of age or older and had histologically confirmed metastatic or recurrent gastric adenocarcinoma. Additional entry criteria included an Eastern Cooperative Oncology Group performance status of 0–2 and normal renal, hepatic, and bone marrow function. All patients had received earlier first-line combination chemotherapy with a fluoropyrimidine (5-FU, capecitabine, doxifluridine, or UFT) and platinum (cisplatinum, heptaplatin, or OXA)-containing regimen. Patients with any earlier second-line chemotherapy were excluded, as were patients with secondary malignancy, gastric or esophageal cancer other than adenocarcinoma; central nervous system metastases; unresolved bowel obstruction or subobstruction; chronic diarrhea; and other serious uncontrolled medical or psychiatric diseases. All patients gave written, informed consent before enrollment into the study. The study protocol was reviewed and approved by the institutional review board of each author's institution.

### Study design and treatment

This open-label nonrandomized trial was conducted at four Chinese institutions. Centers were selected based on their proven compliance with treatment guidelines and clinical research trials.

On day 1, eligible patients received DOC ) (60 mg/m$^2$) as a 1 h infusion followed by OXA (130 mg/m$^2$) as a 2 h infusion. Both drugs were administered on day 1 of a 21-day treatment cycle. All patients received 5-hydroxytryptamine antagonists intravenously for prophylaxis of nausea and vomiting. The primary use of granulocyte colony-stimulating factors was not allowed. Treatment was continued until disease progression or intolerable toxicity. Patients who achieved a complete response (CR) could receive two additional cycles of treatment at the investigator's discretion. Doses were recalculated before each cycle and adjusted as needed.

### Study endpoints

The primary endpoint of this study was RR. A subjective/objective symptom evaluation and blood tests twice weekly were done. Every 4 weeks a comprehensive biochemistry blood examination was carried out.

After every two cycles of treatment, the response was evaluated using Response Evaluation Criteria in Solid Tumors criteria. Of the lesions observed before the treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In the cases of partial or CR, a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was graded according to version 2.0 of the National Cancer Institute-Common Toxicity Criteria (NCI-CTC; available at *http://ctep.cancer.gov/reporting/ctc_archive.html*).

### Statistical analysis

The current trial used a two-stage optimal design as proposed by Simon [17], with an 80% power to accept the

hypothesis and 5% significance to reject the hypothesis. The current trial was designed to detect a RR of 40% as compared with a minimal, clinically meaningful RR of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 48 patients with measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response, TTP, and survival analyses were all estimated using the Kaplan–Meier method. The duration of response was defined as the interval from the onset of a CR or partial response (PR) until evidence of disease progression was found. Meanwhile, the TTP was calculated from the initiation of chemotherapy to the date of disease progression, whereas overall survival (OS) was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, Illinois, USA).

## Results

### Patient characteristics

From October 2004 to June 2006, a total of 48 patients were enrolled in the current study from four centers. The characteristics of the patients are summarized in Table 1. The median age was 53 (range, 22–71) years, with 33 male and 15 female patients. The majority of the patients (83.3%) had either Eastern Cooperative Oncology Group performance status 0 or 1. Twenty-eight (58.3%) patients presented with metastatic disease, whereas 20 patients presented with recurrent disease after earlier gastrectomy. Distant lymph nodes, peritoneum or liver were the most common sites of the metastatic disease. Twenty-seven of the 48 patients (56.3%) had earlier received first-line combination chemotherapy with capecitabine and cisplatinum combination chemotherapy. At the time of study enrollment, nine patients had experienced a recurrence at least 6 months after the concluding adjuvant chemotherapy; six patients developed recurrence within 6 months after the end of adjuvant chemotherapy; and 33 study patients had clinical progression after first-line chemotherapy for metastatic disease.

### Efficacy and survival

Forty-six (95.8%) of the 48 patients were assessable for response; both of the two patients that were not assessable, were lost to follow-up after the first cycle of the treatment. All efficacy data are reported using the intention-to-treat principle. PR was confirmed in 11 of the 48 cases yielding a RR of 22.9% (95% CI: 10.9–34.9%). Of these 11 responses, three (27.3%) were observed after three cycles, six (54.5%) after four cycles and two (18.2%) after six cycles (Table 2). The median follow-up period was 13.6 months (range, 9.5–32.3 month). The median overall TTP was 4.4 months (95% CI: 3.4–5.4 months). The estimated median OS was 7.2 months (95% CI: 6.6–12.1 months) (Fig. 1).

### Toxicity

A total of 186 cycles of DOC and OXA were administered to the 46 patients, with the median number of 5 cycles administered per patient (range, 1–8 cycles). Dose reduction was required in 9 cycles (out of 186), but no delay in the start of chemotherapy was required. The treatment was well tolerated and no toxic death occurred. Table 3 summarizes the toxicity data. Grade 3 and grade 4 neutropenia was documented in 10 (21.7%) patients and

**Table 1 Patient characteristics ($n=48$)**

| Characteristic | Number of patients (%) |
|---|---|
| Age (years) | |
| Median (range) | 53 (22–71) |
| Male/female | 33/15 |
| ECOG PS | |
| 0 | 11 (22.9) |
| 1 | 29 (60.4) |
| 2 | 8 (16.7) |
| Disease status | |
| Initially metastatic | 28 (58.3) |
| Recurrent or resected metastatic[a] | 20 (41.7) |
| Location of primary tumor | |
| Cardia/fundus | 10 (20.8) |
| Body/antrum | 32 (66.7) |
| Diffuse | 4 (8.3) |
| Unknown | 2 (4.2) |
| Histology | |
| Well/moderately adenocarcinoma | 16 (33.3) |
| Poorly/undifferentiated or signet-ring cell carcinoma | 32 (66.7) |
| Metastatic sites | |
| Lymph node | 35 (72.9) |
| Liver | 17 (35.4) |
| Peritoneum | 21 (43.8) |
| Lung | 6 (12.5) |
| Bone | 4 (8.3) |
| Others (ovary, kidney, pancreas) | 3 (6.3) |
| Number of metastases | |
| 1 | 18 (37.5) |
| 2 | 14 (29.2) |
| $\geq 3$ | 16 (33.3) |
| Previous chemotherapy | |
| 5-FU/cisplatin | 9 (18.8) |
| 5-FU/heptaplatin | 4 (8.3) |
| Capecitabine/cisplatin | 27 (56.3) |
| Capecitabine/oxalipatin | 8 (16.7) |
| Disease status at enrollment | |
| Recurrence $<6$ months after the end of adjuvant CTx | 6 (12.5) |
| Recurrence $\geq 6$ months after the end of adjuvant CTx | 9 (18.8) |
| Progression after first-line CTx | 33 (68.8) |

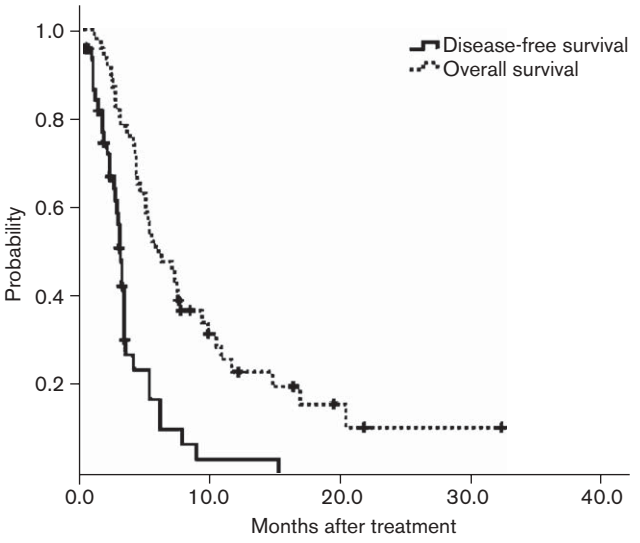
CTx, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status.
[a]Patients with recurrent disease after curative gastrectomy or noncurative gastrectomy.

**Table 2 Tumor response (intention-to-treat analysis, $n=48$)**

| Response | *n* (%) |
|---|---|
| Complete response | – |
| Partial response | 11 (22.9)[a] |
| Stable disease | 20 (41.7) |
| Progressive disease | 16 (33.3) |
| CR + PR + SD | 31 (64.6) |
| Not assessable | 2 (4.2) |

CR, complete response; PR, progressive disease; SD, stable disease.
[a]95% confidential interval = 10.9–34.9%.

**Fig. 1**




Time to disease progression and overall survival for all patients.

**Table 3 Adverse reactions (by patients, $n=46$)**

| | Grade[a], *n* (%) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Hematologic | | | | |
| Anemia | 6 (13.0) | 3 (6.5) | 0 | 0 |
| Leukopenia | 16 | 11 (23.9) | 7 (15.2) | 1 (2.2) |
| Neutropenia | 18 (39.1) | 13 (28.3) | 10 (21.7) | 2 (4.3) |
| Thrombocytopenia | 13 (28.3) | 5 (10.9) | 2 (4.3) | 0 |
| Nonhematologic | | | | |
| Nausea/vomiting | 16 (33.3) | 15 (32.6) | 13 (28.3) | 2 (4.3) |
| Dehydration | 12 (26.1) | 9 (19.6) | 6 (13.0) | 0 |
| Stomatitis | 3 (6.5) | 2 (4.3) | 0 | 0 |
| Fatigue/asthenia | 17 (37.0) | 10 (21.7) | 6 | 0 |
| Alopecia | 21 (45.7) | 13 (28.3) | 0 | 0 |
| Diarrhea | 13 (28.3) | 9 (19.6) | 7 (15.2) | 0 |
| Constipation | 9 (19.6) | 3 (6.5) | 0 | 0 |
| Febrile neutropenia | 13 (28.3) | 5 (10.9) | 3 (6.5) | 0 |
| Neuropathy | 15 (32.6) | 7 (15.2) | 3 (6.5) | 0 |
| Elevated transaminase | 2 (4.3) | 1 (2.2) | 0 | 0 |
| Elevated creatinine | 2 (4.3) | 0 | 0 | 0 |
| Hyperbilirubinemia | 1 (2.2) | 0 | 0 | 0 |

[a]NCI CTC version 2.0.

two (4.3%) patients, respectively. Grade 3 thrombocytopenia occurred in two (4.3%) patients. One patient experienced grade 4 leucopenia. Nausea/vomiting, dehydration, diarrhea, febrile neutropenia, neuropathy, fatigue/asthenia, and alopecia were the most common nonhematological toxicities that were reported. Grade 3 nausea/vomiting, dehydration, diarrhea, febrile neutropenia, and neuropathy were observed in 13 (28.3%), six (13.0%), seven (15.2%), three (6.5%), and three (6.5%) patients, respectively. The only grade 4 nonhematologic toxicity was nausea/vomiting observed in two (4.3%) patients. Grade 1/2 fatigue/asthenia and alopecia were observed in 27 (58.7%) and 34 (73.9%) patients. Five patients (10.9%) were hospitalized because of treatment toxicities (three because of infections and one because of general weakness). There were no treatment-related deaths during this study.

## Discussion

Unresectable and/or metastatic gastric cancer has a poor prognosis, with a median OS of 8–10 months. Several regimens of combination chemotherapy have been developed but the survival advantage seems to be limited to 2–3 months. Despite progress in Western countries, to date no international standard has been established. A recent meta-analysis was carried out to assess the efficacy and tolerability of chemotherapy in patients with AGC. Analysis of chemotherapy versus best supportive care (hazard ratio = 0.39, 95% CI: 0.28–0.52) and combination versus single agent, mainly 5-FU, (hazard ratio = 0.83, 95% CI: 0.74–0.93) showed significant OS advantage in favor of both chemotherapy and specifically combination chemotherapy [18]. Still, most patients receiving first-line chemotherapy will eventually develop progressive disease and there is no established second-line regimen.

In this study, we found that DOC plus OXA is an active and safe second-line chemotherapy program for use in routine clinical practice for patients with AGC for whom fluoropyrimidine and platinum-based first-line chemotherapy had failed earlier. This study demonstrated that a 21-day cycle of DOC (60 mg/m$^2$) followed by OXA (130 mg/m$^2$) was active and well tolerated as a second-line therapy in pretreated Chinese patients with AGC. The overall RR was 22.9%, the median TTP was 4.4 months, and the median OS was 7.2 months. In the current study, the RR and OS are comparable with the published data from most second-line chemotherapy trials of DOC monotherapy in patients with AGC refractory to fluoro-pyrimidine and/or platinum. Taguchi *et al.* [19], Vanhoefer *et al.* [20] and Lee *et al.* [21] have all, respectively, reported a 24% RR with DOC (60 mg/m$^2$) in 59 patients, a 20% RR with DOC (100 mg/m$^2$) in 25 patients, and a 16.3% RR with DOC (75 mg/m$^2$) in 49 patients, all of whom had already been exposed to first-line 5-FU and cisplatinum.

Our results are also comparablewith those reported in earlier studies of DOC–platinum combination regimens as a second-line therapy. Park *et al.* [22], Kim *et al.* [23], Kunisaki *et al.* [24], and Barone *et al.* [25] reported a 17.1% RR with a median TTP and OS of 3.9 and 5.8 months in 43 patients, a 32.4% RR with a median TTP and OS of 136 and 235 days in 37 patients, a 26.7% RR with a median TTP and OS of 4.5 and 6 months in 30 patients, and a 10.5% RR with a median TTP and OS of 4.0 and 8.1 months in 38 patients, respectively.

**Table 4 Docetaxel + cisplatin (or oxaliplatin) chemotherapy in patients with AGC**

| Method | Study | Treatment | Line | No. of patients | RR (%) | TTP | OS |
|---|---|---|---|---|---|---|---|
| Docetaxel + cisplatin | | | | | | | |
| | Roth *et al.* [9] | D: 80 mg/m$^2$, day 1; C: 75 mg/m$^2$, day 1; q3w | First | 48 | 56 | 6.6 months | 9 months |
| | Ridwelski *et al.* [10] | D: 75 mg/m$^2$, day 1; C: 75 mg/m$^2$, day 1; q3w | First | 39 | 37.2 | 6.1 months | 10.4 months |
| | Park *et al.* [22] | D: 60 mg/m$^2$, day 1; C: 60 mg/m$^2$, day 1; q3w | Second | 43 | 17.1 | 3.9 months | 5.8 months |
| | Kim *et al.* [23] | D: 75 mg/m$^2$, day 1; C: 60 mg/m$^2$, day 1; q4w | Second | 37 | 32.4 | 136 days | 235 days |
| | Ajani *et al.* [26] | D: 85 mg/m$^2$, day 1; C: 75 mg/m$^2$, day 1; q3w | First | 76 | 26 | 5.0 months | 10.5 months |
| | Kunisaki *et al.* [24] | D: 60 mg/m$^2$, day 1; C: 60 mg/m$^2$, day 1; q3w | Second | 30 | 26.7 | 4.5 months | 6 months |
| | Fahlke *et al.* [27] | D: 75 mg/m$^2$, day 1; C: 75 mg/m$^2$, day 1; q3w | First | 113 | 29.6 | 4.8 months | 8.7 months |
| | Park *et al.* [28] | D: 75 mg/m$^2$, day 1; C: 75 mg/m$^2$, day 1; q3w | First | 92 | 43.5 | 7.0 months | 11.5 months |
| Docetaxel + oxaliplatin | | | | | | | |
| | Barone *et al.* [25] | D: 75 mg/m$^2$, day 1; O: 80 mg/m$^2$, day 2; q3w | Second | 38 | 10.5 | 4.0 months | 8.1 months |
| | Richards *et al.* [29] | D: 60 mg/m$^2$, day 1; O: 130 mg/m$^2$day 1; q3w | First | 71 | 36 | 4.3 months | 8.5 months |
| | Kim *et al.* [30] | D: 65 mg/m$^2$, day 1; O: 120 mg/m$^2$, day 1; q3w | First | 42 | 45.2 | 5.7 months | 9.9 months |
| | This study | D: 60 mg/m$^2$, day 1; O: 130 mg/m$^2$, day 1; q3w | Second | 48 | 22.9 | 4.4 months | 7.2 months |

AGC, advanced gastric cancer; AGOC, advanced gastroesophageal cancer; AOC, advanced oesophageal cancer; C, cisplatin; D, docetaxel; O, oxaliplatine; OS, median overall survival; RR, response rate; TTP, median time to progression.

Increasingly, DOC is being used in the first-line setting for AGC. A recent randomized study of DCF versus CF showed the three-drug regimen to provide superior TTP, 2-year OS, and median OS. On the basis of those results DOC is now approved in the United States as the first-line setting of AGC in combination with 5-FU and cisplatinum. Other studies of DOC and OXA or cisplatinum as a first-line therapy for AGC, and/or gastroesophageal cancer are also encouraging, with a RR ranging from 26 to 56% and improved median TTP, and median TTP (4.3–7.0 months) and OS (7.8–11.5 months) [9,10,26–30] (as listed in Table 4).

Our study is also consistent with earlier reports regarding toxicity. The most common hematological toxicity in our study was neutropenia, with grade 3 or 4 neutropenia occurring in 12 (26.1%) patients. Leucopenia and thrombocytopenia also occurred with grade 3 or 4 intensity in eight (17.4%) and two (4.3%) patients, respectively. Nausea/vomiting, dehydration, diarrhea, febrile neutropenia, neuropathy, fatigue/asthenia, and alopecia were the most predictable and common non-hematological toxicities. All other toxicities were manageable as well and no toxic death was observed.

To date, the role of second-line chemotherapy in AGC has not been defined by randomized phase III trials. In nonsmall-cell lung cancer, the role of DOC salvage chemotherapy in survival prolongation has been established through randomized phase III trials [31], even though the salvage chemotherapy showed limited activity in terms of RR and progression-free survival.

We have noted some significant limitations to our study such as evaluation of potential prognostic factors in pretreated Chinese patients with AGC. Jo *et al.* [32] reported that PS was an independent prognostic factor for both TTP (HR, 1.753; 95% CI: 1.081–2.844; $P = 0.023$) and OS (HR, 1.974; 95% CI: 1.217–3.200; $P = 0.006$). Lee *et al.* [33] have reported that disease status at the start of first-line chemotherapy is also a prognostic factor for TTP (HR, 1.423; 95% CI: 1.006–2.013; $P = 0.046$) but not for OS. This may be explained by changes in the tumor during first-line chemotherapy and hence, the disease status at the start of first-line chemotherapy may not reflect the tumor burden at the start of salvage chemotherapy. In contrast, the TTP of first-line chemotherapy may reflect not only the sensitivity of the tumor to first-line fluoropyrimidine and platinum combination chemotherapy but also the general chemosensitivity or the biologic aggressiveness of the tumor. Therefore, the TTP and/or OS of second-line therapy may be dependent on the TTP of first-line chemotherapy.

In conclusion, this study showed that DOC and OXA every 21 days are an active and tolerable regimen as a second-line treatment for AGC. Further investigation of this regimen is warranted, including in combination with new chemotherapeutic and biological agents such as irinotecan, epirubicin, bevacizumab, or cetuximab. Despite the development of new chemotherapeutic and biological agents, 5-FU and platinum remain the basis for primary treatment for AGC. A need for better salvage treatment after initial 5-FU and platinum based chemotherapy remains.

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