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Evaluation of Treatment Response and Toxicities of Capecitabine Oxaliplatin Versus Epirubicin, Oxaliplatin & Capecitabine in advanced Gastric Carcinoma: A Quasi-Experimental Study

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ABSTRACT

Introduction: Gastric cancer remains a leading cause of cancer-related mortality worldwide, with most cases diagnosed at advanced stages where systemic chemotherapy is the main therapeutic approach. Among commonly used regimens, XELOX and EOX are frequently selected in first-line settings; however, their relative efficacy and toxicity profiles require further clarification.

Aim of the study: This study aimed to compare treatment response, survival outcomes, and adverse events between XELOX and EOX in advanced gastric carcinoma.

Methods: This quasi-experimental study was conducted at the CMH Cancer Center, Dhaka (June 2022–July 2025; ERC approval CMH Dhaka/ECC/56). Eighty patients with advanced or metastatic gastric adenocarcinoma were equally assigned to XELOX or EOX regimens. XELOX included oxaliplatin 130 mg/m² (day 1) plus capecitabine 1000 mg/m² twice daily (days 1–14), while EOX comprised epirubicin 50 mg/m² and oxaliplatin 130 mg/m² (day 1) plus continuous capecitabine 625 mg/m² twice daily, each given every 21 days for 6–8 cycles. Tumor response (RECIST v1.1) was evaluated every two cycles, and toxicities were graded with CTCAE v5.0. PFS and OS were estimated using Kaplan–Meier and compared by log-rank test; additional analyses used chi-square/t-tests and Cox regression. All patients provided written informed consent.

Results: In this study EOX demonstrated a higher overall response rate (55% vs. 35%, p = 0.284) and a significantly better disease control rate (90% vs. 75%, p = 0.041), along with fewer cases of progressive disease (10% vs. 25%). However, this improved disease control came with substantially higher toxicity: EOX showed significantly more grade 3–4 neutropenia (30% vs. 10%, p = 0.018) and grade 3–4 anemia (15% vs. 5%, p = 0.041), as well as significantly higher rates of nausea/vomiting (60% vs. 35%, p = 0.019), diarrhea (45% vs. 25%, p = 0.046), and stomatitis (35% vs. 10%, p = 0.006). XELOX was consistently better tolerated across hematologic and gastrointestinal parameters. Survival analysis favored EOX, which achieved a longer median progression-free survival (8.9 vs. 6.8 months).

Conclusion: The EOX regimen resulted in tumor contraction, stabilization of disease and improved progression-free survival, but these benefits were offset by an increased burden of hematologic and gastrointestinal toxicity. XELOX offers a more tolerated option and may be preferred in patients with poor performance status or significant comorbidities. These findings highlight the need to adapt treatment options based on individual patient fitness, toxicity risk and treatment priorities.

***Keywords**: Gastric cancer, XELOX, EOX, Chemotherapy.*

INTRODUCTION

Gastric cancer remains a major global health challenge. Despite advances in discovery and treatment, it remains one of the leading causes of cancer-related deaths worldwide [1]. GLOBOCAN 2020 estimates that more than one million people are diagnosed with stomach cancer each year, with a mortality rate of approximately 768,000. GLOBOCAN 2020 estimates that more than one million people are diagnosed with stomach cancer each year, with a mortality rate of approximately 768,000. These figures rank stomach cancer among the top five most commonly diagnosed cancers in the world and the fourth leading cause of cancer death.[1] The distribution of this disease is by no means uniform. East Asian countries, particularly Japan, South Korea and China, still bear the greatest burden. In contrast, although incidence rates are low in many Western countries, worrying trends have emerged in recent years. In some Western countries, young adults are being diagnosed with stomach cancer more frequently than before.[2] Despite improvements in screening programs and diagnostic tools, many patients continue to complain of advanced or metastatic disease, even when treatment options are limited and long-term survival rates are generally low [3]. For patients with unresectable or metastatic gastric adenocarcinoma, systemic chemotherapy is the primary treatment. The main objectives are to relieve symptoms, suppress tumor growth, prolong survival, and maintain quality of life [3]. Over the past 20 years, combination chemotherapy has gradually become the recommended approach, as it tends to provide better therapeutic efficacy than single-agent treatment. Currently, dual treatment combining platinum agents and fluoropyrimidines is widely accepted as the first-line treatment [4]. Capecitabine, an oral fluoropyrimidine prodrug, is widely adopted because it avoids continuous intravenous fluids and has shown non-inferiority to 5-fluorouracil in randomized trials [5]. A triplet regimen was developed for further outcome improvement. One of the most studied combinations is EOX, which includes epirubicin, oxaliplatin, and capecitabine. The REAL-2 trial showed that replacing cisplatin with oxaliplatin and intravenous 5-FU with capecitabine could maintain or improve efficacy while providing acceptable tolerance, contributing to establishing EOX as an effective option for advanced esophagogastric cancer [6]. Ipiribicin may add anthracycline cytotoxicity and contribute to tumor shrinkage and improved disease control, but it may also increase the risk of myelosuppression and mucosal side effects [7]. There is still much debate as to whether dual or triple therapy is the better choice. Triple terms such as EOX can provide small improvements in response and survival rates in selected patients, but these benefits are often accompanied by increased hematological and gastrointestinal toxicity compared with dual drugs such as XELOX [8]. A meta-analysis by Guo et al. showed that triplet therapy improved overall survival and progression-free survival, primarily in patients with good performance status [9]. Given these uncertainties, selecting the optimal treatment requires balancing expected benefits with potential toxicity, taking into account the patient's systemic condition and therapeutic objectives. As the treatment landscape continues to evolve, a direct comparison of XELOX and EOX can guide personalized treatment decisions and is essential for improving the prognosis of advanced gastric cancer. This study aimed to compare treatment response, survival outcomes, and adverse events of XELOX and EOX in advanced gastric cancer

METHODS

This quasi-experimental comparative study was conducted from June 2022 to July 2025 at the Joint Military Hospital (CMH) Cancer Center, Dhaka, following ethical approval by the Ethical Review Committee (approval number). CMH Dhaka/ECC/56). Eighty patients with histologically confirmed advanced or metastatic gastric adenocarcinoma were enrolled and equally assigned to two treatment groups: XELOX regimen (group A, n=40) and EOX group (group B, n=40). Patients in arm A received the XELOX regimen. On day 1, intravenous oxaliplatin (platinum-based chemotherapy drug 130 mg/m²) was administered repeatedly on day 1, followed by capecitabine (oral fluopyrimidine prodrug 1000 mg/m²) twice daily from days 1 to 14. The planning period was 6〜8 cycles every 21 days. Patients in group B received an EOX regimen: epirubicin (anthracycline) 50 mg/m² intravenously on day 1, oxaliplatin 130 mg/m² intravenously on day 1, and capecitabine 625 mg/m² twice daily consecutively. Treatment was continued for 6〜8 cycles in a 21-day cycle or until disease progression or unacceptable toxicity. Baseline evaluation included laboratory tests, hematological and biochemical evaluations, and contrast-enhanced chest and abdominal CT imaging. Tumor response was assessed every 2 cycles according to RECIST v1.1 criteria, and treatment-related toxicity was assessed at each visit using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 0. Progression-free survival (PFS) and total survival (OS) were calculated from treatment initiation to disease progression or death, whichever occurred first, and were censored at last follow-up for event-free patients. Survival curves were constructed using the Kaplan–Meier method, and comparisons between groups were made using the log-rank test. Categorical variables were compared using chi-square or Fisher exact tests, and continuous variables were assessed with t tests. Multivariate Cox proportional hazards regression analysis was used to estimate hazard ratios with 95% confidence intervals. A p value <0.05 was considered statistically significant. All participants provided written informed consent before enrollment and strict adherence was observed throughout the study period.

Inclusion Criteria

- Age 18–75 years

- Histologically confirmed advanced or metastatic gastric adenocarcinoma
- ECOG performance status 0–2

Exclusion Criteria

- Uncontrolled infection or significant cardiac disease (e.g., low LVEF, arrhythmia)
- Concurrent active malignancy
- Pregnancy or lactation

RESULTS

Table 1: Baseline Characteristics of the Patients (N = 80)

Variable	XELOX (n=40)	EOX (n=40)	p-value
Age (years), mean ± SD	54.8 ± 9.6	55.9 ± 8.9	0.412
Gender			0.642
Male	26 (65%)	28 (70%)	
Female	14 (35%)	12 (30%)	
ECOG Performance Status			0.737
0–1	28 (70%)	30 (75%)	
2	12 (30%)	10 (25%)	
Tumor Location			0.588
Antrum	20 (50%)	18 (45%)	
Body	14 (35%)	16 (40%)	
GE Junction	6 (15%)	6 (15%)	
Stage (AJCC 8th Ed.)			0.821
Stage III	18 (45%)	20 (50%)	
Stage IV	22 (55%)	20 (50%)	

No statistically significant differences were observed in baseline characteristics between groups.

According to Table 1, the mean age of the XELOX group was 54.8 ± 9.6 years, while the EOX group had a mean age of 55.9 ± 8.9 years, with no statistically significant difference (p = 0.412). Male patients were slightly more common in both groups (65% in XELOX vs. 70% in EOX), but the difference was not significant (p = 0.642). Similarly, ECOG performance status, tumor location, and cancer staging showed no significant differences between arms (all p > 0.05).

Table 2: Radiological Tumor Response (RECIST v1.1)

Response Category	XELOX (n=40)	EOX (n=40)	p-value
Complete Response (CR)	2 (5%)	4 (10%)	0.389
Partial Response (PR)	12 (30%)	18 (45%)	0.142
Stable Disease (SD)	16 (40%)	14 (35%)	0.654
Progressive Disease (PD)	10 (25%)	4 (10%)	0.081
ORR (CR + PR)	**35%**	**55%**	**0.284**
DCR (CR + PR + SD)	**75%**	**90%**	**0.041***

The EOX regimen showed a significantly better disease control rate.

According to Table 2, the overall response rate (ORR) was higher in the EOX group (55%) compared with the XELOX group (35%), although this difference was not statistically significant (p = 0.284). However, the disease control rate (DCR) was significantly higher in the EOX arm (90% vs 75%, p = 0.041), indicating better tumor stabilization. The XELOX regimen had a higher proportion of progressive disease (25%), compared with 10% in the EOX arm.

Table 3: Hematologic Toxicities (CTCAE v5.0)

Toxicity Type	Grade 1–2	Grade 3–4	XELOX (n=40)	EOX (n=40)	p-value
Neutropenia					**0.018***
Grade 1–2	10 (25%)	–	14 (35%)	20 (50%)	
Grade 3–4	–	6 (15%)	4 (10%)	12 (30%)	
Anemia					0.041*
Grade 1–2	18 (45%)	–	20 (50%)	26 (65%)	
Grade 3–4	–	4 (10%)	2 (5%)	6 (15%)	
Thrombocytopenia					0.223
Grade 1–2	8 (20%)	–	10 (25%)	14 (35%)	
Grade 3–4	–	2 (5%)	1 (2.5%)	4 (10%)	

EOX demonstrated significantly higher rates of grade 3–4 neutropenia and anemia.

According to Table 3, grade 3–4 neutropenia occurred significantly more frequently in the EOX arm (30%) compared with the XELOX arm (10%) (p = 0.018). Grade 3–4 anemia was also higher in the EOX group (15%) than XELOX (5%) with a significant p-value (0.041). Thrombocytopenia showed no significant difference between the two groups (p = 0.223).

Table 4: Non-hematologic Toxicities

Toxicity	XELOX (n=40)	EOX (n=40)	p-value
Nausea/Vomiting (Grade 1–2)	14 (35%)	24 (60%)	0.019*
Diarrhea (Grade 1–2)	10 (25%)	18 (45%)	0.046*
Stomatitis (Grade 1–2)	4 (10%)	14 (35%)	0.006**
Hand–Foot Syndrome	8 (20%)	12 (30%)	0.317
Peripheral Neuropathy (Grade 1–2)	18 (45%)	12 (30%)	0.184

EOX had significantly higher GI and mucosal toxicities.

According to Table 4, nausea and vomiting were significantly more common in the EOX group (60%) than in the XELOX group (35%) (p = 0.019). Similarly, diarrhea was reported in 45% of EOX patients vs 25% of XELOX patients (p = 0.046), and stomatitis was observed significantly more in EOX (35%) compared with XELOX (10%), with p = 0.006.

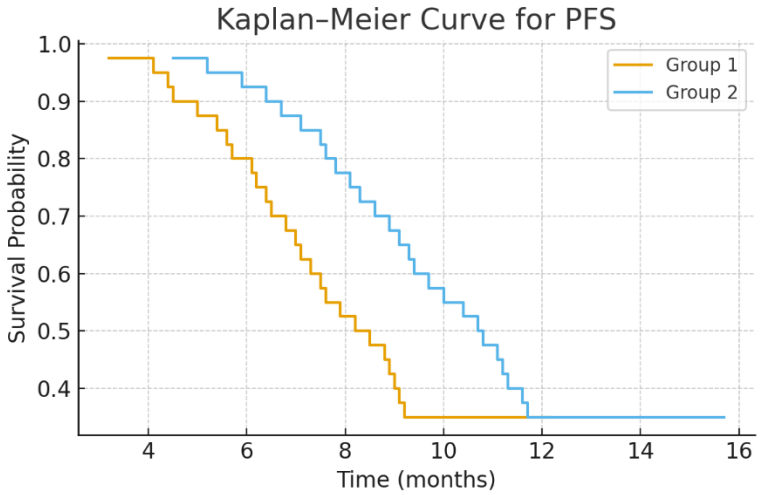

Figure 1: Kaplan–Meier Curve for Progression-Free Survival (PFS) Between XELOX and EOX Regimens

Patients treated with EOX demonstrated a consistently higher cumulative survival probability over time, with a slower decline in the survival curve compared to XELOX. The median PFS was 6.8 months for XELOX and 8.9 months for EOX. Censoring points are indicated along each curve.

DISCUSSION

In the present study, the EOX regimen showed a higher overall response rate (ORR) than XELOX, with the latter showing an ORR of 35%. The strong tumor response observed with EOX is in good agreement with the results of previous studies. A similar study by Cunningham et al. found ORRs of EOX ranging from 47% to 57% in the REAL-2 study supporting the enhanced cytotoxicity of this triplet regimen [7]. Similarly, another study by Park et al. recorded an ORR of 37–42% for XELOX, which is similar to the 35% response rate seen in our XELOX cohort [6]. Another study by Guo et al. also found superior tumor control with anthracycline triplet regimens compared with doublet chemotherapy [9], further supporting the observation that EOX may result in better response outcomes in appropriately selected patients. In the present study disease control rate (DCR) in the EOX group was higher than that in the XELOX group (75%). This finding is similar to a study by Guo et al., who found that epirubicin-containing triad has a superior disease-stabilizing effect compared with platinum-fluoropyrimidine duplexes [9]. Wang et al. also reported DCR values of approximately 80–85% in Asian patients receiving EOX, which is in close agreement with our results [10]. These data suggest that EOX may provide stronger tumor suppression, especially in patients with good baseline performance. Progression-free survival (PFS) outcomes also further support the benefits of EOX. In the present study, the median PFS was 6.8 months for XELOX and 8.9 months for EOX. Another similar study by Cunningham et al. also reported PFS values of 7.0 ～ 7.6 months in EOX-treated patients [7]. Other studies by Bang et al. and Guo et al. have similarly shown that more intensive triplet regimens improve disease control and prolong PFS in advanced gastric cancer [11, 9]. These results specify that the addition of epirubicin may contribute to delayed disease progress in selected patients. However, the improved efficacy of EOX is accompanied by increased toxicity. In our study, 30% of EOX-treated patients developed grade 3～4 neutropenia, with a 10% increase in the XELOX group. In this study findings are also similar to a study by Wang et al., who found a significantly higher incidence of neutropenia in epirubicin triplets [10]. Similarly, a study by Ilhan-Mutlu et al. found increased bone marrow

suppression with EOX compared with other intensive regimens, such as DCF [12]. Another study by Guo et al. also confirmed that triple combination therapy carries a high risk of severe hematologic toxicity [9]. These observations underscore the need for careful patient selection and close monitoring when using EOX, notably in patients at high risk for myelosuppression. Non-hematologic toxicities showed a similar trend. Nausea and vomiting were more frequent in the EOX group (60% vs. 35%). Chen et al. also documented increased gastrointestinal adverse events with EOX [13]. In our study, stomatitis was reported in 35% of EOX patients versus 10% of XELOX patients, which is also consistent with the mucosal toxicity profile observed by Cunningham et al. in the REAL-2 study [7]. Another study also found that triple combination therapy increased mucositis and gastrointestinal toxicity.[14] This suggests that while EOX may lead to improved tumor control, it also carries a significant burden of gastrointestinal and mucosal toxicity. Evidence from our study and the prior literature suggests that EOX provides better response rates, better disease control, and longer PFS compared to XELOX, but at the cost of substantially higher toxicity. A study by He et al. reached similar conclusions, reporting improved survival outcomes with EOX alongside increased side effects [15]. These observations underscore the importance of personalized treatment [16,17]. XELOX may be more suitable for patients requiring a better-tolerated regimen, while EOX may be reserved for healthier patients seeking a more aggressive treatment approach. Similar study by Guo et al. also confirmed the higher risk of severe hematologic toxicity with triple-agent therapy [9]. These results emphasize the need for careful patient selection and meticulous monitoring when using EOX, especially for patients at high risk of myelosuppression. Non-hematological toxicity showed similar trends. Nausea and vomiting were more frequent in the EOX group (60% vs. 35%). Chen et al. also documented an increase in gastrointestinal adverse events with EOX. [13]. In our study, stomatitis was reported in 35% of EOX patients and 10% of XELOX patients, which is also consistent with the mucosal toxicity profile observed by Cunningham et al. in the REAL-2 study [7]. Another study also found increased mucositis and gastrointestinal toxicity with triple therapy [14]. Suggests that EOX may result in better tumor control, but carries a high burden of gastrointestinal and mucosal toxicity. Our study and previous literature evidence suggest that EOX provides better response rates, better disease control, and prolonged PFS compared to XELOX, but at the expense of significantly higher toxicity. A study by He et al. reached a similar conclusion, reporting improved survival outcomes and increased side effects with EOX [15]. These observations underline the importance of personalised treatment. [16,17] XELOX may be suitable for patients requiring more well-tolerated treatment, and EOX may be limited to healthy patients seeking a more aggressive treatment approach.

Limitations of the Study:

The primary limitation of this study is its quasi-experimental design with a relatively small sample size, which may limit the generalizability of the findings.

CONCLUSION

In this study, EOX therapy was more effective than XELOX therapy in tumor response, disease control, and survival. It also showed a higher incidence of hematological and gastrointestinal toxicity. Though EOX may be suitable for healthy patients who can tolerate intensive treatment, XELOX is a better option for patients with significant comorbidities and those who value tolerability.

RECOMMENDATION

Future studies had better use larger randomized controlled trials to validate these results and identify patient subgroups that would benefit most from triplet chemotherapy. Combining quality of life assessment with real-world toxicity monitoring can enhance the effectiveness of personalized medicine. In indicating between XELOX and EOX regimens, physicians must weigh the potential benefits against the risk of toxicity and make decisions that match the patient's health status and treatment goals.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021 May;71(3):209-49.
2. Forma A, Chilimoniuk Z, Januszewski J, Sitarz R. The potential application of allium extracts in the treatment of gastrointestinal cancers. Gastroenterology Insights. 2021 Mar 27;12(2):136-46.
3. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. The Lancet. 2020 Aug 29;396(10251):635-48.
4. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, Denlinger CS, Fanta P, Farjah F, Fuchs CS, Gerdes H. Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network. 2016 Oct 1;14(10):1286-312.
5. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. The Lancet. 2016 Nov 26;388(10060):2654-64.
6. Park YH, Kim BS, Ryoo BY, Yang SH. A phase II study of capecitabine plus 3-weekly oxaliplatin as first-line therapy for patients with advanced gastric cancer. British Journal of Cancer. 2006 Apr;94(7):959-63.

7. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. New England Journal of Medicine. 2008 Jan 3;358(1):36-46.
8. Wagner AD, Syn NL, Moehler M, Grothe W, Yong WP, Tai BC, Ho J, Unverzagt S. Chemotherapy for advanced gastric cancer. Cochrane database of systematic reviews. 2017(8).
9. Guo X, Zhao F, Ma X, Shen G, Ren D, Zheng F, Du F, Wang Z, Ahmad R, Yuan X, Zhao J. A comparison between triplet and doublet chemotherapy in improving the survival of patients with advanced gastric cancer: a systematic review and meta-analysis. BMC cancer. 2019 Nov 20;19(1):1125.
10. Wang Y, Zhuang RY, Yu YY, Yu S, Hou J, Ji Y, Sun YH, Shen KT, Shen ZB, Liu FL, Zhao NQ. Efficacy of preoperative chemotherapy regimens in patients with initially unresectable locally advanced gastric adenocarcinoma: capecitabine and oxaliplatin (XELOX) or with epirubicin (EOX). Oncotarget. 2016 Sep 1;7(46):76298.
11. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. The Lancet. 2010 Aug 28;376(9742):687-97.
12. Ilhan-Mutlu A, Preusser M, Schoppmann SF, Asari R, Ba-Ssalamah A, Schwameis K, Pluschnig U, Birner P, Puespoek A, Zacherl J, Hejna M. Comparison between DCF (Docetaxel, Cisplatin and 5-Fluorouracil) and modified EOX (Epirubicin, Oxaliplatin and Capecitabine) as palliative first-line chemotherapy for adenocarcinoma of the upper gastrointestinal tract. Anticancer Research. 2013 Aug 1;33(8):3455-9.
13. Chen W, Shen J, Pan T, Hu W, Jiang Z, Yuan X, Wang L. FOLFOX versus EOX as a neoadjuvant chemotherapy regimen for patients with advanced gastric cancer. Experimental and therapeutic medicine. 2014 Feb 1;7(2):461-7.
14. Kim HS, Kim HJ, Kim SY, et al. Triplet vs doublet therapy efficacy. *PLoS One.* 2013;8:e83704.
15. He Q, Zhao J, Yuan J, Gong Z, Yi T. Combined perioperative EOX chemotherapy and postoperative chemoradiotherapy for locally advanced gastric cancer. Molecular and clinical oncology. 2017 Aug 1;7(2):211-6.
16. Ficorella C, Bruera G, Cannita K, Porzio G, Baldi PL, Tinari N, Natoli C, Ricevuto E. Triplet chemotherapy in patients with metastatic colorectal cancer: toward the best way to safely administer a highly active regimen in clinical practice. Clinical Colorectal Cancer. 2012 Dec 1;11(4):229-37.
17. Meng Z, Zheng H, Li Y, Bai J, Zhang L, Li L. Efficacy and Safety of triplet versus doublet regimens in patients with multiple myeloma: A systematic review and meta-analysis. Current Problems in Cancer. 2025 Jun 1;56:101202.