BSMMU Journal

Original Article

Comparative outcome of cisplatin-capecitabine regimen with oxaliplatin-capecitabine regimen in advanced gastric carcinoma: a quasi-experimental study

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Abstract

Chemotherapy is the primary therapeutic choice for advanced gastric cancer. The goal of this study was to assess the effectiveness and toxicity of the cisplatin-capecitabine regimen versus the oxaliplatin-capecitabine regimen in treating advanced gastric cancer. Between February 2021 and March 2022, this quasi-experimental study was conducted on 64 advanced gastric cancer patients. Purposive sampling was used to include those who met the inclusion criteria and distributed them evenly between the two arms. Arm A got an injection of cisplatin (80 mg/m^2 on day 1) with oral capecitabine (1000 mg/m2 b.i.d. on days 1–14), whereas arm B received an injection of oxaliplatin (130 mg/m^2 on day 1) plus oral capecitabine (1000 mg/m^2 b.i.d. on days 1–14), every 3 weeks for 6 cycles. A final check-up was done at 12 weeks after the treatment. In arm A, 18 (56.2%) patients exhibited partial response compared to 15 (46.9%) in arm B. Stable diseases were also reported in both arms (18.8% in arm A and 21.9% in arm B). There were 8 (25.0%) cases of progressive disease in arm A and 10 (31.2%) cases in Arm B. The median progression-free survival in arms A (5.6 months) was almost similar to arm B (5.9 months). The most prevalent toxicities in both arms were vomiting, diarrhea, anemia, neutropenia, oral mucositis, paresthesia, hand-foot syndrome, and renal toxicity. There were no statistically significant variations in outcomes between the two arms. In conclusion, the cisplatin-capecitabine regimen is as effective as the oxaliplatin-capecitabine regimen in advanced gastric cancer.

Key words: Gastric carcinoma, chemotherapy, quasi-experimental.

Introduction

Gastric cancer is still a major malignancy worldwide, with over one million new cases expected in 2020 and an estimated 769,000 fatalities, ranking fifth in incidence and fourth in fatalities.[1] According to the National Institute of Cancer Research and Hospital's Cancer Registry Report 2015-17, gastric cancer is the fifth most prevalent cancer in both men and women.[2] The term "gastric cancer" refers to adenocarcinoma of the stomach which accounts for approximately

Article Info

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Received: 29 Nov 2022
Accepted: 21 Dec 2022
Available Online: 00 November 2022

The publication history and additional supplemental material for these paper are available online. To view these files, please visit: http://dx.doi.org/10.3329/bsmmuj.v15i3.63445

ISSN: 2224-7750 (Online)
2074-2908 (Print)

A Journal of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

95% of all gastric cancers.[3] The optimal treatment for advanced gastric cancer is now a source of debate. Systemic chemotherapy is the backbone of treatment for advanced gastric cancer.[4] Chemotherapy has already been found to enhance symptom control and lengthen survival when compared to best supportive treatment alone[5], but no worldwide standard chemotherapy regimen has been established. A chemotherapy regimen comprising oxaliplatin and capecitabine is widely used in our institute. Following encouraging phase II research findings, oxaliplatin was compared to cisplatin in a randomized controlled experiment. The purpose of that trial was to demonstrate oxaliplatin's non-inferiority to cisplatin. In the oxaliplatin-cisplatin comparison, it was demonstrated that oxaliplatin is not inferior to cisplatin. In comparison to cisplatin's toxicity, oxaliplatin was linked with greater rates of diarrhea and neuropathy but reduced rates of neutropenia and nephrotoxicity.[6] In terms of cost, the Cisplatin-Capecitabine regimen is less expensive than the Oxaliplatin-Capecitabine regimen. If the cisplatin-capecitabine combination provides better or comparable palliation, it will benefit patients by lowering overall treatment costs. The aim of this trial was to compare the effectiveness of Cisplatin-Capecitabine regimen with that of Oxaliplatin-Capecitabine regimen in patients with advanced gastric cancer.

Methods

Patients

This study was conducted on 64 patients with advanced gastric cancer. Patients with histologically proven stage IV gastric cancer were eligible. Patients with a performance score of more than 2 on the Eastern Cooperative Oncology Group (ECOG) scale, a history of chemotherapy, radiation, or surgery, or a serious concurrent medical condition were excluded.

Study design and treatment

It is a quasi-experimental study at Bangabandhu Sheikh Mujib Medical University (BSMMU)'s Department of Clinical Oncology from February 2021 to March 2022. Patients were purposively assigned to one of two arms after meeting inclusion and exclusion criteria (see Figure 1). Arm A got an injection of Cisplatin (80 mg/m2 on day 1) with oral Capecitabine (1000 mg/m2 b.i.d. on days 1–14), whereas arm B received an injection of Oxaliplatin (130 mg/m2 on day 1) plus oral Capecitabine (1000 mg/m2 b.i.d. on days 1–14), every 3 weeks for 6 cycles.[7] Chemotherapy-related toxicities were managed accordingly. Vitamin B6 was supplemented to prevent and/or reduce the incidence and severity of the hand-foot syndrome. The patients were also advised to avoid friction of the hands and feet, do any hard work, bear heavy weights, and wash or rinse clothes. A proper hydration policy was maintained according to our institutional protocol for cisplatin.

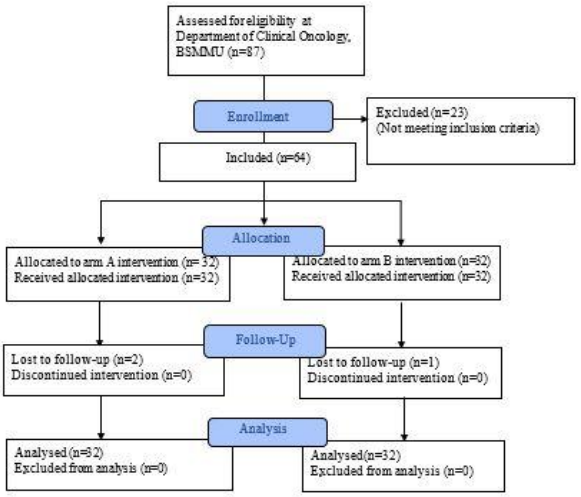

FIGURE 1 Consort flow chart of the patients enrolled in this study. Using the intention to treat principle, we analysed every patient, including those who were lost to follow-up

Assessment

During chemotherapy, patients were evaluated every three weeks. Following the end of therapy, the patients were closely monitored at 6 and 12 weeks. Follow-up examinations included clinical examinations, laboratory tests, and imaging tests. Tumor assessments were performed according to the World Health Organization (WHO) guidelines of response assessment criteria.[8] To assess toxicity, the American National Cancer Institute's 'Common Terminology Criteria for Adverse Events, v.4.0' published on June 14, 2010, was used.[9]

Ethical considerations

The BSMMU Institutional Review Board (IRB) gave ethical approval (No. BSMMU/2021/1265) on 13 February 2021. All patients were given an explanation of the study, including the risks and benefits. They were accepted into the study after signing an informed consent form in Bengali and English. Investigators

explained to them that they have the right to refuse or accept to participate in the study. To safeguard confidentiality and protect anonymity, each patient was given a special code number, which was used at every step. All data obtained from the patient during the study period remained confidential. This study was conducted in accordance with the protocol and the Good Clinical Practice standard.

Statistical analysis

The data was analyzed using the IBM SPSS software package for Windows. A p-value of less than 0.05 was considered significant when comparing the results between arms using the Chi-square test. Fisher's Exact test was done when more than 25 percent of cells in the cross table had an expected frequency of less than 5. The log-rank test was performed to compare the two arms in terms of progression-free survival (PFS). The Kaplan-Meier curve was generated to compare the PFS of the two arms. In the analysis of clinical trial results, dropouts need to be addressed during the trial. In this trial, the Intention-to-treat analysis (ITT) method was used. We assessed every patient, including those who were lost to follow-up, using the intention to treat principle.

Grading of Common Terminology Criteria for Adverse Events

Grade 0: There is no toxicity. Grade 1 symptoms are mild and asymptomatic. Intervention is not required. Grade 2 is considered moderate; limited, local, or noninvasive intervention is required. Grade 3 symptoms are severe or medically significant but not life-threatening.

Drugs

Cisplatin is a platinum analog that covalently binds to DNA at the N-7 position of guanine and adenine, produces intra-strand and inter-strand DNA cross-links, and results in the inhibition of DNA synthesis and function. Oxaliplatin is a platinum analog that inhibits DNA replication by forming both inter and intra-strand cross-links. Capecitabine is an antimetabolite prodrug that, in the tumor, undergoes enzymatic conversion to fluorouracil, which inhibits DNA synthesis and decreases the development of tumor tissue.

Results

In this study, 64 patients were enrolled to investigate the efficacy of two different systemic chemotherapy regimens in advanced gastric cancer. The patients were aged 18 to 70 years. Their mean age at diagnosis was 55.9 years in arm A and 56.8 years in arm B. Seventy-eight percent in Arm A and 69 % in Arm B were men.

TABLE 1 Characteristics of the patients

Characteristics	Arm A (n=32) No. (%)	Arm B (n=32) No. (%)	*P*
Age (years)			
18-30	2 (06.3)	1 (03.1)	
31-40	3 (09.4)	2 (06.3)	
41-50	6 (18.7)	5 (15.6)	0.94
51-60	7 (21.9)	8 (25.0)	
61-70	14 (43.7)	16 (50.0)	
Sex			
Male	25 (78.0)	22 (69.0)	0.40
Female	7 (22.0)	10 (31.0)	
Site of metastasis*			
Lung	4 (12.5)	3 (09.4)	
Liver	18 (56.3)	16 (50.0)	0.90
Peritoneum	11 (34.4)	13 (40.6)	
Ovary	3 (09.4)	2 (06.3)	
ECOG Performance			
0	3 (09.4)	5 (15.6)	
1	7 (21.9)	8 (25.0)	0.68
2	22 (68.7)	19 (59.4)	
Site of primary tumor			
Fundus	6 (18.7)	4 (12.5)	
Antrum	16 (50.0)	17 (53.1)	0.79
Body	10 (31.3)	11 (34.4)	
Risk factors*			
Helicobacter Pylori	22 (68.8)	25 (78.1)	
Smoking	10 (31.3)	13 (40.6)	0.75
Type A blood	13 (40.6)	11 (34.4)	

*Multiple responses, ECOG: Eastern Cooperative Oncology Group

Most patients in both arms had an ECOG performance rating of 2 (68.7% in Arm A and 59.4% in Arm B). In both arms, the liver was the most prevalent location of metastasis (56.3% in Arm A and 50.0% in Arm B). The pyloric antrum was the most prevalent site. In both arms, Helicobacter pylori infection was the most frequent risk factor (68.8% in arm A and 78.1% in arm B) (**Table 1**).

TABLE 2 Treatment responses at 12 weeks after the completion of treatment for both Arm A and Arm B

Response	Arm A (n = 32) No. (%)	Arm B (n=32) No. (%)	*P*
Partial response	18 (56.2)	15 (46.9)	
Stable disease	6 (18.8)	7 (21.9)	0.75
Progressive disease	8 (25.0)	10 (31.2)	
Overall response rate	18 (56.2)	15 (46.9)	

Overall response rate= Complete + partial response (Complete response was not observed in this study)

In arm A, 18 (56.2%) patients had a partial response (PR), while 15 (46.9%) patients in arm B had a PR. In both groups, stable diseases (SD) were also detected (18.8% in arm A and 21.9% in arm B). There were 8 (25.0%) cases of progressive disease (PD) in arm A and 10 (31.2%) cases of PD in arm B. According to the intention to treat analysis, lost to follow-up patients were considered as PD (**Table 2**). Median progression-free survival (PFS) was 5.6 months in arm A compared to 5.9 months in arm B (**Figure 2**).

TABLE 3 Distribution of patients by toxicities

Toxicities	Arm A (n=32) No. (%)	Arm B (n=32) No. (%)	*P*
Anemia			
Grade0	07 (21.9)	05 (15.6)	0.51
Grade1	21 (65.6)	25 (78.1)	
Grade2	04 (12.5)	02 (06.3)	
Neutropenia			
Grade0	18 (56.3)	23 (71.9)	
Grade1	09 (28.1)	04 (12.5)	0.25
Grade2	04 (12.5)	05 (15.6)	
Grade3	01 (03.1)	00 (00.0)	
Diarrhea			
Grade 0	07 (21.9)	03 (09.4)	
Grade 1	24 (75.0)	27 (84.3)	0.35
Grade 2	01 (03.1)	02 (06.3)	
Mucositis			
Grade 0	27 (84.3)	25 (78.1)	
Grade 1	03 (09.4)	05 (15.6)	0.75
Grade 2	02 (06.3)	02 (06.3)	
Hand-Foot Syndrome			
Grade 0	25 (78.1)	27 (84.4)	0.77
Grade 1	05 (15.6)	04 (12.5)	
Grade 2	02 (06.3)	01 (03.1)	
Vomiting			
Grade 0	07 (21.9)	12 (37.5)	
Grade 1	16 (50.0)	14 (43.7)	0.32
Grade 2	07 (21.9)	06 (18.8)	
Grade 3	02 (06.2)	00 (00.0)	
Paresthesia			
Grade 0	24 (75.0)	20 (62.5)	
Grade 1	06 (18.7)	07 (21.9)	0.55
Grade 2	02 (06.3)	04 (12.5)	
Grade 3	00 (00.0)	01 (03.1)	
Nephrotoxicity			
Grade 0	18 (56.3)	25 (78.1)	
Grade 1	08 (25.0)	05 (15.6)	0.21
Grade 2	04 (12.5)	02 (06.3)	
Grade 3	02 (06.2)	00 (00.0)	

Grade 0: no toxicity, Grade 1: mild toxicity, Grade 2: moderate toxicity, and Grade 3: severe toxicity

The commonest adverse effects were grade 1 anemia (65.6% in arm A and 78.1% in arm B), diarrhea (75.0% and 84.3%) and vomiting (50.0% and 43.7%). Relatively uncommon adverse effects were hand-foot syndrome, paresthesia, mucositis, nephrotoxicity, and nephrotoxicity (**Table 3**).

Discussion

Various chemotherapy combinations have been designed, primarily based on anthracyclines, taxanes, platinums, and fluoropyrimidines for gastric cancer. To our knowledge, this study is the first to compare the cisplatin-capecitabine regimen with the oxaliplatin-capecitabine regimen for advanced gastric cancer. It is believed that DNA adducts play a major role in determining the cytotoxicity of platinum compounds.

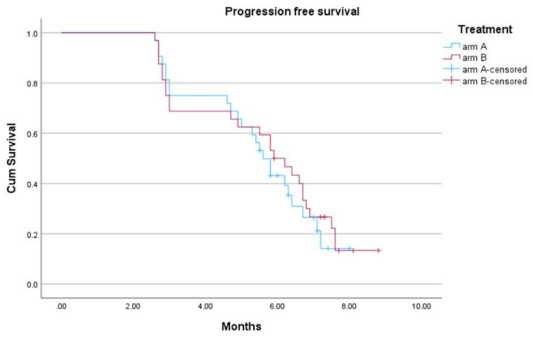

FIGURE 2 Kaplan–Meier plot of progression-free survival (PFS) in advanced gastric cancer patients treated with Cis-platin-Capecitabine regimen versus Oxaliplatin-Capecitabine regimen

Oxaliplatin and cisplatin are structurally different, yet they produce the same kinds of adducts at the same locations on DNA. It is understood that oxaliplatin causes more double-strand breaks in DNA adducts than cisplatin, which results in more cytotoxicity.[10] Capecitabine, an oral fluoropyrimidine, enhances drug concentration in tumor cells while minimizingthe systemic toxicity of chemotherapy by ge nerating cytotoxicity at the location of the liver and soli d tumors, replacing the previously utilized infusion of 5 -fluorouracil.[11] This study shows that the cisplatin-capecitabine regimen is as effective as the oxaliplatin-capecitabine regimen in terms of response and PFS in the treatment of advanced gastric cancer. The overall response rate (ORR) in arm A was 56.2%, with a median PFS of 5.6 months, whereas the ORR in arm B was 46.9%, with a median PFS of 5.9 months.

There has been no randomized controlled trial comparing these two regimens in advanced gastric cancer patients. In a phase 2 study using the cisplatin-capecitabine combination for advanced gastric cancer,

Kim et al. observed a 54.8% ORR and a median PFS of 5.8 months that almost correlated with arm A.[12] Salah-Eldin et al. reported that the median PFS for the same treatment was 6 months which is slighty higher than arm A observasion.[13]They used a higher capecitabine dose but a smaller cisplatin dose, a larger sample size, and a longer duration than our study. Quek et al. conducted a phase 2 study of an oxaliplatin-capecitabine regimen in advanced gastric cancer and observed a 61% ORR, which was higher than the arm B observation.[14] However, they had a smaller sample size and used a higher capecitabine dose than our study. According to Park et al., the median PFS for advanced gastric cancer patients receiving the oxaliplatin-capecitabine combination was 7.5 months, which is slightly longer than arm B and most likely due to the small sample size.[15] Since these studies lacked a typical control group, it was hard to draw any firm conclusions from them.

The most common toxicities in both groups throughout therapy were vomiting, diarrhea, anemia, neutropenia, oral mucositis, paresthesia, hand-foot syndrome, and nephrotoxicity. According to our observation, Cisplatin -Capecitabine was as well tolerated as Oxaliplatin-Capecitabine. Both regimens had a similar safety profile and there was no unexpected toxic effect. In both treatment groups, gastrointestinal adverse events were among the most common toxic consequences. Paresthesia, diarrhea and oral mucositis were more frequent in the Oxaliplatin-Capecitabine arm. The occurrence of neutropenia and renal toxicity were more in Cisplatin-Capecitabine arm. No patient from both the arms discontinued treatment due to the adverse effect of toxicity. Most of the patients from both arms suffered from low-grade toxicities. The number of patients who had a higher grade of toxicities were very few. All the cases of the toxicities were duly managed. There was no statistically significant difference in the number of harmful events between the arms (p-value > 0.05). Most of these findings correlate with the previous observations.[12-15] In this study, small sample size was our limitation. The COVID-19 situation prevented us from obtaining the estimated sample (n = 76) at that time. Selection bias could not be avoided in the study due to the fact that it was unblinded, non-randomized, and quasi-experimental.

Conclusion

This study's findings suggest that the cisplatin-capecitabine regimen is equally effective as the oxaliplatin-capecitabine regimen with comparable toxicities in advanced gastric cancer. This cisplatin-capecitabine regimen could be utilized as an alternate choice for the treatment of advanced gastric cancer.

Acknowledgments

The authors express their gratitude to all the doctors and employees of Department of Clinical Oncology, BSMMU.

Author Contribution

Study design and concept: MJS, SA, SKT; Data acquisition, analysis or interpretation: MJS, SKT, MHN, MG, MMR, MZH, SA, MZRB; Manuscript drafting: MJS, SKT, MHN, MG, MMR and MZH; Critical revision of the manuscript: SA, MZRB and SKT; Statistical analysis: MJS and SKT; Study supervision: SA and MZRB

Conflict of Interest

None

Funding

The BSMMU Research Grant Committee provided funding for this study.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021. DOI: 10.3322/caac.21660
2. Directorate General of Health Services (DGHS). Hospital Cancer Registry Report 2015-2017 [Internet]. https://dghs.gov.bd. [cited 2021 Apr 12]. Available from: https://dghs.gov.bd/images/docs/Publicaations/Cancer%20registry_2.pdf

3. Avital L, Stojadinovic A, Pisters P, Kelsen D, Willett C. Cancer of the Stomach. In: Devita V, Lawrence T, Rosenberg S, editors. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 2014. p. 614–34. Philadelphia: Wolters Kluwer.

4. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Combination chemotherapies in advanced gastric cancer: An updated systematic review and meta-analysis. J. Clin. Oncol. 2007. DOI: 10.1200/jco.2007.25.18_suppl.4555

5. Bilici A. Treatment options in patients with metastatic gastric cancer: current status and future perspectives. World J Gastroenterol. 2014. DOI: 10.3748/wjg.v20.i14.3905

6. Louvet C, André T, Tigaud JM, Gamelin E, Douillard JY, Brunet R, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol. 2002. DOI: 10.1200/JCO.2002.02.021

7. Chu E, DeVita VT Jr. Physicians' cancer chemotherapy drug manual 2020. 20th ed. Sudbury, MA: Jones and Bartlett; 2019. p. 676-77.

8. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur. J. Cancer. 2009.DOI: 10.1016/j.ejca.2008.10.026

9. U.S. Department of Health and Human Services. National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. [cited 2021 Apr 17]. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

10. Chaney SG, Campbell SL, Bassett E, Wu Y. Recognition and processing of cisplatin- and oxaliplatin-DNA adducts. Crit Rev Oncol Hematol. 2005. DOI: 10.1016/j.critrevonc.2004.08.008

11. Popa EC, Shah MA. Capecitabine in the treatment of esophageal and gastric cancers. Expert Opin Investig Drugs. 2013. DOI: 10.1517/13543784.2013.842974

12. Kim TW, Kang YK, Ahn JH, Chang HM, Yook JH, Oh ST, et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced gastric cancer. Ann. Oncol. 2002. DOI: 10.1093/annonc/mdf323

13. Quek R, Teck Lim W, Fong Foo K, Hsin Koo W, A-Manaf A, Chong Toh H. Capecitabine and oxaliplatin (XELOX) is safe and effective in patients with advanced gastric cancer. Acta Oncol 2007. DOI: 10.1080/02841860701253060

14. Salah-Eldin MA, Ebrahim MA, AL-Ashry MS. Phase II study of capecitabine plus cisplatin in patients with gastric cancer. Anti-Cancer Drugs. 2009. DOI: 10.1097/CAD.0b013e328325a9ec

15. Park YH, Kim B-S, Ryoo B-Y, Yang SH. A phase II study of capecitabine plus 3-weekly oxaliplatin as first-line therapy for patients with advanced gastric cancer. Br J Cancer 2006. DOI: 10.1038/sj.bjc.6603046