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The Effect of Capecitabine in Combination of Platinum Either Cisplatin or Oxaliplatin in The Advanced Gastric Cancer: An Observational Study

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Abstract **Original Research Article**

Introduction: Chemotherapy is the primary therapeutic choice for advanced gastric cancer. Different types of medicine combinations are can be used for chemotherapy treatment, but oxaliplatin is one of the more common ones, used to treat metastasized cancer. But recently, cisplatin has shown similar outcome, while costing less for the patients and the hospital. The goal of this study was to assess the effectiveness of cisplatin-capecitabine versus oxaliplatin-capecitabine in treating advanced gastric cancer by measuring disease response and toxicity levels. ***Methods:*** This Quasi-Experimental study was conducted at the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The study duration was 2 year, from February 2019 to March 2021. During this period, a total of 90 cases of advanced gastric cancer were divided in two equal groups, Arm A who had received cisplatin capecitabine, and Arm B who received oxaliplatin capecitabine. ***Result:*** In Arm A, 25 (55.5%) patients exhibited partial response (PR), whereas 21 (46.7%) patients in Arm B showed PR. Stable diseases (SD) were also reported in both arms (17.7% in arm A and 22.2% in arm B). There were 11 (24.4%) cases of progressive disease (PD) in Arm A and 14 (31.1%) cases in Arm B. 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 (p-value > 0.75). ***Conclusion:*** In advanced gastric cancer, the Cisplatin-Capecitabine regimen is equally effective as Oxaliplatin-Capecitabine, and there was no significant difference between the presenting toxic effects. As the Cisplatin-Capecitabine regimen is less costly than the combination of Oxaliplatin-Capecitabine, and shows similar outcomes in terms of response and toxicity, it is a valid alternative choice of medicine for patients who are unable to afford an oxaliplatin-based regimen.

Keywords: Carcinoma, Cancer, Chemotherapy, Cisplatin, Oxaliplatin.

INTRODUCTION

Cancer is the leading cause of death in many countries of the world, and globally is among the top 5 causes of death [1]. Among the different types of cancer, gastric cancer remains as one of the more prevalent and deadly types of cancer, being the 4th most common cancer among men and the 7th most common cancer among women [2, 3]. Gastric Cancer has extremely high mortality, as the 5-year survival rate is <40%, and just in 2020, almost a million deaths were observed worldwide [4, 5]. Stomach adenocarcinoma is referred to as "gastric cancer." Adenocarcinoma makes up about 95% of all cases of stomach cancer [6]. The accumulation of particular genetic abnormalities and a mix of environmental variables lead to gastric cancer. Healthy eating, anti-H. pylori treatments, chemoprevention, and screening for early detection are the main ways to avoid stomach cancer. Dietary factors play a significant role in the development of stomach cancer, particularly when it comes to intestinal adenocarcinoma. A lower risk of stomach cancer may be linked to healthy dietary practices, such as a high intake of fresh fruits and vegetables, the Mediterranean

diet, a low-sodium diet, salt-preserved food, red and high-cured meat, moderation in alcohol use, and keeping a healthy weight [7-9]. Conversely, an adverse dietary lifestyle can also become a risk factor for gastric cancer. Other than dietary risk factors, family history of gastric cancer, or genetic marker, as well as helicobacter pylori infection are considered the most common risk factors of gastric cancer. Some studies have also reported an association between gastric cancer and smoking and alcohol consumption [10, 11]. Chemotherapy, radiotherapy, chemo-radiotherapy, surgery, and immunotherapy are all used to treat stomach cancer. There is currently discussion on the best course of action for advanced stomach cancer. When compared to the greatest supportive care alone, chemotherapy has already been shown to improve symptom control and lengthen survival, but no global standard chemotherapy regimen has been established [12]. In our institute, a chemotherapy regimen with oxaliplatin and capecitabine is frequently employed. A randomized controlled trial comparing oxaliplatin to cisplatin was conducted in response to favorable phase II research findings. That trial's goal was to show that oxaliplatin wasn't inferior to cisplatin. It was shown that oxaliplatin is not less effective than cisplatin in the oxaliplatin-cisplatin comparison. Oxaliplatin was associated with higher rates of diarrhea and neuropathy but lower rates of neutropenia and nephrotoxicity when compared to cisplatin [13]. The cost of the Cisplatin-Capecitabine combination is less than that of the Oxaliplatin-Capecitabine combination. Patients will benefit from lower total therapy costs if the cisplatin-capecitabine combination offers greater or equivalent palliation. In this experiment, individuals with advanced gastric cancer were compared for efficacy between cisplatin-capecitabine and oxaliplatin-capecitabine.

OBJECTIVE

General Objective

- To observe the response status of patients of advanced gastric carcinoma after treatment with cisplatin-capecitabine vs with oxaliplatin capecitabine
- To evaluate the toxicity among advanced gastric cancer patients after treatment with cisplatin-capecitabine vs with oxaliplatin capecitabine

METHODS

This Quasi-Experimental study was conducted at the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The study duration was 2 year, from February 2019 to March 2021. During this period, a total of 90 patients with inoperable advanced gastric carcinoma attending the Department of Clinical Oncology, BSMMU, following the inclusion and exclusion criteria were selected for the study. The selected patients were divided in two equal groups of 45 patients each, “Arm A” and “Arm B”. Arm A patients got injection Cisplatin (80 mg/m2 IV on day 1) plus oral Capecitabine (1000 mg/m2 twice a day on days 1–14) every 3 weeks for 6 cycles. Arm B patients got injection Oxaliplatin (130 mg/m2 IV on day 1) plus oral Capecitabine (1000 mg/m2 twice a day on days 1–14) every 3 weeks for 6 cycles. Before inclusion of the patients in the study, informed written consent was obtained from each participant, and ethical approval regarding the study was also obtained from the ethical review committee of the institution. Patient’s refusal to continue in this study and occurrence of unacceptable toxicity necessitating major modification of treatment were grounds for discontinuation of the study for that particular patient. A structured data collection form was used as the research instrument, and all collected data was analyzed using SPSS software. A p-value of less than 0.05 was considered significant when comparing the results of the two arms using the Chi-square test.

Inclusion Criteria

- Patients ≤70 years of age
- Histopathologically proven inoperable advanced gastric adenocarcinoma
- Stage IV adenocarcinoma only
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Patients <18 years of age
- Patients with A structured data collection form was used as the research instrument >2
- Patients with a history of chemotherapy, radiotherapy or surgery
- Pregnant or Lactating women
- Unable to answer the criteria question.
- Exclude those affected with other chronic diseases.

RESULTS

Table 1: Distribution of the participants by basic characteristics

Characteristics	Arm A (n=45)	Arm B (n=45)
Age groups (years)		
18-30	03 (06.7%)	01 (02.2%)
31-40	04 (08.9%)	03 (06.7%)
41-50	08 (17.8%)	07 (15.6%)

51-60	10 (22.2%)	11 (24.4%)
61-70	20 (44.4%)	23 (51.1%)
Sex		
Male	35 (78.0%)	31 (69.0%)
Female	10 (22.0%)	14 (31.0%)
Site of Metastasis		
Lung	06 (13.3%)	04 (08.9%)
Liver	25 (55.6%)	23 (51.1%)
Peritoneum	15 (33.3%)	18 (40.0%)
Ovary	04 (08.9%)	03 (06.7%)
ECOG Performance		
0	04 (08.9%)	07 (15.6%)
1	10 (22.2%)	11 (24.4%)
2	31 (68.9%)	27 (60.0%)
Site of Primary Tumor		
Fundus	08 (17.8%)	06 (13.3%)
Antrum	23 (51.1%)	24 (53.3%)
Body	14 (31.1%)	15 (33.3%)
Risk Factors		
Helicobacter Pylori	31 (68.9%)	35 (77.8%)
Smoking	14 (31.1%)	18 (40.0%)
Type A blood	18 (40.0%)	15 (33.3%)

In arm A and arm B, the patients' mean ages at diagnosis were 55.85 and 56.76, respectively. The majority of the patients ranged in age from 61 to 70. Arm A had 78 percent male patients, compared to Arm B's 69 percent male patients, in terms of gender. In both arms, the majority of patients received an ECOG performance rating of 2. (68.9 percent in arm A and 60 percent in arm B). The liver was the most common metastatic site in both arms (55.6 percent in arm A and 51.1 percent in arm B). The pyloric antrum was the most frequent site of initial tumors. The most frequent risk factor in both arms was Helicobacter pylori infection (68.9 percent in arm A and 77.8 percent in arm B).

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

Response	**Arm A (n = 45)**	**Arm B (n=45)**	***P*-value**
Partial response (PR)	25 (55.5%)	21 (46.7%)	0.751
Stable disease (SD)	08 (17.7%)	10 (22.2%)	
Progressive disease (PD)	11 (24.4%)	14 (31.1%)	

In Arm A, 25 (55.5%) patients had a partial response (PR), while 21 (46.7%) patients in Arm B had a PR. In both groups, stable diseases (SD) were also detected (17.7% in arm A and 22.2% in arm B). There were 11 (24.4%) cases of progressive disease (PD) in Arm A and 14 (31.1%) cases of PD in Arm B.

Table 3: Distribution of participants by type and grade of toxicities for both Arm A and Arm B

Toxicities	**Arm A (n=45)**	**Arm B (n=45)**	**p-value**
Anemia			
Grade 0	10 (22.2%)	07 (15.6%)	0.509
Grade 1	30 (66.7%)	35 (77.8%)	
Grade 2	06 (13.3%)	03 (6.7%)	
Neutropenia			
Grade 0	25 (55.6%)	32 (71.1%)	0.303
Grade 1	13 (28.9%)	06 (13.3%)	
Grade 2	06 (13.3%)	07 (15.6%)	
Grade 3	01 (02.2%)	00 (00.0%)	
Diarrhea			
Grade 0	10 (22.2%)	04 (08.89%)	0.348
Grade 1	34 (76.0%)	38 (84.44%)	
Grade 2	01 (02.2%)	03 (6.67%)	
Mucositis			
Grade 0	38 (84.4%)	35 (77.8%)	0.749

Grade 1	04 (08.9%)	07 (15.6%)	
Grade 2	03 (06.7%)	03 (6.7%)	
Hand-Foot Syndrome			
Grade 0	35 (77.8%)	38 (84.4%)	0.771
Grade 1	07 (15.6%)	06 (13.3%)	
Grade 2	03 (06.7%)	01 (02.2%)	
Vomiting			
Grade 0	10 (22.2%)	17 (37.8%)	0.317
Grade 1	23 (51.1%)	20 (44.4%)	
Grade 2	10 (22.2%)	08 (17.8%)	
Grade 3	03 (06.7%)	00 (00.0%)	
Paresthesia			
Grade 0	34 (76.0%)	28 (62.2%)	0.551
Grade 1	08 (18.0%)	10 (22.2%)	
Grade 2	03 (07.0%)	6 (13.3%)	
Grade 3	00 (00.0%)	01 (02.2%)	
Nephrotoxicity			
Grade 0	25 (55.6%)	35 (77.8%)	0.212
Grade 1	11 (24.4%)	07 (15.6%)	
Grade 2	06 (13.3%)	03 (06.7%)	
Grade 3	03 (6.7%)	00 (00.0%)	

In Arm A, 30 patients (66.7%) and 06 (13.3%) had grade 1 and 2 anemia, respectively, whereas in Arm B, 35 patients (77.8%) and 03 patients (6.7%) had grade 1 and 2 anemia, respectively. In Arm A, 6 patients (13.3 percent) and 1 patient (2.2%), respectively, had neutropenia of grade 2 and 3. Individuals in arm B had grade 2 neutropenia in 07 (15.6%). The vast majority of patients in both groups suffered from Grade 1 diarrhea (76.0 percent in Arm A and 84.4 percent in Arm B). Arm A (84.4 percent) had a higher number of grade 0 oral mucositis than Arm B (77.8%). In terms of hand foot syndrome, 15.6% and 6.7% of patients in Arm A, respectively, had Grade 1 and Grade 2 illness. In contrast, 13.3% and 2.2% of patients in Arm B developed Grade 1 and 2 syndromes, respectively. In Arm B, only 2.2% of patients developed Grade 3 paresthesia. Grade 2 paresthesia affected 7.0% of patients in arm A and 13.3% of patients in arm B. In terms of nephrotoxicity, 13.3% of patients in Arm A and 6.7% of patients in Arm B had grade 2 toxicity. In arm A, only 6.7% of patients experienced grade 3 toxicity.

DISCUSSION

Systemic chemotherapy is the backbone of treatment for advanced gastric cancer. In the present study, a total of 90 patients with histopathologically proven advanced gastric carcinoma were included for treatment, and the patients were divided in two equal groups of 45 patients. Arm A patients had been given of Cisplatin-Capecitabine, while Arm B patients had been given Oxaliplatin-Capecitabine for the treatment of advanced gastric cancer. In base characteristics, it was observed that very few participants had been under 50 years of age, with the largest portion of participants being from 61-70 years age group (44.4% in Arm A and 51.1% in Arm B). Although the underlying cause hasn't been determined yet, studied have observed a high prevalence of gastric cancer among the elderly, which was similar to our study findings [14]. High male prevalence was observed among the study population, with an overall male: female ratio of 1.36:1. This high prevalence of gastric cancer cases among the men was not uncommon, as some studies have recorded over 2 times the prevalence of female population [15, 16]. By design, the present study did not include any patients with ECOG score of >2. Among the existing participants, 68.9% of Arm A and 60.0% of Arm B had been of ECOG scale 2, while 22.2% of Arm A and 24.4% of Arm B had been of ECOG scale 1. The site of primary tumor was the antrum for both Arms, 51.1% In Arm A and 53.3% in Arm B. following highest prevalence was in terms of body tumor, observed in 31.1% of Arm A and 33.3% of Arm B. Among the observable risk factors, Helicobacter Pylori infection had the highest prevalence, observed in 68.9% of Arm A and 77.8% of Arm B participants. Smoking and type A blood had also been highly prevalent among the participants. Among Arm A participants, type A blood had a slightly higher prevalence compared to smoking, while in Arm B, the situation was reversed. H. Pylori infection is a common risk factor for gastric cancer, observed in many other studies [17-19]. Patients were evaluated before and after treatment to determine how well it worked. Twelve weeks following the end of therapy for both Arm A and Arm B, the last follow-up was conducted. Partial responses (PR) were seen in 25 (55.5%) of the patients in Arm A and 21 (46.7%) of the patients in Arm B. Additionally, stable conditions (SD) were seen in both arms (17.7 percent in arm A and 22.2 percent in arm B). Progressive disease (PD) affected 11 (24.4%) patients in Arm A and 14 (31.1%) patients in Arm B. The differences in treatment outcomes between

the two groups were not statistically significant (p-value=0.751). There had never been any head-to-head studies contrasting the two arms that we looked at. Similar to our study, Kim et al. conducted a phase 2 trial of cisplatin with capecitabine in advanced gastric cancer where he reported 55.5% partial response, 17.7% stable disease, and 24.4% progressing disease. This was really similar to the findings of Arm A participants of the present study [20]. In any type of chemotherapy, some toxicities are unavoidable, and the best option can't always be determined based solely on presence or absence of any form of toxicity. In the present study, the most common toxicities in both groups throughout therapy were vomiting, diarrhea, anemia, neutropenia, oral mucositis, paresthesia, hand-foot syndrome, and nephrotoxicity. Grade 1 anemia had the highest prevalence in both arms, but it was more common in Arm B patients at 77.8%, while 66.7% of Arm A participants had grade 1 anemia. However, this slight increase in the prevalence among Arm B participants was not statistically significant. Overall, Grade 1 and above levels of toxicity were higher among Arm B patients in terms of all types of toxicity, while Grade 1 nephrotoxicity had higher prevalence among Arm A patients compared to Arm-B. None of the toxicity had any significant difference in terms of toxicity grade among the two arms. Our observations show that Cisplatin-Capecitabine was as well tolerated to Oxaliplatin-Capecitabine. There were no unanticipated adverse effects with either regimen, which had a similar safety profile. The most frequent harmful effects in both treatment groups were gastrointestinal unpleasant episodes. The Oxaliplatin-Capecitabine arm had a higher incidence of paresthesia, diarrhea, and oral mucositis. Neutropenia and renal toxicity were more common in the Cisplatin-Capecitabine arm. No patient from either arm of treatment quit because of toxicity's negative effects. Low-grade toxicities affected the majority of the participants in both arms. There were very few patients who suffered toxicity of a higher grade. All toxicity situations were handled properly. 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 [21, 22].

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

In advanced gastric cancer, the Cisplatin-Capecitabine regimen is equally effective as Oxaliplatin-Capecitabine, and there was no significant difference between the presenting toxic effects. As the Cisplatin-Capecitabine regimen is less costly than the combination of Oxaliplatin-Capecitabine, and shows similar outcomes in terms of response and toxicity, it is a valid alternative choice of medicine for patients who are unable to afford an oxaliplatin-based regimen.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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