Original Research Paper

Volume-8 | Issue-9 | September-2018 | PRINT ISSN No 2249-555X

Pharmacology

EFFICACY AND SAFETY OF EPIRUBICIN, OXALIPLATIN AND CAPECITABINE COMBINATION IN TREATMENT OF NON-RESECTABLE OR ADVANCED GASTRIC CARCINOMA

Aritra Ghosh* MD, Senior Resident, Department of Pharmacology, Burdwan Medical College & Hospital, Purba Bardhhaman – 713104, West Bengal, India. *Corresponding Author

Angana Datta MD, Assistant Professor, Department of Pharmacology, Burdwan Medical College & Hospital, Purba Bardhhaman – 713104, West Bengal, India.

Saswati Sarkar MD, Associate Professor, Department of Pharmacology, Burdwan Medical College &Hospital, Purba Bardhhaman – 713104, West Bengal, India.

Mithilesh Haldar MD, Assistant Professor, Department of Pharmacology, Burdwan Medical College &Hospital, Purba Bardhhaman – 713104, West Bengal, India.

ABSTRACT

BACKGROUND- Assessment of clinical efficacy and safety of epirubicin, oxaliplatin and capecitabine (EOX) in the treatment of non-resectable or advanced gastric carcinoma.

METHODS- Total 50 patients were evaluated in the study for 425 days and they received epirubicin 50 mg/m2 and oxaliplatin 130 mg/m2 as IV infusion on day one, capecitabine 1250 mg/m^2 in two divided doses orally from day 1 to14. This cycle had been repetitively used every three weeks and given for six cycles.

RESULTS- Number of patients with complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) were 4 (8%), 24 (48%), 10 (20%) and 12 (24%) respectively. Median progression free survival was 210 days. Haematological toxicities like anaemia, leukopenia, thrombocytopenia were most common. Alopecia, nausea-vomiting, anorexia, lethargy, neuropathy and diarrhoea were commonly occurred non-haematological toxicities.

CONCLUSION- EOX regimen showed good results in advanced gastric carcinoma both efficacy and safety wise. Larger study is required to establish the safety and efficacy of this regimen in our country.

KEYWORDS : gastric, progression free survival, carcinoma, open-label

INTRODUCTION-

Cancer, a leading health problem in India, accounts for approximately 1 million cases occurring each year. Amongst this, the leading cause of cancer related death in India is gastric cancer. Gastric cancer is responsible for 10% of all cancer deaths, and it is one of the most commonly diagnosed malignancies in Asia.[1,2] Gastric cancer is a multi-factorial disease.[3] High salt consumption, low dietary fibres consumption, poor drinking water, H. Pylori infection, cigarette smoking, chronic atrophic gastritis, many genetic familial diseases etc. are some of the risk factors of gastric cancer. Now in treating gastric cancer, surgery is till date the most effective and acceptable method, but surgical treatment alone has a high rate of locoregional and distant recurrence.[4,5] So in advanced/metastatic stage, where surgery cannot be done, chemotherapy is the only treatment for palliation. Many chemotherapeutic agents were tried as single or combination drug regime. The potential advantage of giving combination chemotherapy versus single agents has been evaluated by Wagner et al. 2010 in the Cochrane review.[6] They found that combination chemotherapy had a significant survival advantage when compared to single-agent chemotherapy (HR 0.5; 95% CI 0.75 to 0.96). So, today combination chemotherapy is generally preferred. Many regimens were tried previously like FAMTX[7], FOLFIRI[8], FOLFOX[9] etc. EOX (epirubicin,oxaliplatin plus capecitabine) is one of the most commonly used regimen now a days.[10]

Based on the previous regimens' results and REAL-2 study[10], we planned this prospective single arm study to evaluate the efficacy and toxicity profile in non-resectable advanced/metastatic gastric cancer rural and urban Indian population.

METHODS-

The study was designed as an open label, non-interventional, prospective, observational study.

Patient Characteristics-

The data that were collected, were from patients who attended the Radiotherapy OPD of a tertiary care teaching hospital in Burdwan, Burdwan Medical College and Hospital, diagnosed of having inoperable advanced/metastatic gastric carcinoma.

Main inclusion criteria were: 1. In those patients where surgery cannot be possible due to extensive organ involvement, 2. Patients with distant metastasis, 3. Age less than 70 years, 4. No history of myocardial infarction, ischaemia, respiratory failure in patients, 5. No renal compromise.

Exclusion criteria were: 1. Myocardial infarction, ischaemic heart disease, heart block, respiratory failure, 2. Renal compromised patients, 3. Pregnancy, 6. Patients not giving consent to the study.

Institutional Ethics Committee (IEC) of Burdwan Medical College and Hospital gave approval for the study and recruitment was subjected to satisfactory completion of the informed consent process.

Treatments- The patients received chemotherapy as per the assessment of the treating physician. No changes were made in the treatment decision, schedule or duration during the study period. Patients received epirubicin in a dose of 50 mg/m^{2}as IV infusion on day one; oxaliplatin in a dose of 130 mg/m^2 as IV infusion on day one; capecitabine 1250 mg/m^2 in two divided doses orally from day 1to day14. Cycle was repeated every three weeks and for a total of six cycles. After completion patients were put into follow up period.

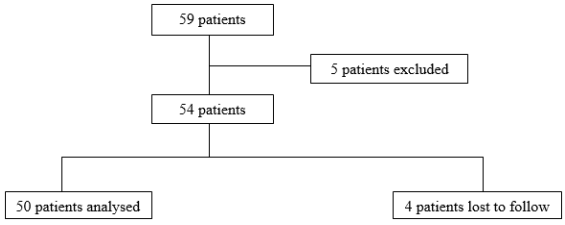
EVALUATION & OUTCOME-

Before starting the treatment, thorough physical examination, blood count, biochemistry profile and CT scan of abdomen were done. Patients were asked to visit the OPD after 15 days of receiving chemotherapy. Patients were questioned regarding compliance and adverse drug reactions which might have occurred following chemotherapy. Patients' blood was collected for measuring serum urea, creatinine, haemoglobin (Hb), total leucocyte count (TLC), differential count (DLC) and patients were examined clinically and date for subsequent chemotherapy was given. After 3rd and 6th cycle of chemotherapy CT scan was done. In the follow up visits previously mentioned tests were done. Tumour size was assessed by CT scan and outcome was defined as follows: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to RECIST criteria.[11] The length of time during and after the treatment of cancer was used to calculate Progression free survival(PFS), which denotes the time the patient lives with the disease but it does not get further worse.Toxicities were documented also.

Statistical analysis was done with the help of SPSS version 21. Distributions of quantitative data are presented as Mean ± Standard deviation and that of qualitative data are presented as absolute number and percentage. Statistical analyses of quantitative data were done using Wilcoxon's Signed Ranks test as the data were non-parametric.

RESULTS-

Patient characteristics-A total of 59 patients attending the out-patient Department (OPD) of Radiotherapy, Burdwan Medical College and Hospital, Burdwan, and diagnosed advanced/metastatic gastric carcinoma were screened for this study. Among them 54 were recruited in the study. Out of these, 50 were analysed and 4 were lost to follow up.



Maximum study subjects had adenocarcinoma of corpus followed by adenocarcinoma of cardia. Among 50 patients, 18 patients had locally advanced gastric carcinoma whereas 32 patients had metastatic disease. Most patients were male and age in their sixties.

EFFICACY-

According to the RECIST criteria 4 patients (8%) had radiologically (CT scan) proven complete response (CR). Number of patients with partial response (PR) were 24 (48%). 12 (24%) cases of stable disease (SD) were found and progressive disease (PD) was encountered in 10 patients (20%). The details of tumour response to treatment are depicted in the following figure 1.

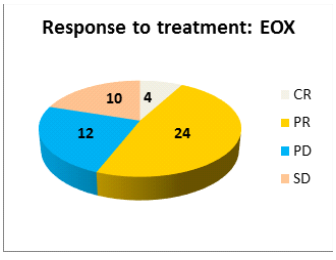


Figure 1: Tumour Response in EOX regimen

Progression free survival:

Kaplan- Meier survival analysis showed median progression free survival days were 210 days (95% CI 199-220). Progression free survival was calculated from the first day of chemotherapy to the date on which disease "progressed" or the date on which the patient died. Number of patients died or who had progression were 38 (76%). Progression free survival plot is shown in figure 2.

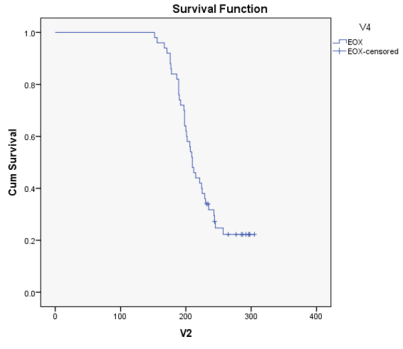


Figure 2: Progression Free Survival Plot from Kaplan-Meier Survival Analysis

Toxicities-

Commonly occurred toxicities were alopecia (60%), nausea-vomiting (76%), anorexia (52%), diarrhoea (64%), lethargy (68%) and peripheral tingling sensation (60%). Few patients also reported stomatitis, hand-foot syndrome and constipation. Figure 3 depicting toxicity profiles of the patients. All 50 subjects developed toxicities. From them 230 were tabulated. As combination chemotherapy had been given to patients, hence toxicities could not be attributed to a single agent.

Table 1: Toxicity Profiles of the Patients

Toxicities	n= 50 (%)
Alopecia	30 (60.0)
Anorexia	26 (52.0)
Nausea- vomiting	38 (76.0)
Lethargy	34 (68.0)
Neuropathy/ tingling sensation	30 (60.0)
Diarrhoea	32 (64.0)
Stomatitis	18 (36.0)
Hand-foot syndrome	18 (36.0)
Constipation	4 (8.0)

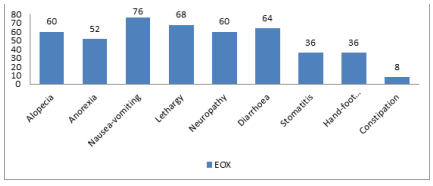


Figure 3:Toxicity Profile of the Study Subjects during Chemotherapy

In case of haematological safety parameter, there was statistically significant decrease in haemoglobin level after completion of chemotherapy (Table-2). Initially 80% patients in EOX arm had mild anaemia and 20% had moderate anaemia. At end of six cycles of chemotherapy 48% had mild and 52% had moderate anaemia. No patients developed life-threatening anaemia. There was also statistically significant fall in total leukocyte count following chemotherapy. Only two patients in EOX group developed grade 1 leukopenia. There was statistically significant fall in neutrophil count in EOX regimen. 28% patients had neutropenia initially, at the end of six cycles of chemotherapy 56% developed neutropenia and among them 24% had grade 3 neutropenia. Statistically significant drop in platelet count was observed at the end of treatment.

Table 2: Changes in Haematological Parameters

Category	Mean ± SD (n=50)		p-value
	Baseline	After 6th cycle	
Haemoglobin(g/dl)	11.34 ± 1.45	10.67 ± 1.33	0.0001
TLC (cells/mm3)	6440.0 ± 845.5	5900.8 ± 879.7	0.0001
Neutrophils (%)	61.80 ± 5.07	56.48 ± 7.11	0.008
Lymphocytes (%)	32.32 ± 5.12	33.88 ± 4.19	0.151
Monocytes (%)	1.12 ± 0.33	1.32 ± 0.63	0.219
Eosinophils (%)	5.60 ± 1.94	6.08 ± 2.59	0.304
Basophils (%)	0.16 ± 0.47	0.24 ± 0.52	0.578
Platelet (in lakhs/ mm3)	1.94 ± 0.53	1.74 ± 0.46	0.011

- Abbreviations used: SD= Standard deviation
- p value for before-after comparison is from Wilcoxon's Signed Ranks test

Assessment of renal function was done by measuring serum urea and creatinine.There was no statistically significant difference in serum urea level butstatistically significant difference in serum creatinine level before and after chemotherapy.

Table 3: Changes in Renal Parameters (Urea and Creatinine)

Category	Mean ± SD (n=50)		p value
	Baseline	After 6th cycle	
Urea(mg/dl)	31.44 ± 3.86	31.04 ± 3.91	0.702
Creatinine (mg/dl)	0.89 ± 0.13	0.99 ± 0.19	**0.004**

- Abbreviations used: SD= Standard deviation
- *p* value for before-after comparison is from Wilcoxon's Signed Ranks test

DISCUSSION-

The result of this study shows that EOX regimen has major survival benefits when used as first line therapy in advanced/metastatic gastric

cancer. Only 4 patients (8%) had complete response (CR), number of patients with partial response (PR) was 24 (48%) in EOX arm. Number of stable disease was 12 (24%). This result is more or less comparable to Cunningham et al study[10] which showed complete response in EOX arm 3.9%. In our study complete response in EOX arm was slightly better (8% to 3.9%). Partial response in EOX arm was 44% in Cunningham et al study.[10] Result in our study was almost same.

Median progression free survival was 210 days in EOX group. 38 patients were died or progressed clinically or radiologically in study period. According to Cunningham et al study median progression free survival in EOX group was 7 months which is same to our result[10], but Jatoi et al study showed median PFS was 4 months which is much inferior than our result.[12] Schonnemann et al study showed 6.8 months PFS for Oxaliplatin group which is slightly less than our study.[13] Our study showed better efficacy than previous studies because the regimen was modified and given for only 6 cycles at an interval of 21 days and capecitabine was given for 14 days. This may be because in the hospital, there is no indoor facility in Radiotherapy Department and the patients received chemotherapy as day care procedures and there is excessive patient load in Radiotherapy department. Small sample size is also a major factor.

Patients suffered many adverse effects during the treatment as combination regimen was administered hence adverse effects could not be attributed to a single agent. 60 percent patients in EOX group developed peripheral neuropathy which is much less than REAL-2[10] study (83.7%). In this study other adverse effects like alopecia, diarrhoea, nausea vomiting, stomatitis, hand foot syndrome, lethargy were better than REAL-2 trial[10] and Schonnemann et al study[13], due to the reason that in our study the patients received six cycles of chemotherapy instead of eight like that in the aforementioned two studies. Small sample size is also a deciding factor here for better toxicity profile.

In our study initially 80% patients in EOX arm had mild anaemia and 20% had moderate anaemia. At the end of six cycles of chemotherapy, 48% had mild and 52% had moderate anaemia. REAL-2 study showed development of mild and moderate anaemia in 55.6%, severe and life-threatening anaemia in 8.6% EOX arm.The incidence of anaemia is high in this study. The reason behind this occurrence could be due to the fact that majority of our study patients resided in the rural areas and came from poor socio-economic background which resulted in malnutrition.This study showed significant fall in total leukocyte count following chemotherapy, only two patients developed grade 1 leukopenia.Statistically significant fall in neutrophil count was observed, 28% patients had neutropenia initially, at the end of six cycles of chemotherapy 56% developed neutropenia and amongst them 24% had grade 3 neutropenia. None of the patients had grade 4 neutropenia. Cunningham et al study showed development of neutropenia (all grades) in 62.9%, grade 3 or 4 neutropenia in 27.6% patients.[10] There was statistically significant drop in platelet count post treatment. So above results showed that this regimen is myelotoxic.

There was statistically significant difference in serum creatinine level before and after chemotherapy,result is comparable with Cunningham et al study which also showed increase level of creatinine level in EOX group.[10]

As the first line treatment of late stage gastric cancer- an encouraging, well tolerated and a better survival benefit of EOX regimen were observed in our study. The limitations of the study were single arm, small sample size, small duration. Though a large-scale study with better equipments is necessary to establish the efficacy of this regimen and particularly which sub-groups of gastric cancer show better result with the treatment should also be evaluated.

DECLARATIONS:-

Conflict of Interests-

The authors have declared that no conflict of interests exist.

Funding- No funding sources

Ethical Approval -IEC approved study

REFERENCES-

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61: 69–90.
2. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol. 2006; 20: 633–49.
3. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process-First American Cancer Society Award Lecture on cancer epidemiology and prevention. Cancer Res. 1992; 52(24): 6735.
4. Theuer CP, Kurosaki T, Ziogas A, Butler J, Anton-Culver H. Asian patients with gastric carcinoma in the United States exhibit unique clinical features and superior overall and cancer specific survival rates. Cancer. 2000; 89: 1883–92.
5. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japan and the United States. Cancer. 2000; 89: 2237–46.
6. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. The Cochrane collaboration. Cochrane Database Sys Rev. 2010; 3: 10-7.
7. Wils JA, Klein HO, Wagener DJ, Bleiberg H, Reis H, Korsten F, et al. Sequential high-dosemethotrexate and fluorouracil combined with doxorubicin-A step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol. 1991;9(5): 827-31.
8. Assersohn L, Brown G, Cunningham D, Ward C, Oates J, Waters JS, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory orrelapsed advanced oesophageal and gastric carcinoma. AnnOncol. 2004; 15(1): 64-9.
9. Kim DY, Kim JH, Lee S, Kim TY, Heo DS, Bang YJ, et al. Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastriccancer. Ann Oncol. 2003;14: 383-7.
10. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabineand oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358(1): 36-46.
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228–47.
12. Jatoi A, Murphy BR, Foster NR, Nikcevich DA, Alberts SR, Knost JA, et al. Oxaliplatin and capecitabine in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia: aphase II study from the North Central CancerTreatment Group. Ann Oncol. 2006; 17:29-34.
13. Schønnemann KR, Jensen HA, Yilmaz M, Jensen BV, Larsen O, Pfeiffer P. Phase II study of short-time oxaliplatin, capecitabine and epirubicin (EXE) as first-line therapy in patients with non-resectable gastric cancer. Br J Cancer 2008; 99: 858–861.