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# Outcome Analysis of Cisplatin-5 Flurouracil and Weekly 5-Flurouracil in Advanced Gastric Cancer.

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## Abstract

**Background:** Advanced gastric cancer patients has poor survival rate of < 20% at 5 years. We intended to evaluate the outcomes of Cisplatin and 5-Flurouracil combination chemotherapy or 5 FU alone in this setting. **Objectives:** In this study we analyzed the outcomes such as response rate, progression free survival (PFS) at 6 months, and toxicity profiles of 3 weekly Cisplatin and 5-Flurouracil (PF) regimen and Weekly 5-Flurouracil (5-FU) therapy in advanced gastric cancer. **Subjects and Methods:** The outcomes of the chemotherapeutic regimens such as intravenous infusion of Cisplatin 75mg/m2 in divided doses and 5-Flurouracil 750mg/m2 for consecutive 3 days every 21 days (Group A) and intravenous infusion of 5-Flurouracil 500mg flat dose every week for 16 weeks (Group B) in stage III/IV gastric cancer were analyzed. Baseline parameters were obtained. **Results:** Twenty patients for both PF and weekly 5-FU regimens were recruited. The Overall response rate of Group A and B regimen was 40% and 20% respectively. PFS at the end 6 months was 60% and 35% respectively. Median time to progression was 5 months in group A and 3.6 months in group B. Hematological toxicity and Non hematological toxicity rates were in the acceptable range in Group A. **Conclusion:** Three weekly Cisplatin and 5-Flurouracil could be a good regimen when the performance status of the patient is good. Weekly 5-Flurouracil gives good quality of life and this regimen can be considered when the patient is not eligible for Cisplatin and 5-Flurouracil regimen in advanced gastric cancers.

**Keywords:** Stomach neoplasm, Cisplatin, Fluorouracil, Progression free survival.

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## Introduction

Adenocarcinoma of the stomach was the leading cause of cancer- related deaths worldwide through most of the 20th century.[1] It now ranks second only to lung cancer and an estimated 8,70,000 new cases are diagnosed annually and second leading cause of cancer deaths (10% of all cancer deaths) worldwide.

A large majority of these patients present in advanced stage, a problem compounded further by poor access to tertiary cancer centers. The prognosis remains poor in these patients despite the advances in the chemotherapeutic regimens.

There is no worldwide consensus available for the standard regimen in-spite of many number of chemotherapeutic Regimens developed in advanced gastric cancer. 5-Flurouracil (5-FU) based regimens, commonly used either alone or in combination with other drugs, but the response rate is only 20-50%. Cisplatin is probably the second most common agent administered for gastric cancer. The efficacy combination of 5-FU and Cisplatin in patients with gastric cancer has been well known.[2-7] Synergism between the Cisplatin and 5-FU has been established well. Cisplatin inhibits intracellular L-methionine, thus resulting in a several fold rise in reduced folate and enhanced 5-FU cytotoxicity.[8] The 5-FU and Cisplatin combination is considered to be one of the standard and reference regimens in many centers. There have been three phase II studies in European countries, using 5-FU with Cisplatin. The response rate ranged from 41 to 48 % and median overall survival was 9 to 10 months.[9-11] Additionally a randomized study in Korea showed that this combination was better than 5FU, Adriamycin, Mitomycin C (FAM) or 5FU alone in terms of response rate and time to progression.[12] Hence we also analyzed the outcomes of 3 weekly Cisplatin and 5FU regimen and weekly 5FU therapy in advanced Gastric cancer at our center.

## Subjects and Methods

This is a prospective study aimed to assess the outcomes such as overall response rate, progression free survival (PFS) at 6 months, and toxicity profiles of 3 weekly Cisplatin and 5 –Fluorouracil regimen and weekly 5 – fluorouracil therapy in advanced and metastatic gastric cancer.

**Patient Selection**

Patients with histopathologically confirmed stage III/IV gastric cancer were included in this study. Other inclusion criterias for 3 weekly regimen were performance status 2-3 by ECOG, age 18 – 75 years, creatinine clearance of ≥ 50

ml/min and should have normal hepatic function and adequate blood counts. Patients with severe cardiac, Renal, Hepatic diseases were excluded from the study. Those who are not eligible for Cisplatin-5FU regimen were considered for palliative weekly 5FU regimen.

The eligible patients were evaluated by physical examination, chest X-ray, computed tomography (CT) abdomen, and blood parameters. Written informed consent from each patients and Ethics committee clearance were obtained before this study.

**Treatment**

The patients who are recruited for 3 weekly regimen received intravenous infusion of Cisplatin 75mg/m2 in divided doses and 5-Flurouracil 750mg/m2 for consecutive 3 days every 21 days for 6 cycles (Group A) and the patients who are recruited under weekly regimen received intravenous infusion of 5-Flurouracil 500mg flat dose every week for 16 weeks (Group B). The standard premedication with anti emetics such as steroids and 5 – HT3 inhibitors was given. After completion of chemotherapy the patients were reevaluated with CT abdomen, X-Ray chest and Blood parameters.

**Response evaluation and Statistical Methods**

The response rate was evaluated with clinical examination, blood counts, Renal function test, Liver function tests every 21 days. Response to treatment assessed with imaging and evaluated with RECIST version 1.1 criteria and the toxicity to chemotherapy was graded according to CTCAE version 4.0. Tumor response rate (Partial response + complete response) and disease control rate (Partial response + complete response + stable disease) were analyzed. Statistical analyses were done using the software SPSS version 16.0 for windows.

## Results

This study was done from September 2015 to March 2016. Totally twenty (n=20) patients were enrolled for each regimen. The patient and tumor characteristics of both regimens are given in the [Table 1].

The median age of the patients was 53 years in Group A and 51 years in Group B. Among them 14 patients were male, 6 were female in Group A and 16 males, 4 females in Group B. The performance status of all patients in Group A was 2 and Group B was 3 by ECOG.

A total of 120 chemotherapy treatments were given in Group A and 320 chemotherapy treatments were given in Group B with the mean of 6 and 16 doses respectively. The response rates of both groups are given in [Table 2].

Overall response rate (complete response + partial response) in Group A was 40 % and 20 % in Group B. Disease control rate (complete response + partial response + stable disease) was 60 % in Group A and 35 % in Group B. Progression of disease was seen in 40 % of Group A patients and 65 % in Group B (figure.1). The Progression free survival rate at 6 months was 60 % and 35 % in Group A and B respectively. Median time to progression was 5 months in Group A and 3.6 months in Group B.

**Toxicity**

Grade II Anemia and Thrombocytopenia was seen in 60% and neutropenia in 10% of patients in Group A. Among Group B, 30% of patients developed grade II anemia and no thrombocytopenia or neutropenia were noted. Non hematological toxicity included nausea in 12(60%) patients, vomiting 12(60%), sensory neuropathy 3(15%), reduced GFR 4(20%), constipation 9(45%), diarrhea and mucositis in 4(20%) in group A. Diarrhea and mucositis (40% and 45% respectively) were noted more in group B.

**Table 1: Patients and tumor characteristics of Group A and Group B.**

| | 3 weekly Cisplatin And 5 –FU (Group A) (n = 20) | Weekly 5 – FU (Group B) (n = 20) |
|---|---|---|
| **Patient Characteristics** | | |
| Gender<br>Male | 14 | 16 |
| Female | 6 | 4 |
| Age (median) | 53 years (Range 37-67 years) | 51 years (Range 36-70 years) |
| Performance Status | 2 (100 %) | 3 (100 %) |
| Tumor Characteristics | | |
| Locally Advanced | 14 | 6 |
| Peritoneal Disease | 3 | 7 |
| Lymph Node | 0 | 3 |
| Liver | 2 | 3 |
| Ovary | 1 | 0 |
| Lung | 0 | 1 |

**Table 2: The response rate of both chemotherapeutic regimens.**

| Parameters | Group A, n (%) | Group B, n (%) |
|---|---|---|
| Complete Response | 0 (0 %) | 0 (0 %) |
| Partial Response | 8 (40 %) | 4 (20 %) |
| Stable Disease | 4 (20 %) | 3 (15 %) |
| Progressive Disease | 8 (40 %) | 13 (65 %) |

**Table 3: Comparison of Cisplatin – 5 FU regimen studies with the present study.**

| Study | Patients (n) | Responses n (%) | Survival (months) |
|---|---|---|---|
| Lacave et al | 56 | 22 (41) | 10.6 |
| Ohtsu et al. | 20 | 9 (45) | N/A |
| KRGCGC et al. | 21 | 5 (24) | N/A |
| Wilke et al. | 44 | 12 (27) | 8 |
| Cervantes et al. | 119 | 59 (50) | 9.3 |
| Present Study | 20 | 8 (40) | N/A |

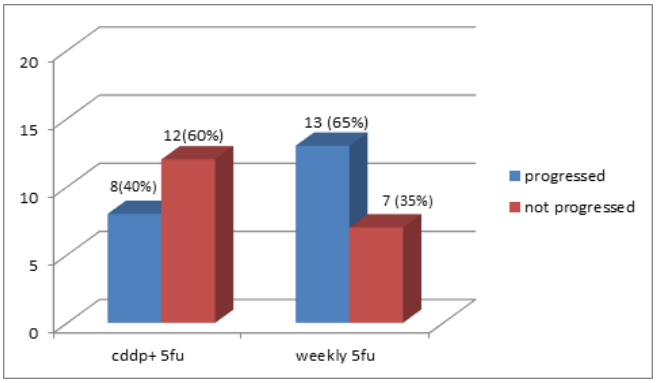


**Figure 1: shows progression of disease in both Groups**

## Discussion

The management of advanced gastric malignancy is based upon clinical predicament. In this study, two simple and economically feasible regimens were taken for analysis. According to Wohrer et al in the treatment of advanced gastric cancer, chemotherapy is superior to best supportive care. In this study, combination chemotherapy is associated with high over all response rate than monotherapy.[13]

The overall response rate in our study in Group A was 40% which is comparable with the study done by Kim et al,[12] who compared combination chemotherapy regimens FP (Cisplatin/5FU) vs. 5FU vs. FAM (5FU/ ADRIAMYCIN/ MTX) in advanced gastric cancer. A total of 324 patients were enrolled in the trial and 295 patients (103 for FP, 98 for FAM, 94 for FU) were evaluated. The ORR for FP is 51%, for FAM is 25% and for 5FU is 21%. Nausea, vomiting, diarrhea, stomatitis, alopecia, and skin pigmentation were common non hematological side effects. Significantly higher frequencies of anemia and neutropenia were observed in patients receiving FP or FAM therapy, but these were mild and tolerable. Nausea, vomiting and peripheral neuropathy were observed more frequently in the FP arm (nausea and vomiting, $P < 0.01$; neuropathy, $P < 0.05$ ;).[12]

In a study by Lacave A. J et al,[9] 46 patients underwent Cisplatin and 5FU combination chemotherapy showed a response rate of 41% with an overall median survival time of 10.6 months. Leukopenia and thrombocytopenia were mild. Nausea and vomiting were common and 23.5% of patients had grade 3 stomatitis. Peripheral neuropathy and renal in-sufficiency increased with the number of cycles. The response rates are in comparable with our study (40% in Cisplatin and 5FU) but the rate of emesis was higher in our study (60%).

Rougier P et al,[10] studied about the efficacy of combined 5FU and Cisplatinum. In this study, 87 patients who underwent the treatment showed 43% response rate (complete response 5% and partial response 39%). Responses were more frequent in patients with good performance status. Toxicity was acceptable, neutropenia was reported in 22% and mucositis in 13%. In our study neutropenia was reported in 10% and mucositis in 20% of patients.

Five studies,[9,11,14-16] have examined the combination of Cisplatin with 5-FU (FP) in a total of 260 evaluable patients in advanced gastric cancer and demonstrated an overall response rate of 41%. In one study, the addition of the anthracycline/ epirubicin to FP did not improve the response rates or survival times.

The overall response rate of our study was 20 % in Group B (WEEKLY 5FU) which is comparable with a study done by Miller et al using single agent 5FU, and showed overall response rate of 21% and median overall survival of 10 months.

A retrospective review of 392 patients with gastric cancer treated with 5-FU before 1974 demonstrated an overall response rate of 21%.[17] More recent randomized trials of 5-FU used as a single agent have demonstrated a nearly identical response rate of 20%.[18-21]

In our study, the quality of life of the patient and compliance for chemotherapy was also good in weekly 5 FU.

## Conclusion

Three weekly Cisplatin and 5-Flurouracil could be a good regimen in advanced gastric cancer with better response rate and it is useful when the performance status of the patient is good. Weekly 5-Flurouracil gives good quality of life and this regimen can be considered when the patient is not eligible for Cisplatin and 5-Flurouracil regimen in advanced gastric cancers.

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