Outcome of Chemotherapeutic Regimens Cisplatin and 5-Fluorouracil vs Weekly 5-Fluorouracil in Advanced Gastric Cancer

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ABSTRACT

Introduction: Gastric cancer is the second leading cause of cancer death worldwide, with a 5-year survival rate of less than 20%. About 25% of patients with gastric cancer present with disseminated disease and more than half of those with apparently localized disease recur within 5 years. Study aimed to evaluate the response rate, median PFS, overall survival and toxicity to 3 Weekly Cisplatin/5-Fluorouracil Vs Weekly 5-Fluorouracil in patients with advanced gastric cancer.

Material and Methods: Patients were recruited for chemotherapy with Cisplatin 75mg/mg^2 in divided doses and 5-Fluorouracil 750mg/m^2 for 3 days in every 21 days for 6 cycles in one arm and 20 patients for treatment with Weekly 5- Fluorouracil 500mg for 16 weeks. Within two months of completion of chemotherapy, CT abdomen was done to compare with the baseline CT abdomen to assess the response rate using RESIST criteria Version V1.1. Also the improvement in ECOG PS was ascertained as an endpoint.

Results: In the Cisplatin /5FU arm had an overall response rate of 20%, median PFS of 6 months,45% had a partial response (PR), 10% had stable disease (SD) 25% had progression (PD), 20% achieved CR and more of haematological and non-hematological toxicity. In the 5FU arm, 35% had stable disease (SD),40% had progression (PD) 5% achieved CR and less of haematological and non-hematological toxicity.

Conclusion: In advanced gastric cancer, Cisplatin /5FU had more response rate, more median PFS and more toxicity. Weekly 5FU is better tolerable regimen with

Keywords: Advanced Gastric Cancer, CISPLATIN/5FU, Weekly 5FU, Response Rate, Toxicity

INTRODUCTION

Adenocarcinoma of the stomach was the leading cause of cancer-related death worldwide through most of the 20th century. It now ranks second only to lung cancer and an estimated 8,70,000 new cases are diagnosed annually and second on 6,50,00 deaths (10% of all cancer deaths) worldwide.[1]

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. The explanations are multifactorial, lack of defined risk factors, specific symptoms and the low incidence has contributed to the late stage at diagnosis seen in most centers.[2]

These tumours are biologically more aggressive and heterogeneous. Even after what is believed to be a curative gastrectomy disease tend to recur in the majority of patients. Efforts to improve these poor results have focused on developing effective pre-and postoperative systemic, regional and palliative therapies. Universally palliative chemotherapy is the main modality of treatment. A low-cost, well-tolerated, and easy to access strategy is an attractive therapeutic option in resource-limited countries.[3] The most extensively studied single agent drugs are 5-FLUOROURACIL (5-FU), DOXORUBICIN, MITOMYCIN C (MMC) and CISPLATIN. 5-FLUOROURACIL is the most extensively studied single agent in patients with advanced gastric cancer. An overall response rate of 21% and a median survival of 10 months has been achieved in a few studies. Compared with best supportive care, a consistent survival benefit (3–9 months) of combination chemotherapy has been demonstrated in advanced gastric cancer. It is supposed that the combination of CISPLATIN plus 5-FLUOROURACIL (FP) is synergic or has at least additive antitumor activity.[4] Hematological toxic effects were mild, nausea and vomiting were common and a cumulative nephro and neurotoxicity represented the dose-limiting toxicity of this regimen.[5] This study is to evaluate the response rate, median progression-free survival and adverse effect profile of palliative chemotherapy with and CISPLATIN/5-FLUOROURACIL every 21 days for 6 cycles vs. WEEKLY 5-FLUOROURACIL 5FU in patients with advanced (stage III/IV) stomach cancer.

Study aimed to evaluate the response rate to 3 Weekly CISPLATIN/5-FLUOROURACIL vs WEEKLY 5-FLUOROURACIL in patients with advanced gastric cancer.

MATERIAL AND METHODS

This prospective study was conducted in the Department of Medical Oncology at Madras Medical College. All patients with advanced (stage III/IV) / gastric cancer attending Medical Oncology OP were evaluated clinically and with radiologically on the initial visit. Their baseline blood counts

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and biochemical parameters assessed before randomizing them to receive palliative chemotherapy. The patients were studied from September 2015 to March 2016. In one arm 20 patients were recruited for chemotherapy with CISPLATIN 75mg/mg^2 in divided doses and 5-FLUOROURACIL 750mg/m^2 for 3 days in every 21 days for 6 cycles. All patients in this arm were given appropriate antiemetic premedication and adequate hydration. In another arm 20 patients were recruited for treatment with WEEKLY 5-FLUOROURACIL 500 mg for 16 weeks. All patients were treated as inpatients only. Patients evaluated clinically for symptom control, response rate and toxicity profile at 2,4,6 months after starting iv chemotherapy. Blood counts, renal and hepatic function tests, and documentation of adverse effects to chemotherapy done once in 21 days. Within two months of completion of chemotherapy, CT abdomen was done to compare with the baseline CT abdomen to assess the response rate using RESIST criteria Version V1.1. Also the improvement in ECOG PS was ascertained as an endpoint.

Inclusion Criteria

1. Both Male and Female gender
2. Age > 20y <70 years
3. Stage III/IV gastric cancer.
4. Performance status 2 - 3

Exclusion Criteria

1. Stage I/II gastric cancer
2. Age < 20 years or > 70 years
3. Performance status 0,1 and 4
4. Patients with severe co-morbidity (Cardiac, Renal, Hepatic disease)

Assessments of Parameters

1. Blood counts, Renal function tests, liver function tests at baseline before starting chemotherapy.
2. Blood counts, Renal function tests, liver function tests are done once in 21 days.
3. Response to treatment assessed clinically at 2,4,6 months and with imaging whenever necessary.
4. Toxicity of chemotherapy is graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events(CTCAE), Version 4.03
5. CT abdomen was done after completion of treatment.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS Software (Version 16). Chi-square test and Pearson chi-square test used to establish the significance of response on the outcome.

RESULTS

Results were analyzed after the stipulated study period of 6 months. The response rate and toxicity profile were compared between the two arms. The response rate was assessed by comparing baseline CT abdomen with post-treatment CT abdomen within two months of completion of treatment. The toxicity in both the arms was assessed using Common Terminology Criteria for Adverse Events (CTCAE Version 4.0). Nausea and vomiting were higher

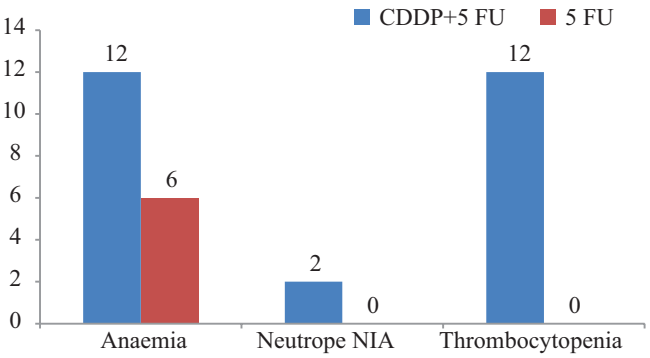

Figure-1: Haematological toxicity

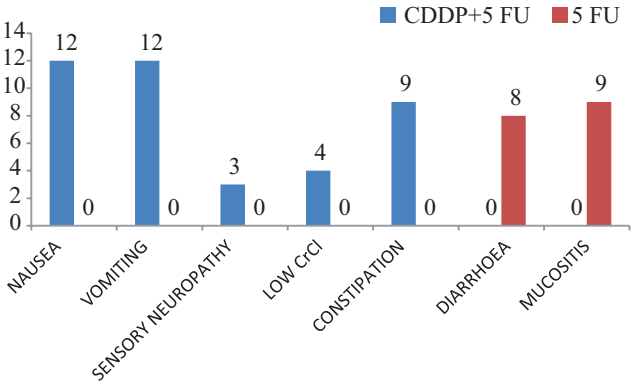

Figure-2: Non Haematological Toxicity

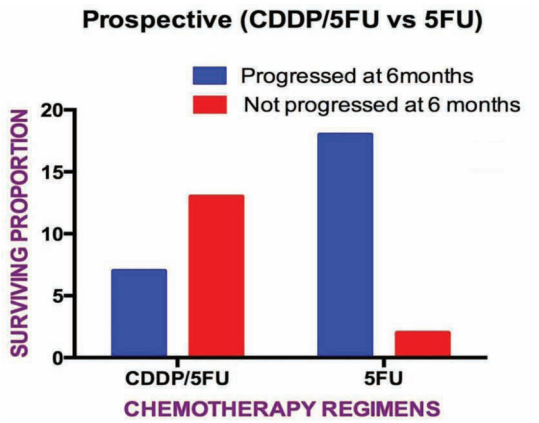

Figure-3: Progression

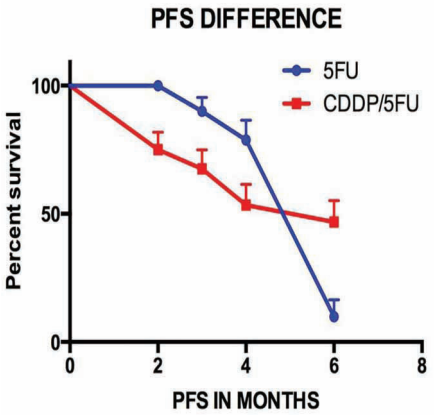

Figure-4: Survival curves

in CISPLATIN/5FU arm. 12 patients (60%) had grade I/II vomiting with a significant P value (0.001) compared to none

(0%) in the WEEKLY 5FU arm. Only in CISPLATIN/5FU arm, 3 patients (15%) developed Grade I/II sensory neuropathy. Decreased creatinine clearance was observed during the course of chemotherapy in 4 patients (20%) in CISPLATIN/5FU arm with significant P value (0.035) compared to the WEEKLY 5FU arm. 9 patients (45%) developed constipation in CISPLATIN/5FU arm which was not encountered in WEEKLY 5FU arm with significant P value (0.001). Diarrhoea was rather higher in the WEEKLY 5FU arm which was seen in 8 patients (40%) with a significant P value (0.002) compared to the WEEKLY 5FU arm. A total of 9 patients (45%) developed mucositis in WEEKLY 5FU arm with a significant P value (0.001). 12 patients (60%) developed anaemia in CISPLATIN/5FU arm and 30% in WEEKLY 5FU arm with a P value of 0.057. Only 2(10%) patients in CISPLATIN/5FU arm had Grade I/II neutropenia whilst none had neutropenia in the WEEKLY 5FU arm. A total of 12 (60%) patients in CISPLATIN/5FU developed Grade I/II thrombocytopenia with a significant p-value (0.001). The number of patients who had progressed at the end of 6 months in CISPLATIN/5FU arm was 13patients (65%) whereas in the WEEKLY 5FU arm, it is 2 patients (10%). The P value (0.001) was significant in this aspect. In WEEKLY 5FU group a total of 9 patients (45%) progressed at the end of two months. The improvement in PS (which indirectly indicates a good response to chemotherapy) was higher in the CISPLATIN/5FU arm. In this group, at the end of 6 months, there were 4 (20%) patients with PS 1 compared to baseline, when there were no PS 1 patients. This signifies a response rate of 20%. 8 (40%) patients are in both stable disease and progressive disease. At the end of 6 months, more patients had progression in the WEEKLY 5FU arm compared to the platinum-containing arm (65% vs 40%). Also, a number of patients who were progression-free at the end of 6 months were higher in the CISPLATIN/5FU arm (60% vs. 35%).

This study had an overall response rate of 20% in the CISPLATIN 5FU arm, with a median progression-free survival of 6 months. The response was assessed at the end of the planned 6 cycles (at least within 2 months after completion). The assessment was done using RESIST V1.1 on all measurable lesions. Totally, 12 (60%) patients had a partial response (PD), 9 (45%) patients had stable disease (SD) in both arms combined. In the CISPLATIN arm, 9 (45%) had a partial response (PR) and 3 (15%) patients in the other arm. In the CISPLATIN/5FU arm, 2(10%) patients had stable disease (SD) and 5 (25%) patients had progression (PD). In the 5FU arm, 7(35%) patients had stable disease (SD) and 8 (40%) patients had progression (PD). CR was achieved in 4(20%) patients in CISPLATIN/5FU arm and 1(5%) patient in the 5FU arm. There was more of haematological and non-haematological toxicity in this arm than the WEEKLY 5FU arm (graph-1). Non-haematological toxicity such as nausea, vomiting, sensory neuropathy, constipation is more than WEEKLY 5FU group (graph-2). Haematological toxicity such as anaemia, neutropenia and thrombocytopenia are more common than WEEKLY 5FU. Few toxicities such as neutropenia-related infections, skin pigmentation and alopecia did not occur in both groups. In WEEKLY 5FU group overall response rate was only 5% with a median progression-free survival of 3 months. Both haematological and non-haematological toxicity is less common in this group than CISPLATIN 5FU group. The toxicity parameters like diarrhoea, mucositis and anaemia were higher in the combination arm.

Kaplan-Meier analysis shows that the survival projections are significantly better for CISPLATIN/5FU chemotherapy (~50%) when compared to WEEKLY 5FU alone (~13%). At the end of the study period, when the surviving proportion of patients were plotted against the two study arms, Cisplatin+5FU chemotherapy has a better PFS although the toxicity profile was inferior (figure- 3,4).

DISCUSSION

The management of advanced gastric malignancy is based upon clinical predicament. In this study, two simple and economically feasible regimens were taken for comparison. 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 overall response rate than monotherapy.[5] In one study reported by Miller et al using single agent 5FU, the overall response rate was 21% and the median overall survival of 10 months was reported. This study showed that 5FU when given as a continuous infusion, was associated with mucositis as dose limiting toxicity (DLT) though the incidence is less.[6] In an attempt to increase the overall response rate with 5FU infusion, Leucovorin was added as an adjunct. It was reported by Hsu et al.[7] and Lin et al.[8] that on adding Leucovorin with continuous infusion, the response rate increased from 33% to 44%. But there is no randomized trial to prove this observation. The combination of 5FU and Leucovorin is one of the standard of care in the past for advanced gastric cancer, whose PS was unsuitable for combination regimens. Capecitabine (oral analogue of 5FU) studied as monotherapy in advanced gastric cancer by Koizumi et al.[9] showed ORR of 18.4%. Hand-foot syndrome, anorexia, nausea and diarrhoea were the most common adverse events. Thus, Capecitabine seems to be safe and effective in patients with advanced gastric carcinoma. Few other single agent drugs had shown moderate response rate. But due to the toxicity profile, they are not considered as the standard of care in advanced gastric cancer and the available data is limited to phase-2 studies only. Some of these agents include single agents include CISPLATIN by Lacave et al.[10] (ORR 18%), PACLITAXEL by Cascinu et al.[11] (ORR 17-23%), DOCETAXEL by Guilani et al.[12] (ORR 17-29%). Combination chemotherapy was initially tried in patients with good PS and younger patients with stage IV disease. In Kim et ala combination chemotherapy comparing FP (CISPLATIN 5FU) vs 5FU vs FAM (5FU ADRIAMYCIN MTX) in advanced gastric cancer. A total of 324patients 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%. Duration of response was not statistically significant. Despite the differences in response rate and time to progression, there was no statistical difference between treatment groups in overall survival (36.9 weeks for FP, 29.3 weeks for FAM, 30.6 weeks for FU). Nausea, vomiting, diarrhoea, stomatitis, alopecia, and skin pigmentation were common non-hematologic side effects. Significantly higher frequencies of anemia and neutropenia were observed in patients receiving FP or FAM therapy, but these were mild and tolerable. Alopecia was observed more frequently in the FAM arm.[13] Nausea, vomiting and peripheral neuropathy were observed more frequently in the FP arm (nausea and vomiting, $P < 0.01$; neuropathy, $P < 0.05$;). The North Central Cancer Therapy Group reported results of a randomized trial in which the original FAM regimen was compared to 5-FU plus doxorubicin (FA) and with 5-FU alone. No survival advantage was demonstrated for FAM or FA compared to 5-FU alone in this study. Beer et al.[14] and Lacave et al.[10] used cisplatin as a single agent for previously treated gastric cancer patients and reported overall response rates of 22%. Because it rarely causes bone marrow suppression, cisplatin is an ideal agent to test in combination with the myelosuppressive agent. Schabel et al.[15] reported the synergistic effects of 5-FU and cisplatin in the L1210 leukemia model.

CONCLUSION

In advanced gastric cancer, CISPLATIN/5FU had an approximate response rate of 20% while the response rate in the 5FU arm was 5%. The median PFS in CISPLATIN/5FU arm was 6 months and in the WEEKLY 5FU arm it was 3 months. Both haematological and non-hematological toxicity is more in CISPLAIN/5FU arm than in the WEEKLY 5FU arm. Patients who cannot tolerate toxic combination chemotherapy can be treated with WEEKLY 5FU as monotherapy which has comparably less toxicity.

REFERENCES

1. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol. 2006;12:354-62.
2. Donkor P, Boateng KA. Prevalence of orofacial squamous cell carcinoma seen at Komfo Anokye Teaching Hospital. Ghana Med J. 2000;34:139–143.
3. Aurello P, Petrucciani N, Antolino L, Giulitti D, D'Angelo F, Ramacciato G. Follow-up after curative resection for gastric cancer: Is it time to tailor it?. World J Gastroenterol. 2017;23:3379-3387.
4. Cascinu S, Baldelli AM, Catalano V, et al. Infusional 5-fluorouracil, cisplatin and mitomycin C in advanced gastric cancer: a low cost effective regimen. Br J Cancer. 2002;86:213-7.
5. Wöhrer S, Raderer M, Hejna M. Palliative chemotherapy for advanced gastric cancer. Annals of Oncology. 2004;15:1585-1595.
6. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–214.
7. Hsu CH, Yeh KH, Chen LT et al. Weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of advanced gastric cancers. An effective and low-toxic regimen for patients with poor general condition. Oncology 1997; 54: 275–280.
8. Lin YC, Liu HE, Wang CH et al. Clinical benefit and response in patients with gastric cancer to Weekly 24-hour infusion of high-dose 5-fluorouracil (5-FU) and leucovorin (LV). Anticancer Res 1999; 19: 5615–5620.
9. Koizumi W, Saigenji K, Ujiie S et al. A pilot phase II study of capecitabine in advanced or recurrent gastric cancer. Oncology 2003; 64: 232–236.
10. Lacave AJ, Baron FJ, Anton LM et al. Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer: a phase II trial. Ann Oncol 1991; 2: 751–754.
11. Cascinu S, Graziano F, Cardarelli N et al. Phase II study of paclitaxel in pretreated advanced gastric cancer. Anticancer Drugs 1998; 9: 307–310.
12. Giuliani F, DeVita F, Gebbia V, Maiello E et al. Docetaxel as salvage chemotherapy in advanced gastric cancer patients. A phase II study of the Southern Italy Oncology Group (GOIM). Eur J Cancer 1999; 35: 577.
13. Williams K, Cheng G, Pusic I, Jagasia M, Burns L, Ho V et al. Fluticasone, Azithromycin, and Montelukast Treatment for New-Onset Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation. 2016;22:710-716.
14. Beer M, Cocconi G, Ceci G. A phase II study of cisplatin in advanced gastric cancer. Eur J Cancer Clin Oncol. 1983;19:717–720.
15. Schabel FM Jr, Trader MW, Laster WR Jr, et al. Cis-dichlorodiammineplatinum (II): Combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 1979; 63: 1459–1473.

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