

# Retrospective study of oxaliplatin, leucovorin and 5 fluorouracil regimen in patients with advanced gastric cancer with poor performance status: A study at a tertiary center of South India

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## Abstract

**Background:** Gastric carcinoma is the leading cause of cancer in south India. Gastric cancer is frequently diagnosed in locally advanced or metastatic setting in Indian scenario and has a poor survival. There is no standard chemotherapy regimen which can be used in advanced gastric cancer (AGC) patients.

**Objective:** The aim of this study was to assess the clinical activity and toxicity of oxaliplatin with infusional 5-fluorouracil and leucovorin administered every 3 weeks in patients with locally advanced and inoperable gastric cancer. **Patients and Methods:** In this retrospective study, the case records of 25 patients who have received OLF regimen were analyzed. **Results:** The median number of cycles for patients was 6 (range: 4–12 cycles). Overall response rate was 36%, with all patients having stable disease. Median survival of patients was 6 months (7 months in locally advanced). Compared to other regimens, there was less toxicity (less hematologic toxicity, less nausea and vomiting, no hair loss, no renal toxicity, no hand foot syndrome, and lesser admissions).

**Conclusions:** OLF regimen is an acceptable regimen in poor performance status AGC patients with adequate response and an acceptable toxicity profile.

**Key words:** Gastric cancer, India, OLF regimen

## Introduction

Gastric carcinoma is the second most common cause of cancer-related mortality.<sup>[1]</sup> Gastric cancer is the leading cause of cancer in South India, probably due to high consumption of rice, chili, and high-temperature food.<sup>[2]</sup> Gastric cancer is frequently diagnosed in or locally advanced or metastatic stage where the 5-year survival is only about 6% in the Indian scenario.<sup>[3]</sup> Advanced gastric cancer (AGC) remains incurable with a median survival of 6–9 months.<sup>[4]</sup> As majority of patients present at later stages with poor performance status, effective chemotherapy regimen with minimal side effects is the need of the hour.

## Rationale of study

There is no worldwide accepted standard chemotherapy regimen in AGC. In AGC, the therapeutic decision is usually between a strict supportive care and exposing patients to side effects of potential ineffective therapy. Chemotherapy has demonstrated to result in both a significant survival advantage and an improved quality of life when compared to best supportive care.<sup>[5,6]</sup> We selected OLF regimen which has lesser toxicity, can be given in poor performance status, and can be administered in patients with gastric obstruction. Both 5-fluorouracil (5FU) and oxaliplatin do not cause hair loss, can be used in inlet/outlet obstruction, and both do not cause significant febrile neutropenia. The dose of oxaliplatin used was 130 mg/m<sup>2</sup> as per the REAL-2 study.<sup>[7]</sup> The 3 weekly dose of 5-FU was derived from the ML17032 trial, the original trial used only 5FU 800 mg/m<sup>2</sup> on days 1–5 every 21 days. 5FU can be bio-modulated with leucovorin (LV); however, the most effective dosage of LV has not been determined. We biomodulated 5FU by adding LV 50 mg/m<sup>2</sup> and reducing the duration of 5FU to 3 days. The final regimen being oxaliplatin 130 mg/m<sup>2</sup> on day 1 over 2 h, LV 50 mg/m<sup>2</sup> daily by 2 h infusion on day 1–3, and 5FU 1000 mg/m<sup>2</sup> daily by continuous infusion on day 1–3 every 21 days.

The aim of this study was to assess the clinical activity and toxicity of oxaliplatin with infusional 5-FU and leucovorin administered every 3 weeks in patients with locally advanced and inoperable gastric cancer. We also evaluated the progression-free survival and toxicity profile of this regimen.

## Patients and Methods

This retrospective study was done at the department of oncology, Yenepoya Medical College Mangalore. Data of cases of advanced gastric adenocarcinoma on OLF regimen during a period of 2 years from February 2015 to February 2017 were collected from the medical case records. Histologically confirmed cases of advanced gastric adenocarcinoma on OLF regimen, over the age of 18 years of either gender, were included in the study. The WHO performance status was used, and patients with performance status of 2 or more were considered for the study. A semi-structured pro forma was used to collect information from the medical case records. Records were checked for any evidence of toxicity and response to the treatment regimen. Chemotherapy regimen: oxaliplatin (130 mg/m<sup>2</sup> on day 1) as a 2 h infusion in 1 unit 5% dextrose followed IV infusion of LV 50 mg/m<sup>2</sup> in 100 mL normal saline over 2 h from day 1 to 3 and 5-FU IV (5FU 1000 mg/m<sup>2</sup> daily by continuous infusion on day 1–3). Cycles were repeated at 3-week intervals till tumor progression.

## Statistical analysis

Data were entered in Microsoft Office Excel worksheet and analyzed using statistical software SPSS version 17.0 (SPSS Inc., USA). For qualitative data, Chi-square test was used and  $P < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

Twenty-five cases were eligible for this study after satisfying the inclusion and exclusion criteria. Twenty-five patients

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received 180 cycles of 3 weekly regimen with a median of six cycles (range: 3–12 cycles) per patient. The patient characteristics are shown in Table 1. Median age was 64 years (range: 30–79 years). Majority of the study population were males (18 out of 25). The predominant site of metastasis was the liver. Fifteen (60%) patients did not have ascites at presentation. One patient has human epidermal growth factor receptor 2 overexpression. The characteristics are summarized in Table 1.

**Survival**

The median progression-free survival for patients was 6 months (7 months in locally advanced), while the projected 1-year progression-free survival rate was 9% ±4.7% [Figure 1]. Progression-free survival was 3 months in patients with peritoneal involvement. No difference was found between body mass index (BMI) and outcome. Three patients with locally advanced cancer, who progressed on OLF regimen were given weekly paclitaxel. Celiac plexus block was done in five patients without ascites for pain relief. Four patients underwent gastrojejunostomy with gastric outlet obstruction.

**Toxicities**

The median number of cycles for patients was 6 (range: 3–12 cycles). The most common toxicities were nonhematologic. Six patients developed neurotoxicity (Grade: 1–2 in 5 patients and Grade 3–4 in one patient). Two patients discontinued treatment, one due to severe diarrhea and other due to neurotoxicity. No treatment-related death was reported.

**Discussion**

This study assessed the clinical efficacy and toxicity of OLF regimen in patients with AGC and poor performance

status. Although gastric cancer is considered a relatively chemosensitive tumor with an overall response rate ranging between 30% and 60%, survival of AGC patients remains unsatisfactory, with a median survival time of only 6–9 months.<sup>[4]</sup> Therefore, effective treatment approaches with minimal toxicity profiles are needed, especially in patients with poor general condition.

Listed below are some of the common regimens in gastric cancer and their problems we face in routine clinical practice:

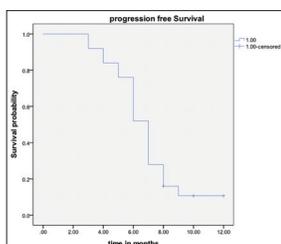
1. Capecitabine plus oxaliplatin (CAPOX) is an established regimen in stomach cancer (CLASSIC trial).<sup>[8]</sup> But problems with CAPOX are:
  - a. Patients with advanced gastric carcinoma may not able to swallow capecitabine tablets as they have vomiting, due to inlet/outlet obstruction
  - b. Capecitabine produces severe hand-foot syndrome in up to 50% of patients, hence quality of life is affected
  - c. Not many tolerate the full dose of capecitabine 1250 mg/m<sup>2</sup> (2500 mg/m<sup>2</sup> daily) and dose reductions or interruptions are needed in 33% of patients.<sup>[9]</sup> These problems are not seen with OLF regimen.
2. Discounted Cash Flow (DCF) is also an established regimen in gastric cancer (V-325 study).<sup>[10]</sup> But the problems with DCF are:
  - a. Myelotoxicity with Grade 3 and Grade 4 neutropenia in 82% of patients. This is detrimental in poor performance status patients
  - b. Nausea, vomiting, and renal toxicity due to cisplatin is a frequent problem
  - c. Hair loss.

These problems are not seen with OLF regimen, needing lesser admission, and better tolerability
3. FOLFOX is also an established regimen in gastric cancer.<sup>[11,12]</sup> But the problems with FOLFOX are:
  - a. It's a 2 weekly regimen, difficult to administer as frequent visits, and hospitalizations are needed
  - b. Less frequent admission in OLF regimen is advantageous in elderly, in poor socioeconomic strata, and in patients who come from the remote area. Less frequent admission also reduces the burden on health service providers
4. Extracellular fluid (ECF) is also an established regimen in gastric cancer based on a Phase III study.<sup>[13]</sup> But the problems with ECF are:
  - a. It is a continuous infusion regimen of 5 FU, 200 mg/m<sup>2</sup> daily for 21 days. The main disadvantage of this regimen is that an indwelling venous catheter is required to deliver the infusional 5FU and this is associated with infection and thromboembolism risk
  - b. Myelotoxicity with Grade 3 and Grade 4 neutropenia seen in 42% of patients
  - c. Cardiotoxicity seen in 2.1% of patients
  - d. Hair loss
  - e. Epirubicin can cause serious extravasation
  - f. Nausea, vomiting (Grade 2–4 in 50%), and renal toxicity (all Grades 7%) due to cisplatin.<sup>[14]</sup> These problems are not seen with OLF regimen, needing lesser admission, and better tolerability.
5. Paclitaxel with carboplatin is also an effective regimen in gastric cancer.<sup>[15]</sup> But the problems with this regimen are:

**Table 1: Patient characteristics**

Variable	Number of patients (n=25), n (%)
Sex	
Male	18 (72)
Female	7 (28)
Age (years)	
Median	64
Range	30–79
Locally advanced inoperable	7
Site of metastasis (some had multiple sites)	
Liver	13
Ascites (including peritoneal carcinomatosis)	7
Ovary (Krukenberg tumor)	1
Response rate	
CR	0
Stable disease	9 (36)
HER2 over-expression	1 (4)

CR=Complete response



**Figure 1: Progression-free survival in advanced gastric cancer with poor performance**

- a. Grade III and IV neutropenia seen in 33% of patients
  - b. Grade III peripheral neuropathy is seen in 7% of patients
  - c. Hair loss is also a common problem with this regimen.
6. Cisplatin with 5FU is also an effective regimen in gastric cancer. But the problems with this regimen are:
- a. Nearly double the incidence of Grade 3 and 4 neutropenia, alopecia, thromboembolism, and renal dysfunction compared to oxaliplatin 5FU doublet.<sup>[7,16]</sup>
7. Irinotecan with 5FU is also an effective regimen in gastric cancer. But the problems with this regimen are:
- a. Diarrhea with irinotecan is seen in up to 22% of patients<sup>[17]</sup>
  - b. Hair loss
  - c. Grade III and IV neutropenia is seen in 25% of patients on weekly irinotecan regimen.

A combination of 5-FU and platinum compounds is commonly used as first-line treatment in AGC and has a response rate of 30%–50%. Similar response rate is seen when any of the above-mentioned drug combination is used.<sup>[18]</sup> The response rate in our regimen was 36%, with all patients having stable disease. No patient had a complete response. Median survival of patients was 6 months (7 months in locally advanced). Survival was 3 months in patients with peritoneal carcinomatosis. This is lower than other studies done worldwide where the survival ranged from 8 to 11.2 months.<sup>[18]</sup> The lower survival in our study was probably due to the poor performance status in most of our patients. Poor survival was seen in patients with peritoneal carcinomatosis and Stage IV disease at presentation. No difference was found between BMI and outcome.

In most of the trials with oxaliplatin-based therapies, neurotoxicity was the most frequent side effect that led to treatment discontinuation. The incidence of this chronic event is around 30%, occurring commonly in female, diabetic patients with the prolonged use of oxaliplatin.<sup>[19]</sup> Only one patient in our study discontinued the treatment due to this adverse effect.

HER2 overexpression is seen in 4%–8% of Indian patients with gastric cancer.<sup>[20]</sup> One patient (4%) had HER2 overexpression, but he could not afford trastuzumab.

None of the current regimens can be considered as an optimal therapy for AGC and new therapeutic strategies are needed to achieve a better clinical efficacy with an acceptable toxicity profile. Our regimen (OLF) has significant effects as a chemotherapeutic regimen for AGC patients because of encouraging response and mild toxicities.

### Conclusions

The results of our study suggest that OLF regimen has activity and acceptable toxicity in patients with AGC with poor performance status and merits further studies.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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