

# Modified 5-fluorouracil/leucovorin/irinotecan as a feasible and efficacious second-line chemotherapeutic regimen in advanced gastric cancers

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## Abstract

**Background:** Modified 5-fluorouracil/leucovorin/irinotecan (mFOLFIRI) is a commonly used combination second-line chemotherapeutic regimen in advanced gastric cancer (AGC). **Materials and Methods:** Patients diagnosed with AGC, receiving biweekly mFOLFIRI between July 2013 and June 2016, as second-line chemotherapy were retrospectively analyzed for tolerance, prognostic factors, event-free survival (EFS), and overall survival (OS). **Results:** Overall, 91 patients were administered a median of 6 cycles of therapy. Response rate was 29.7% and clinical benefit rate was 57.2%. With a median follow-up of 11.5 months, median EFS was 3.98 months (95% confidence interval [CI]: 2.54–5.41) and median OS was 7.73 months (95% CI: 5.30–10.15). Common Grade 3 and Grade 4 adverse events were neutropenia (18.7%), febrile neutropenia (9.9%), thrombocytopenia (7.7%), and vomiting (4.4%). Nearly 33% of patients required dose modification during therapy. **Conclusions:** mFOLFIRI regimen as a second-line therapy in AGCs appears feasible and efficacious in clinical practice.

**Key words:** Advanced gastric cancers, modified 5-fluorouracil/leucovorin/irinotecan, second-line chemotherapy

## Introduction

The median survival of advanced gastric cancers (AGC) is approximately 8–13 months with first-line chemotherapy (CT1).<sup>[1–3]</sup> Once the disease progresses after first-line therapy, the median overall survival (mOS) is  $\leq 4$  months without any anticancer treatment. Postprogression on CT1, there exists evidence for second-line chemotherapy (CT2) improving survival over best supportive care (BSC). Second-line therapy, with approved chemotherapeutic agents and recently ramucirumab, has demonstrated survival benefit as opposed to BSC in Phase III trials, with a meta-analysis confirming the same. Monotherapy with either docetaxel, irinotecan, or paclitaxel versus BSC has been shown to improve the survival significantly with a mOS in the range between 5.2 and 9.6 months, but none of these agents are superior to each other as per the survival or toxicity profiles are concerned.<sup>[4–8]</sup>

The doublet therapy with irinotecan + cisplatin versus irinotecan alone in BIRIP study showed a significant improvement in progression-free survival with no difference in toxicity profile as a CT2 in AGC.<sup>[9]</sup> The RAINBOW study had shown a survival benefit for paclitaxel–ramucirumab combination over paclitaxel alone and also had increased rates of Grade 3/4 toxicity in the combination arm.<sup>[10]</sup>

The 5-fluorouracil/leucovorin/irinotecan (FOLFIRI)/modified FOLFIRI (mFOLFIRI) regimens have been commonly used in AGC, both as first-line and second-line therapies with an acceptable adverse event rate.<sup>[11–13]</sup> The FOLFIRI regimen is an appropriate doublet to be considered since it has shown equivalent efficacy to a triplet combination as CT1 (vs. Epirubicin Cisplatin Capecitabine (ECX), although this was not the primary endpoint of this study) as well as comprising drugs that are active in AGC.<sup>[14]</sup>

In this retrospective analysis, we present one of the largest single-institution experiences with the mFOLFIRI regimen as second-line therapy in AGC. To the best of our knowledge, this is also the first study from India with regard to second-line palliative chemotherapy in AGC.

## Materials and Methods

The study is a retrospective analysis of metastatic gastric cancer patients who were offered palliative CT2 with FOLFIRI regimen during the period of July 2013–June 2016 in the Department of Gastrointestinal Medical Oncology, Tata Memorial Hospital, Mumbai. The study for evaluation of CT2 with mFOLFIRI was part of an Institutional Review Board and Ethics Committee (IEC/0417/1847/001) approved project. Patients satisfying all the following criteria were included in the analysis:

1. Histologically proven gastric cancer
2. Definitive evidence of metastatic disease, either by scans or a staging laparotomy
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2
4. Previously received one line of chemotherapy, either in the adjuvant setting or as CT1 in the metastatic setting
5. Did not receive FOLFIRI as CT1.

All patients were assessed and optimized by nutrition clinic department. The doses and schedule used for mFOLFIRI (biweekly) were as follows:

- 5-Fluorouracil – 2400 mg/m<sup>2</sup> intravenous (IV) infusion over 48 h
- Leucovorin – 350 mg IV flat dose
- Irinotecan – 180 mg/m<sup>2</sup> IV on D1.

Toxicity assessment was done at every patient visit and recorded as per National Cancer Institute common Terminology Criteria for Adverse Events version 4.0. Dose modifications were made as per clinician assessment. Response to treatment was evaluated clinically on every visit and with contrast-enhanced computed tomography scan after 4–6 cycles of chemotherapy or earlier as per physician decision. Responses were calculated by RECIST criteria,<sup>[15]</sup> with responses reported as complete response (CR), partial response (PR), stable disease (SD), and progressive disease

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(PD), where feasible. If RECIST was not calculable, then the response was quantified based on collusion between treating physician and the gastrointestinal (GI) radiologist as follows: CR – disappearance of all baseline lesions; PR – significant regression of lesions at baseline; SD – no significant regression of baseline lesions and no new lesions; and PD – appearance of new lesions or significant increase in baseline lesions. Patients who had clinical progression of disease (e.g., progressive ascites and dysphagia) before evaluation with scans are reported separately as clinical PD. Response rates (RRs) and clinical benefit rate were reported as percentages.

Prognostic factors evaluated included ECOG PS (0/1 vs. 2), presence versus absence of liver/peritoneal metastases, grades of differentiation, signet ring morphology (presence vs. absence), and previous history of curative resection (presence vs. absence).

Primary endpoints of the study were estimation of median event-free survival (mEFS) and mOS. EFS was calculated from date of beginning CT2 to date of clinical and/or radiological progression, cessation of chemotherapy due to adverse events, loss to follow-up, withdrawal from therapy, or death (in case of no documented progression). OS was calculated from date of beginning CT2 to date of death.

#### Clinical data collection and statistics

For the purposes of this study, demographic data and baseline clinical data were collected retrospectively from GI medical oncology information system and electronic medical record system. All data were entered in IBM SPSS software version 21.0. and used for analysis. Descriptive statistics including median, frequency, and percentage for categorical variables were used to describe age, gender distribution, treatment, and response to treatment. mEFS and mOS were calculated using Kaplan–Meier method while log-rank test was used for univariate comparisons.

#### Results

A total of 91 patients were available for analysis in this study. Baseline characteristics are enumerated in Table 1. The patients received docetaxel-oxaliplatin-capecitabine (40 patients), epirubicin-oxaliplatin-capecitabine (24 patients), capecitabine-oxaliplatin (9 patients), docetaxel monotherapy (5 patients), docetaxel-carboplatin (6 patients), paclitaxel-carboplatin (4 patients), paclitaxel-cisplatin (1 patient), and docetaxel-cisplatin-5 fluorouracil (2 patients) as CT1, respectively. Details of administration of mFOLFIRI and adverse events are as per Table 2.

A median number of 6 cycles of mFOLFIRI was administered to patients. Reasons for upfront and from second cycle onward dose modifications are listed in Table 2.

#### Response rates and outcomes

About 70.3% of patients (64/91) had response assessment scans for quantification of response, while 13.2% of patients (12/91) had clinically progressed before performance of a scan [Table 3]. At a median follow-up of 11.5 months, the mEFS [Figure 1] was 3.98 months (95% confidence interval [CI]: 2.54–5.41). At cutoff date for follow-up, 74 patients had died (81.3%), while 11 patients (12.09%) were alive and on further treatment including BSC. The mOS [Figure 2] was 7.73 months (95% CI: 5.30–10.15).

**Table 1: Baseline demographic and clinical characteristics**

| Characteristic                              | n (%)      |
|---------------------------------------------|------------|
| Median age (years; range)                   | 56 (26-78) |
| Gender                                      |            |
| Female                                      | 31 (34.1)  |
| Male                                        | 60 (65.9)  |
| Prior treatment history                     |            |
| Curative resection                          | 18 (19.8)  |
| Curative intent radiotherapy                | 3 (3.3)    |
| Comorbidities                               |            |
| Hypertension                                | 16 (17.6)  |
| Diabetes mellitus                           | 15 (16.5)  |
| Coronary artery disease                     | 3 (3.3)    |
| Histology (differentiation)                 |            |
| Well differentiated                         | 10 (11)    |
| Moderately differentiated                   | 8 (8.8)    |
| Poorly differentiated                       | 40 (44)    |
| Adenocarcinoma, not otherwise specified     | 33 (36.2)  |
| Histology (signet ring morphology)          |            |
| Signet ring morphology                      | 33 (36.3)  |
| Nonsignet ring morphology                   | 58 (63.7)  |
| ECOG PS                                     |            |
| 0, 1                                        | 61 (67)    |
| 2                                           | 30 (33)    |
| Sites of disease                            |            |
| Omentum                                     | 63 (69.2)  |
| Nonregional nodes                           | 34 (37.4)  |
| Liver                                       | 30 (33)    |
| Lungs                                       | 14 (15.4)  |
| Osseous                                     | 10 (11)    |
| Others (including brain and ovarian masses) | 10 (11)    |

ECOG PS=Eastern Cooperative Oncology Group performance status

**Table 2: Dose modifications and adverse events(Grade 3 and Grade 4)**

| Characteristic                               | n (%)      |
|----------------------------------------------|------------|
| Dose modification                            | 30 (33)    |
| During 1 <sup>st</sup> cycle of chemotherapy | 21 (23.07) |
| Reasons for initial dose reduction (n=21)    |            |
| ECOG PS 2                                    | 10 (47.6)  |
| Albumin (<3 g%)                              | 5 (23.8)   |
| Combination of above factors                 | 2 (9.5)    |
| Not available                                | 4 (19)     |
| During later cycles of chemotherapy          | 9 (9.9)    |
| Reasons for dose reductions                  |            |
| Febrile neutropenia                          | 7 (7.7)    |
| Grade 3/4 neutropenia                        | 6 (6.6)    |
| Grade 3/4 diarrhea                           | 2 (2.2)    |
| Multiple adverse events                      | 3 (3.3)    |
| Adverse events                               |            |
| Febrile neutropenia                          | 9 (9.9)    |
| Neutropenia                                  | 17 (18.7)  |
| Thrombocytopenia                             | 7 (7.7)    |
| Vomiting                                     | 4 (4.4)    |
| Diarrhea                                     | 3 (3.3)    |
| Peripheral neuropathy                        | 2 (2.2)    |
| Fatigue                                      | 3 (3.3)    |
| Reasons for delay (>1 week) in chemotherapy  | 17 (18.7)  |
| Adverse events                               | 12 (13.2)  |
| Patient-related logistic reasons             | 5 (5.5)    |

ECOG PS=Eastern Cooperative Oncology Group performance status

**Prognostic factors**

None of the prognostic factors had a statistically significant correlation with EFS or OS.

**Discussion**

Our study reports outcomes with using mFOLFIRI as CT2 in AGC. The baseline demographics of patients in this study are comparable to those seen in other studies. Nearly 33% of patients required dose modifications, with a majority being started on lower doses, as per clinician choice. The major reasons were the presence of an ECOG PS 2 and a lower baseline albumin (<3 g%) before starting therapy. A low baseline albumin level predicting for greater toxicities with chemotherapy is a much-debated question, and the upfront dose modifications in this study are reflective of the same.<sup>[16,17]</sup>

**Table 3: Response rates and outcomes with second-line chemotherapy**

| Characteristics                             | n (percentage where applicable) |
|---------------------------------------------|---------------------------------|
| <b>Response rates</b>                       |                                 |
| Complete response                           | 1 (1.1)                         |
| Partial response                            | 26 (28.6)                       |
| Stable disease                              | 25 (27.5)                       |
| Progressive disease                         | 12 (13.2)                       |
| Response rates                              | 27 (29.7)                       |
| Clinical benefit rate                       | 52 (57.2)                       |
| Clinical progression                        | 12 (13.2)                       |
| Not available                               | 10 (10.9)                       |
| Loss to follow-up                           | 5 (5.5)                         |
| <b>Reasons for cessation of CT2 (event)</b> |                                 |
| Clinical progression                        | 12 (13.2)                       |
| Radiological progression                    | 54 (59.3)                       |
| Adverse events                              | 16 (17.6)                       |
| Loss to follow-up                           | 5 (5.5)                         |
| Death (without documented progression)      | 2 (2.2)                         |
| Patient choice                              | 1 (1.1)                         |
| <b>Outcomes</b>                             |                                 |
| Median EFS (months)                         | 3.98 (95% CI: 2.54-5.41)        |
| Median OS (months)                          | 7.73 (95% CI: 5.30-10.15)       |
| Received third-line chemotherapy            | 23 (25.3)                       |

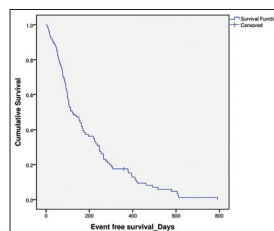
CT2=Second-line chemotherapy, EFS=Event-free survival, OS=Overall survival, CI=Confidence interval

A majority of the Grade 3 and Grade 4 nonhematological side effects seen in our study were comparable to published literature, but a higher incidence of febrile neutropenia (9.9%) and thrombocytopenia than previously quoted was seen.

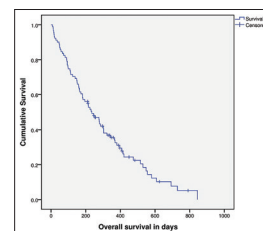
With the RRs (29.7%) and survival outcomes (mEFS – 3.98 months and mOS – 7.73 months) with the mFOLFIRI regimen, marginally superior to published data from other studies with mFOLFIRI [Table 4], our study does show that mFOLFIRI is feasible even in a real-world nontrial.<sup>[18,19]</sup>

When the “benefit versus adverse event” question is discussed, there also looms the aspect of financial considerations. A recent cost-effective analysis of second-line therapy in AGCs, published by the Cleveland Clinic, assessed 6 modalities of second-line treatment (irinotecan, docetaxel, paclitaxel, ramucirumab, paclitaxel plus ramucirumab, and palliative care). They suggested that single-agent irinotecan was the most cost-effective of the evaluated therapies, based on a comparison between incremental cost-effectiveness ratios and a prespecified willingness-to-pay threshold of US\$50000/quality-adjusted life year) gained. The paclitaxel–ramucirumab combination was not considered cost-effective. FOLFIRI or mFOLFIRI was not considered in this analysis.<sup>[20]</sup> Factoring in mFOLFIRI for consideration as CT2 in AGC is a moot point, considering the relatively low additional cost of 5-fluorouracil.

There are multiple caveats in this study. This study had a lost to follow-up rate of 5.5%, there was no evidence of radiological progression in 13.2% of patients, and we had no records of Grade 1 and Grade 2 adverse events. The study also had no quality of life data, which is an important component of measuring outcomes in the palliative setting. The incidence of



**Figure 1: Event-free survival of whole cohort**



**Figure 2: Overall survival of whole cohort**

**Table 4: Comparison of studies using fluorouracil/leucovorin/irinotecan as second-line chemotherapy in advanced gastric cancers**

| Characteristic           | Sym et al. | Maugeri-Sacca et al. | Sym et al. | Kim et al. | Assersohn et al. | TMH        |
|--------------------------|------------|----------------------|------------|------------|------------------|------------|
| Number of patients       | 131        | 70                   | 30/59      | 36         | 40               | 91         |
| Type of study            | R          | R                    | Phase II   | R          | Phase II         | R          |
| ECOG PS                  |            |                      |            |            |                  |            |
| 0/1                      | 77.9       | 71.5                 | 90         | 55.6       | 68.5             | 67         |
| ≥2                       | 22.1       | 28.5                 | 10         | 44.4       | 31.6             | 33         |
| RR (%)                   | 12.3       | 22.8                 | 20         | 10         | 29               | 29.7       |
| Grade 3/4 toxicities (%) |            |                      |            |            |                  |            |
| Febrile neutropenia      | 5.6        | 04                   | 03         | 2.3        | 5.2              | 9.9        |
| Neutropenia              | 54.4       | 28.5                 | 37         | 17.6       | 26.4             | 18.7       |
| Thrombocytopenia         | 1.6        | 03                   | 0          | 0          | -                | 7.7        |
| Diarrhea                 | 6.4        | 14.4                 | 07         | 0          | 7.9              | 4.4        |
| Vomiting                 | 7.2        | 06                   | 0          | 2.8        | 13.2             | 3.3        |
| Median PFS               | 2.2 (TTP)  | 3.8                  | 3.0        | 3.3        | 3.7              | 3.98 (EFS) |
| Median OS                | 6.2        | 6.2                  | 6.7        | 10.9       | 6.4              | 7.73       |

ECOG PS=Eastern Cooperative Oncology Group performance status, PFS=Progression-free survival, EFS=Event-free survival, OS=Overall survival, RR=Response rates, TMH=Tata Memorial Hospital, R=Retrospective, TTP=Time to progression

upfront dose modifications (23.07%) is also high although we have attempted to evaluate reasons of the same.

## Conclusions

mFOLFIRI regimen as a second-line chemotherapeutic regimen in AGCs appears feasible and efficacious in clinical practice.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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