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# Combination of docetaxel and irinotecan as a second-line treatment of metastatic gastric cancer: a phase II study

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## ABSTRACT

**Introduction.** Gastric cancer is one of the aggressive malignancies that negatively impact the performance status of patients and cause a high incidence of cachexia. Docetaxel and irinotecan have confirmed efficacy in the second-line treatment of metastatic patients. However, most patients are not fit enough for third-line options. So, we tested the combination of these two drugs in second-line treatment to give patients the maximum benefit as a "last resort" treatment option.

**Material and methods.** Prospective analysis of metastatic gastric cancer patients was done in the second-line treatment. Patients received a combination of docetaxel and irinotecan. To assess response, we used RECIST version 1.1; toxicity was assessed with CTCAE version 5.0, quality of life was assessed by the QLQ-C30 model, and survival analysis was done by the Kaplan-Meier curves.

**Results.** A total of 32 patients were eligible for statistical analysis. The mean age at diagnosis was 56 years. The clinical control rate was 21.8%, of which 12.5% of patients had a partial response and 9.3% had stationary disease. The most common toxicity was neutropenia (18.8%) despite the routine use of prophylactic filgrastim. The median overall survival was 14 months; of which, 9 months represented median progression-free survival 1 (PFS1) and 12.5 months for progression-free survival 2 (PFS2). Reduction in tumor markers CEA and CA19-9 were predictive factors of survival ($p = 0.004$ and 0.028 respectively). Quality of life was negatively impacted both in responders and non-responders.

**Conclusions.** The combination of docetaxel and irinotecan is a valid choice for second-line treatment of gastric cancer, especially when carefully selecting suitable patients. This regimen serves as a "last resort" for individuals whose subsequent treatment options primarily involve best supportive care. The study is especially important for countries that do not have access to the recently approved immunotherapy options in this setting.

**Keywords:** Gastric cancer, second line, chemotherapy, docetaxel, irinotecan

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## Introduction

Over the past decades, Western Europe and the United States have experienced a notable decrease in the incidence of gastric cancer [1]. Despite this, gastric cancer remains a significant global health issue, particularly in East Asian countries [2]. In 2020, there were over 1 million cases worldwide, resulting in more than 786,000 deaths, making gastric cancer the fifth most commonly diagnosed cancer and the third leading cause of cancer-related mortality globally [3].

Gastric cancer (GC) is a complex disease influenced by both genetic predisposition and environmental factors [4]. Genetic factors contribute to a small percentage of GC cases (approximately 3–5%). Among the genetic alterations linked to familial GC (defined as having

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more than two relatives affected across two generations), microsatellite instability and mutations in the E-cadherin encoding gene (CDH1) are the most common [5].

Systemic therapy can provide palliation of symptoms, increased survival, and improved quality of life in patients with metastatic gastric cancer [6]. First-line systemic therapy regimens with two cytotoxic drugs rather than three are preferred because of their low toxicity. Oxaliplatin is preferred over cisplatin due to its better tolerability [7].

Novel agents have been introduced in the management of gastric cancer. For patients with HER2 overexpression-positive adenocarcinoma, it is recommended to include trastuzumab in the first-line chemotherapy regimen. The preferred combination involves a fluoropyrimidine and a platinum-based agent [8]. Pembrolizumab has also been recently approved for metastatic gastric cancer [9]. For HER2-negative tumors with PD-L1 expression levels (combined positive score $\geq 5$), the preferred treatment regimens include nivolumab in combination with a fluoropyrimidine (such as fluorouracil or capecitabine) and oxaliplatin [10].

Extensive clinical trials have investigated irinotecan-based regimens as a first-line treatment for patients with metastatic gastroesophageal cancers. A randomized phase III study compared the efficacy of irinotecan and fluorouracil (FOLFIRI) with cisplatin and fluorouracil (CF) in patients with advanced gastric adenocarcinoma. The study found that FOLFIRI was non-inferior to CF in terms of progression-free survival (PFS), but did not show superiority in overall survival (OS) or time to progression [11]. FOLFIRI also showed a more favorable safety profile. In a phase III trial (French Intergroup Study), FOLFIRI was compared to ECF (epirubicin, cisplatin, and fluorouracil) as a first-line treatment for patients with advanced or metastatic gastric adenocarcinoma. With a median follow-up of 31 months, the median time to treatment failure was significantly longer for FOLFIRI compared to ECF (5.1 months *vs.* 4.2 months; $p = 0.008$) [12].

The selection of regimens for second-line or subsequent therapy is dependent upon prior therapy and performance status. Ramucirumab in combination with paclitaxel (preferred) or as a single agent are category 1 recommendations for second-line or subsequent therapy [13].

Single-agent docetaxel, paclitaxel, and irinotecan are preferred second-line options as well as subsequent therapy [14]. In the randomized phase III COUGAR-02 trial, single-agent docetaxel significantly improved 12-month OS compared to active symptom control alone, with median OS of 5.2 months versus 3.6 months, respectively [15].

As regards the poor performance status of most patients after failure of the second line, this trial was designed to combine the most active agents in the second line to achieve a better response, before the general condition of the patients deteriorated. This approach might be especially relevant in low/middle-income countries where access to ramucirumab and immune checkpoint inhibitors is not easy.

## Material and methods

This study was a prospective phase II clinical trial that included 32 patients with metastatic gastric cancer diagnosed between January 2021 and July 2022. Follow-up was continued until March 2023 as this date included survival follow-up of all patients till death.

Before being enrolled in the trial, all patients gave their informed consent. The researchers adhered to the Declaration of Helsinki throughout this trial.

### Inclusion criteria

Patients with histopathological evidence of adenocarcinoma of the stomach were recruited if they had metastatic disease with a prior single line of treatment in the metastatic setting and with performance of no more than 2 as per ECOG.

### Exclusion criteria

Patients who received docetaxel or irinotecan before recruitment to this study were excluded. Other exclusion criteria were: Multiple comorbid conditions, Liver or kidney impairment, and severe cachexia.

### Baseline assessment

All patients had baseline full history and clinical examination, complete blood count (CBC), liver function tests (LFT), and kidney function tests (KFT). The disease burden was assessed by contrast-enhanced CT of the chest, abdomen and pelvis, and bone window. Bone scans were limited to patients with bone tenderness, high alkaline phosphatase, or bone lesions evident on CT scans.

### Treatment scheduling

In line with the study protocol, treatment was administered every 2 weeks as follows

— premedication with pantoprazole 40 mg + granisetron 3 mg + dexamethasone 8 mg given as short infusions;
— docetaxel at 30 mg/m$^2$ over 500 cc normal saline over 1-hour infusion;
— irinotecan at 185 mg/m$^2$ with a maximum of 300 mg given over 500 cc normal saline over 2-hour infusion.

The regimen was used until disease progression or a maximum of 6 months. Filgrastim 300 mg was administered for two days after each dose of chemotherapy starting after 24–48 hours.

### Evaluation

Patients were evaluated clinically on each visit, and toxicity was reported as per CTCAE version 5.0. CT scans with comparison were performed every 2–3 months, and the response was described as per RECIST criteria version 1.1. Quality of life questionnaire (QLQ-C30) was conducted at the beginning of the first cycle of chemotherapy and the end of treatment.

### Statistical analysis

Data were tabulated and analyzed using SPSS software version 20. The primary endpoint was the response rate and secondary endpoints included toxicity, quality of life, and survival (PFS and OS). The sample size was calculated at 80% power and considered significant if the p-value was 0.05 or less. The response rate of interest was 20%. Survival analysis was done with the Kaplan-Meier curve.

## Results

Over 18 months, we recruited 59 patients, but only 32 of them were eligible. Most non-eligible patients were excluded due to poor performance status and/or severe cachexia. This study included 20 male patients, who represented 62.5% of the tested patients. The mean age at diagnosis was 56 years. A minority of patients had an ECOG performance status of 2 (28%) while the majority had either the performance status of 0 (34%) or 1 (37.5%). The liver was the most common site of metastasis (56.3%), followed by the lungs (46.9%). Metastasis in two organs was more commonly observed (59.4%) than metastasis in a single organ (40.6%). First-line chemotherapy given to the patients was either the XELOX regimen (53%) or the FOLFOX regimen (47%). None of the studied patients had HER2 overexpression (Tab. 1).

In terms of toxicity (Tab. 2), neutropenia was the most frequently observed grade III toxicity occurring in 18.8% of patients. Other grade III toxicities were rare and did not exceed 10%. Low-grade toxicity was generally well tolerated by the patients and easily managed, not resulting in delayed chemotherapy cycles.

**Table 1. Patient characteristics**

| Total number = 32 | 100% |
|---|---|
| Sex | |
| Males | 20 (62.5%) |
| Females | 12 (37.5%) |
| Age | |
| Mean ± SD | 56.6 ± 5.5 |
| Performance status | |
| ECOG 0 | 11 (34.3%) |
| ECOG 1 | 12 (37.5%) |
| ECOG 2 | 9 (28.1%) |
| Comorbidities | |
| None | 25 (78.1%) |
| DM | 3 (9.3%) |
| HTN | 4 (12.5%) |
| Site of metastasis | |
| Liver | 18 (56.3%) |
| Lung | 15 (46.9%) |
| Bone | 8 (25%) |
| Peritoneum | 10 (31.3%) |
| Number of metastatic sites | |
| Single organ | 13 (40.6%) |
| Two organs | 19 (59.4%) |
| More than two | 0 (0%) |
| First line | |
| XELOX | 17 (53.1%) |
| FOLFOX | 15 (46.9%) |

DM — diabetes mellitus; ECOG — Eastern Cooperative Oncology Group; FOLFOX — folinic acid, fluorouracil, and oxaliplatin; HTN — hypertension; SD — standard deviation; XELOX — capecitabine plus oxaliplatin

**Table 2. Toxicity profile**

| Toxicity | Low grade (0–2) | High grade (3, 4) |
|---|---|---|
| Neutropenia | 26 (81.3) | 6 (18.8) |
| Anemia | 31 (96.9) | 1 (3.1) |
| Thrombocytopenia | 30 (93.6) | 2 (6.3) |
| Diarrhea | 29 (90.6) | 3 (9.3) |
| Vomiting | 29 (90.6) | 3 (9.3) |
| Oral mucositis | 31 (96.9) | 1 (3.1) |
| Peripheral neuropathy | 32 (100) | 0 (0) |

**Table 3. Response outcomes**

| First line | | Second line | |
|---|---|---|---|
| CR | 0 (0) | CR | 0 (0) |
| PR | 17 (53.1) | PR | 4 (12.5) |
| SD | 2 (6.3) | SD | 3 (9.3) |
| DP | 15 (46.9) | DP | 25 (78.1) |

CR — complete response; DP — disease progression; PR — partial response; SD — stationary disease

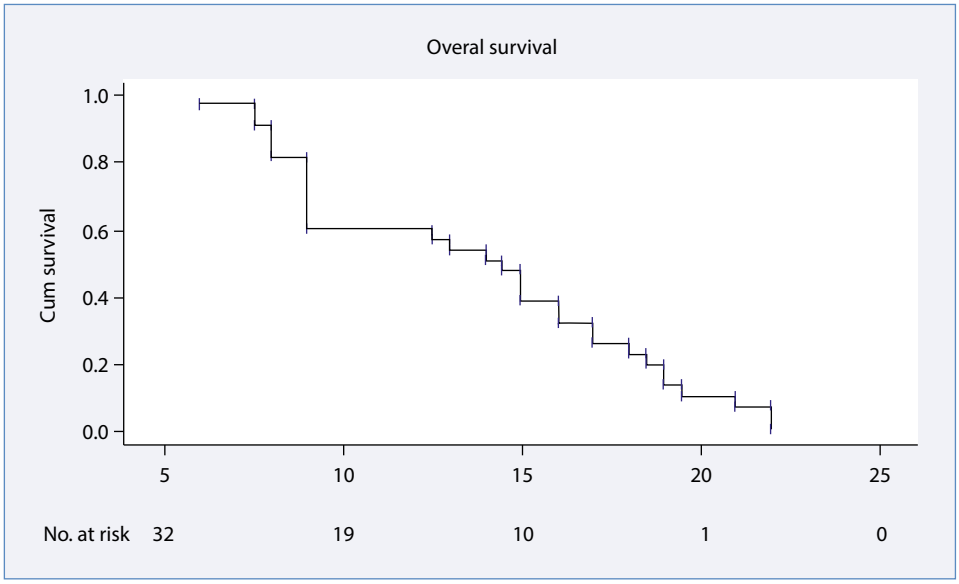


**Figure 1.** Kaplan Meier curve for overall survival (OS)

Complete remission was not observed neither in the first-line nor second-line settings. In the first-line setting, 53% of patients had a partial response and 6% had stationary disease (clinical control rate = 59.4%). These patients were not enrolled in the study until they had disease progression later on after follow-up. In the second line setting, only 12.5% had a partial response, and 9.3% had stationary disease (clinical control rate = 21.8%). The response was not a surrogate marker of survival in this study, an observation that could be due to the small sample size for survival prediction (Tab. 1).

Regarding survival analysis (Fig. 1), the median duration of follow-up was 15 months, and the two-year survival rate was 0%. The median overall survival was 14 months; median progression-free survival 1 (PFS1), calculated from the date of diagnosis till the date of progression, was 9 months. Progression-free survival 2 (PFS2) was calculated from the date of diagnosis till the date of the second relapse, with a median of 12.5 months.

Regression analysis was done to check if there were correlations between changes in body mass index and survival (Tab. 4), but they were negative (p = 0.881).

**Table 4. Median survival and regression analysis**

| | |
|---|---|
| Median Duration of follow-up | 15 months |
| Median (range) of overall survival | 14 (11.7–16.3) |
| Median (range) of PFS 2 | 12.5 (9.7–15.2) |
| Median (range) of PFS 1 | 9 (5.9–12) |
| Predictors of survival according to regression analysis<br>• change in BMI → p = 0.881<br>• change in CEA levels→ p = 0.004<br>• change in CA19-9 levels → p = 0.028 | |

BMI — body mass index; CA19-9 — cancer antigen 19-9; CEA — carcinoembryonic antigen; PFS — progression-free survival

On the contrary, changes in CEA and CA19-9 levels had negative correlations with survival (the more they were reduced, the longer the patient lived), with p-values of 0.004 and 0.028, respectively.

Quality of life was estimated using the QLQ-C30 model general questionnaire before and after treatment. Most patients had poor quality of life before starting treatment. They had even worse quality-of-life scores

after second-line treatment. This finding was observed in patients who responded to chemotherapy and also those who had disease progression.

The global health status score was 28.2 for the control arm and 31.3 for the test arm (p = 0.752) before starting treatment. However, it was 16.7 for the control arm and 19.3 for the test arm at the end of treatment (p = 0.649). Likewise, the functional and symptoms scales showed similar findings, with no significant difference between the test arm and the control arm at the end of treatment.

## Discussion

In this study, we hypothesized that using a combination of the most active chemotherapeutics (irinotecan and docetaxel) in the second-line treatment of gastric cancer would increase the response rate. In the usual clinical situation, only one of these two agents is used (either alone or in a combination regimen e.g. FOLFIRI), and the chance to treat patients with the other agent is lost as most of the patients have a very poor performance status in the third-line setting. The study met its primary endpoint with an overall response rate of 21.8%.

A meta-analysis by Kim et al. [16] demonstrated the efficacy of docetaxel in the second-line treatment of gastric cancer as well as irinotecan in the same setting when compared to best supportive care. At a hazard ratio of 0.64, these two agents resulted in an improvement in overall survival with no superiority of one over the other [16].

Moreover, Lee et al. [17] demonstrated the efficacy of docetaxel in the third-line setting after progression using m-FOLFOX or mFOLFIRI. That/our study showed partial response in 15% and stable disease in 27% of patients with median overall survival of 4.7 months and median PFS of 2.1 months [17]. Similarly, FOLFIRI was found to be effective in first line and subsequent lines as well [18].

A recent retrospective analysis by Yildirim et al. [19] compared FOLFIRI, platinum-based chemotherapy, and taxane-based chemotherapy in the second-line treatment of gastric cancer. Overall survival did not significantly differ among the three groups. The FOLFIRI group (n = 79) had median overall survival of 5 months, the platinum-based group (n = 55) had median overall survival of 6.5 months, and the taxane-based group (n = 40) had median overall survival of 5.6 months (p = 0.554). Similarly, there was no significant difference in progression-free survival among the groups, which was around 3 months [19].

The recruitment of patients was a difficult and long process. This is because gastric adenocarcinoma is a highly debilitating disease that results in rapid loss of weight and worsening performance status, rendering many patients not fit for chemotherapy [20]. Yet, the age distribution in this study was similar to the internationally published data with a median age at diagnosis of 56 years and a trend towards male predominance [21]. The liver was the most common organ of metastatic disease (56.3%) in this study. So, special emphasis on adequate liver functions should be addressed before using this treatment regimen because both irinotecan and docetaxel are metabolized by the liver and excreted mainly in biliary secretions [22, 23].

In terms of tolerability, the regimen was generally well tolerated by most of the patients. Neutropenia was in the range of 18.8% for grade III while other toxicities were lower than 10%. Filgrastim was used as routine prophylaxis for all patients. A similar regimen was tested by Burtness et al. [24] in esophageal cancer but with weekly administration (days 1 and 8). They observed neutropenia in the range of 47% for previously treated patients and diarrhea in the range of 27% [24].

Median overall survival in our study was 14 months. The reduction rate of tumor markers CEA and CA19-9 was found to correlate with survival. Greater reduction in their levels was a surrogate marker of better survival regardless of their baseline value. Although a deterioration in body mass index (BMI) was observed, it did not have an independent effect on survival. PFS1 was 9 months which denotes the greatest benefit of treatment. Second-line treatment had a much smaller share in overall survival as PFS2 was 12.5 months, an extra 3.5 months only gained thanks to the second-line treatment.

In terms of advances in developing combination regimens, the RAINBOW study demonstrated that the addition of ramucirumab to weekly paclitaxel treatment significantly extended survival. The overall survival was 9.6 months in the paclitaxel-ramucirumab arm compared to 7.4 months in the paclitaxel arm. Similarly, progression-free survival was longer in the paclitaxel-ramucirumab arm (4.4 months) than in the paclitaxel arm (2.9 months) [25]. Although our study showed higher numbers than these, it was not designed to detect overall survival benefit. It is noteworthy to report that the OS analysis in the RAINBOW study was calculated from the date of randomization, rather than the date of diagnosis, which may account for the discrepancies observed in our data. Moreover, the genetic and ethnic composition of patients in our study were different from those of the RAINBOW study which may have resulted in altered response to ramucirumab. Neutropenia was in the range of 41% in the RAINBOW study which is much higher than the 18.8% observed in our study [25]. This is another observation that may suggest different responses to ramucirumab based on ethnic groups. Another advancement in oncology is immune checkpoint inhibitors. Pembrolizumab did not show superiority in terms of

survival when compared to paclitaxel in the second-line setting as per the KEYNOTE-061 trial. Median overall survival was in the range of 9 months [26].

The combination that was tested in our trial was previously investigated in a similar study by Park et al. [27] The authors found that the combination of docetaxel and irinotecan resulted in a 45.7% response rate and median overall survival of 8.2 months. Neutropenia was observed in 57% of patients, but this can be explained by excluding granulocyte colony-stimulating factors from their trial. They had a 27.1% one-year survival rate compared to a 0% two-year survival rate in our study [27]. Another study by Sym et al. [28] tested the same combination. They had an ORR of 20.4% and median overall survival of about 9 months. In terms of the toxicity profile, their regimen showed febrile neutropenia in almost half of patients. However, they used higher doses than those tested in our trial [28].

Quality of life was measured using the QLQ-C30 questionnaire. Both responding and non-responding patients experienced worsening QoL. Overall health, emotional and cognitive functions were assessed at baseline, end of treatment, or progression. On the contrary, a study by Park et al. [29] showed an improvement in QoL in gastric cancer patients receiving second-line chemotherapy while in the RAINBOW study, worsening of QoL was observed only in patients experiencing disease progression [30]. These contradictory results might reflect the differences in patient reporting in the QLQ-C30 model and the lack of an accurate tool to measure QoL globally.

## Conclusions

Docetaxel and irinotecan combination is a good choice for second-line treatment of gastric cancer provided that patients are properly selected. It represents the "last resort" regimen for many patients whose next line of treatment is mostly best supportive care. This regimen is considered a good treatment option for patients who do not have access to recently approved immunotherapy. Filgrastim and dose reductions should be considered for patients experiencing significant toxicity to avoid worsening QoL. A phase III study is needed to better outline the benefit in terms of overall survival.

## Article Information and Declarations

### Data availability statement

Raw data are available upon reasonable request.

### Ethics statement

The study was approved by the ethical committee of Menoufia University, Faculty of medicine with IRB number 5-2021ONCO.7-2. All patients sharing in this study signed an informed consent. The study commits to the declaration of Helsinki.

### Author contributions

All authors shared in recruitment and treatment of patients, collection of data and writing of the manuscript. Statistical analysis was conducted by a third party statistical consultation office and charges were paid by the authors.

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None.

### Conflict of interest

All authors declare no conflict of interest.

### Supplementary material

None.

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