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***Retrospective Study***

**Safety and efficacy of a docetaxel-5-FU-oxaliplatin regimen with or without trastuzumab in neoadjuvant treatment of localized gastric or gastro-oesophageal junction cancer: a retrospective study**

Basso V *et al*. Docetaxel-5FU-oxaliplatin regimen in neoadjuvant treatment of gastric cancer

**Valeria Basso, David Orry, Jean Fraisse, Julie Vincent, Audrey Hennequin, Leila Bengrine, Francois Ghiringhelli**

**Valeria Basso, David Orry, Jean Fraisse,** Department of Surgery, Centre Georges Francois Leclerc, Dijon 21000, France

**Julie Vincent, Audrey Hennequin, Leila Bengrine, Francois Ghiringhelli,** Department of Medical Oncology, Centre Georges Francois Leclerc, Dijon 21000, France

**ORCID number:** Valeria Basso (0000-0001-5007-5316); David Orry (0000-0001-9627-1478); Jean Fraisse (0000-0003-4228-8631); Julie Vincent ([0000-0002-4544-5033](https://orcid.org/0000-0002-4544-5033)); Audrey Hennequin (0000-0001-8043-1836); Leila Bengrine ([0000-0002-0762-7303](https://orcid.org/0000-0002-0762-7303)); Francois Ghiringhelli ([0000-0002-5465-8305](https://orcid.org/0000-0002-5465-8305)).

**Author contributions:** Basso V collected the clinical data; Orry D and Ghiringhelli F designed the study; Orry D, Fraisse J, Vincent J, Hennequin A and Ghiringhelli F treated patients included in this study; Ghiringhelli F analysed the data; Ghiringhelli F and Basso V wrote the manuscript; All authors have read and approve the final manuscript.

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**Corresponding author:** **François Ghiringhelli, MD, Professor,** Department of Medical Oncology, Centre George François Leclerc, 1 Rue du Professeur Marion, Dijon 21000, France. fghiringhelli@cgfl.fr

**Telephone:** +33-380-732424

**Fax:** +33-380-737500

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**Abstract**

***Background***

Triplet chemotherapy with a 5-FU-leucovorine-oxaliplatin-docetaxel (commonly referred to as FLOT) regimen recently became the standard perioperative treatment for localized gastric cancer (GC). An adapted regimen called TeFOX was recently tested in a metastatic setting and gave promising results.

***Aim***

To determine the safety and efficacy of the TeFOX perioperative regimen.

***Methods***

This monocentric retrospective study aims to test the efficacy and safety of the perioperative TeFOX regimen given alone or in combination with trastuzumab in patients with localized GC. TeFOX consists of docetaxel (50 mg/m²) with oxaliplatin (85 mg/m²) and leucovorin (400 mg/m2) with a 5-FU bolus (400 mg/m2) on d 1, followed by continuous infusion of 5-FU for 46 h (2400 mg/m2) every 2 wk.

***Results***

Thirty-three consecutive patients were included in this retrospective study. Eighteen patients had gastro-oesophageal junction cancer and 11 had GC. The median follow-up of surviving patients was 32 mo. R0 resection was obtained in 30 (91) patients. Twelve patients (36) had a pathological complete response and eight (24) patients had a nearly complete pathological response. Median overall survival and progression-free survival were not reached by the time of database lock. We observed six metastatic relapses and one localized relapse. No relapse was observed in patients with pathological complete responses. The most common grade 3-4 adverse events were peripheral neuropathy (21) and asthenia (20).

***Conclusion***

The TeFOX regimen can be safely administrated as perioperative treatment of localized GC. TeFOX and the FLOT regimen have comparable efficacy and safety profiles.

**Key words:** gastric cancer; neoadjuvant chemotherapy; TeFOX; retrospective study

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**Core tip:** Triplet chemotherapy with docetaxel-5FU-oxaliplatin FLOT regimen recently became the standard perioperative treatment for localized gastric cancer. An adapted regimen called TeFOX was recently tested in a metastatic setting and gave promising results. We provide evidence based on our experience of the safety and efficacy of this regimen in patients treated in the neoadjuvant setting.

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**Introduction**

Gastric cancer (GC) is a major health problem worldwide. In 2018, 783,000 patients died of GC, making it the third leading cause of cancer death[1].Upon metastatic disease, the prognosis is poor, with less than 2 years of median survival, even with new chemotherapeutic approaches. Prognosis is better in localized tumours, and surgery can cure about 90% of T1 N0 tumours[1]. For more advanced tumours, the prognosis remains poor. Standard of care involves perioperative treatment. With such treatment, the 5-year relapse-free survival reaches 30%-40%. For a long time, based on MAGIC trial and FFCD 9703 phase 3 study, the standard treatment was fluoropyrimidine plus platin with or without epirubicin[2,3]. Such therapies improve the 5-year relapse-free survival rate of around 20% with surgery only to around 35% with perioperative chemotherapy.

Recently, a new combination of platin and taxane improved outcome in patients with metastatic disease. In addition, usage of trastuzumab demonstrated its efficacy as a first line treatment of metastatic GC with HER2-overexpressing tumour[4]. Such HER2-overexpressing tumours represents around 20% of GCs[5]. A German cooperative group developed a taxane-based chemotherapy protocol called FLOT, which was tested in perioperative setting. Such therapy gave better response rates than platin-based chemotherapies and improved relapse-free survival[6,7]. In France, an alternative protocol called TeFOX using 5-FU in a 46 h continuous infusion at the dose of 2400 mg/m2,instead of 24 h continuous infusion at the dose of 2600 mg/m2 asin the FLOT regimen, was developed for metastatic disease. TeFOX is safe and gave impressive response rates in first line metastatic disease[8]. In a retrospective study, this regimen resulted in a disease control rate of 87.6%. Median progression-free survival (PFS) and overall survival (OS) observed in this study were 9.7 mo and 14.3 mo, respectively. In addition, 40% of metastatic patients underwent secondary resection. The toxicity of the TeFOX regimen is modest with less haematological toxicity than observed with the FLOT regimen[8].

Based on these results, neoadjuvant therapy of GC was modified in our centre, and patients received TeFOX or TeFOX with trastuzumab if they had a HER2-overexpressing tumour. Our objective is to describe the safety and the efficacy of this protocol.

**MATERIALS AND METHODS**

***Patients***

All consecutive patients treated for histologically confirmed, previously untreated, non-metastatic, operable adenocarcinoma of the stomach or gastro-oesophageal junction between May 15, 2013 and August 29, 2018 in Centre Georges Francois Leclerc were included. Follow-up ended in December 2018.

Eligibility criteria for inclusion in the study were: (1) local gastric or gastro-oesophageal junction adenocarcinoma without metastases detected following CT-scan and TEP-scan; (2) the possibility of curative resection as assessed by a digestive surgery multidisciplinary staff; (3) WHO performance status of 0 or 1; and (4) absence of previous cancer therapy. The study was conducted in accordance with the Declaration of Helsinki. All participating patients fully agreed with the use of their medical records in clinical research. The study was performed in agreement with the General Data Protection Regulation European law.

***Treatment***

Treatment consisted of an intravenous injection of TeFOX regimen with or without trastuzumab for patients with HER2-overexpressing tumours. TeFOX consisted of docetaxel (50 mg/m2), oxaliplatin (85 mg/m2), and leucovorin (400 mg/m2) plus a 5-FU bolus (400 mg/m2) on d 1, followed by continuous infusion of 5-FU for 46 h (2400 mg/m2) administered every 2 wk. Trastuzumab was given at 4 mg/kg every 2 wk. Prophylactic treatments included corticosteroids and antiemetics given accordingly to standard recommendations. The haematopoietic factor G-CSF was systematically given as a prophylactic treatment in all patients (Filgrastin 34 MUI/d during 4 d, starting the day after the end of 5-FU infusion). The number of cycles of chemotherapy expected was six before and after surgery. Dose reductions and treatment discontinuations were performed according to physician decision based on toxicity.

***Safety***

Toxicity was evaluated before each cycle according to the NCI-CTC-AE v5.

***Efficacy***

The efficacy of neoadjuvant chemotherapy was tested using pathological examination. Tumour regression grade was quantified using the Becker classification[9]. This classification gave an estimation of the percentage of vital tumour cells in the tumour core: TRG1a means complete pathological response; TRG1b means subtotal regression with less than 10% of residual tumour cells; TRG2 means partial regression with around to 10% to 50% of viable tumour cells and TRG3 means no or minor regression[10].

***Statistical analysis***

Toxicity and response to neoadjuvant chemotherapy were evaluated in the intent-to-treat population, defined as patients who received at least one cycle of TeFOX with or without trastuzumab. Toxicity of neoadjuvant and adjuvant chemotherapy as well as surgery related toxicities were evaluated. Time to relapse was defined as the time between surgery and the discovery of the first metastatic site. All patients alive without disease relapse at the last follow-up date were censored. OS was defined as the time between the first cycle of chemotherapy and death (all causes). All patients alive at the last follow-up date were censored. Survival curves were estimated using the Kaplan–Meier method. Median follow-up and its 95% confidence interval (CI) were calculated with the reverse Kaplan–Meier method. All statistical analyses were performed using MedCalc Software.

**Results**

***Patient characteristics***

Between May 15, 2013 and August 29, 2018, 33 patients that received at least one cycle of neoadjuvant chemotherapy for a localized GC were enrolled. The median age was 63 years. The majority of patients had a WHO performance status of 0. Pre-treatment patient characteristics are shown in Table 1. Only five patients had signet ring cell carcinoma. Five patients had HER2-overexpressing tumours and received in addition to TeFOX, trastuzumab during neoadjuvant chemotherapy. The median number of neoadjuvant chemotherapy cycles was five (range 2-8). The median number of adjuvant chemotherapy cycles was three (range 0-6). Eleven patients underwent transthoracic oesophagectomy, 11 underwent total gastrectomy and 11 underwent subtotal gastrectomy. Following surgery, only 28 patients received adjuvant chemotherapy (two patients refused further therapy and three had a poor performance status following surgery and were excluded from further therapy). The median number of therapy cycles was four (range 1-7).

***Safety***

There was no treatment-related death. Toxicities of neoadjuvant chemotherapy are described in Table [2](https://www-nature-com.gate2.inist.fr/articles/s41416-018-0133-7%22%20%5Cl%20%22Tab2). Only two patients presented without side effects during neoadjuvant chemotherapy. Ten patients developed grade 3-4 toxicities. The most common grade 3-4 toxicities were asthenia and peripheral neuropathy, which occurred in 19% and 21% of patients, respectively. Febrile neutropenia occurred in one patient (3). Dose reduction occurred in seven patients with elimination of docetaxel in four patients and oxaliplatin dose reduction in three patients. Discontinuation of therapy occurred in six patients due to important side effects. Granulocyte colony-stimulating factor (G-CSF) was prophylactically given to all patients. Perioperative medical or [surgical](https://www-sciencedirect-com.gate2.inist.fr/topics/medicine-and-dentistry/postoperative-complication%22%20%5Co%20%22Learn%20more%20about%20Postoperative%20Complication) grade 3 and 4 complications according to Clavien-Dindo classification within 90 d of surgery were observed in six patients. Death was not observed in the 90 d post-surgery. The most frequent serious adverse events were pneumonia in seven patients (21) and abdominal infection in five patients (15). The incidence of surgical and perioperative complications were higher in the group of patients that underwent esophagectomy, with 5/11 patients (45) with grade 3 or 4 complications versus 1/22 (4) patients that underwent gastrectomy. Nineteen patients had no or a reduced number of adjuvant chemotherapy cycles, eight of whom had undergone esophagectomy. Seventeen patients within the 28 that received adjuvant chemotherapy had grade 3 or 4 side effects (60). Occurrence of adverse effects was the unique cause of adjuvant therapy ending (Table 3).

***Efficacy outcomes***

The median follow-up for surviving patients was 32 mo. Surgical and pathological results are presented in Table 4. R0 resection was obtained in 30 out of 33 patients. R1 resection was only achieved for one esophagectomy and two subtotal gastrectomies. We used Becker regression criteria classification to estimate [tumour regression](https://www-sciencedirect-com.gate2.inist.fr/topics/medicine-and-dentistry/tumor-regression%22%20%5Co%20%22Learn%20more%20about%20Tumor%20Regression) and response rate. We found 12 (36) patients with complete response TRG1a, eight (24) patients with TRG1b, four (13) patients with TRG2 and nine (27) with TRG3. No particular difference was observed between complete and incomplete responders in term of histological type, tumour stage or number of cycles of neoadjuvant chemotherapies. For HER2-overexpressing tumours, complete response (TRG1a) was observed in three out of five patients. Two-year OS and PFS were 90% and 73%, respectively. Median OS and PFS were not reached at database lock (Figures 1 and 2). We observed six metastatic relapses and one localized relapse. No relapses were observed in patients with TRG1A histological response.

**DISCUSSION**

This study underlines the safety and feasibility of TeFOX or TeFOX plus trastuzumab regimen for patients with localized GC. Neoadjuvant therapy is the standard of care for localized GC. Recently, the FLOT4 study demonstrated the superiority of FLOT perioperative regimen in comparison to the ECX regimen[6,7]. In particular, while ECX led to 6% TRG1A complete response, the FLOT4 regimen increased the rate to 16% of TRG1 (95%CI: 10%-23%). These results are comparable with previous studies like the OEO5[11] and ST03 trials[12], which showed a TRG1a rate of 7% and 8%, respectively. In most clinical trials testing combination of chemotherapies with taxane, the proportion of patients with complete pathological response are similar to the ones obtained with the FLOT regimen, with complete responses ranging from 14% to 20%[13,14]. In our study, we observed 36% of TRG1a (95%CI: 19%-62%). Such data compares favourably to previous trials and suggests that the TeFOX regimen might be at least as efficient as other taxane-based regimens. Importantly, the relapse rate is low, at 21% (95%CI: 8%-43%), with a median follow up of more than 2 years. In the FLOT4 trial, the relapse rates at 2 years were 57% and 47% for ECX and FLOT4 regimen, respectively[6]. Interestingly, no patients with TRG1a had a relapse, suggesting that complete response is a good surrogate to predict absence of recurrence. No clinical variable was associated with complete response or recurrence. Notably, neither signet ring cell presence nor the number of cycles of neoadjuvant chemotherapy were associated with relapse or complete response.

In our study, TeFOX perioperative chemotherapy gives rise to grade 3-4 side effects in 30% of the patients (95%CI: 14%-55%). The main toxicities observed were asthenia and neuropathy. Such results are very similar to the FLOT regimen, which induced 34% grade 3-4 toxicity. In the FLOT4 trial, 52% of patients had grade 3-4 neutropenia, but in our series only 10% was observed. The difference is likely due to the systematic and prophylactic use of G-CSF. Higher rates of neuropathy were observed in our study. This difference may be due to a higher number of chemotherapy cycles. Similarly, surgery morbidity is comparable to the FLOT prospective randomized trial. Not surprisingly, we observed a higher incidence of complications with esophagectomy. Interestingly, adjuvant treatment could not be started in five patients and had to be stopped in 14 patients because of major side effects. The incidence of grade 3-4 side effects reached 60% and required treatment arrest for most patients. Such data suggest a higher toxicity of adjuvant therapy than neoadjuvant therapy.

Limitations of our study include the retrospective and monocentric design and a selection of patients with good performance status. However, we believe that such data support the notion that TeFOX results might be comparable to FLOT regimen results and could be used in the neoadjuvant setting of localized gastric and gastro-oesophageal junction cancer.

In conclusion, our study provides information on the safety and efficacy of the TeFOX regimen in a perioperative setting of localized gastric and gastro-oesophageal junction cancer. These data support further development in phase II clinical trials.

**ARTICLE HIGHLIGHTS**

***Research background***

Localized oeso-gastric cancer (GC) is treated by perioperative chemotherapy and surgery. The use of taxane seems to improve response rate and outcome.

***Research motivation***

Only the efficacy of the German FLOT regimen was previously reported.

***Research objectives***

To determine the efficacy of the French TeFOX regimen.

***Research methods***

This retrospective study aims to test the efficacy and safety of the perioperative TeFOX regimen given alone in patients with localized GC.

***Research results***

Thirty-three consecutive patients were included. The median follow-up of surviving patients was 32 mo. R0 resection was obtained in 30 (91) patients. Twelve patients (36) had a pathological complete response, and eight (24) patients had a nearly complete pathological response.

***Research conclusions***

TeFOX regimen could be safely administrated as perioperative treatment of localized GC.

***Research perspectives***

TeFOX and the FLOT regimen have comparable efficacy and safety profiles and could be considered as alternative regimens.

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Grade E (Poor): 0

**Table 1 Baseline characteristics of included patients\***

|  |  |
| --- | --- |
| Age in yr | 63 (41–80) |
|  | Sex Male | 28 (84) |
|  |  Female | 5 (16) |
|  | WHO performance status |  |
|  |  0 | 20 (60) |
|  |  1 | 13 (40) |
|  | Denutrition > 10% weight loss | 10 (30) |
|  | Localization Gastric | 15 (45) |
|  |  Gastro-oesophageal junction Siewert I | 12 (35) |
|  |  Gastro-oesophageal junction Siewert II | 3 (10) |
|  |  Gastro-oesophageal junction Siewert III | 3 (10) |
|  | Surgery |  |
|  | Lewis Santy | 11 (33) |
|  | Total gastrectomy | 11 (33) |
|  | Subtotal gastrectomy | 11 (33) |
|  | Clinical tumour stage cT3/T4 | 7 (81) |
|  |  cT1/T2 | 5 (18) |
|  |  cTx | 21 (1) |
|  |  cN+ | 22 (77) |
|  |  cN– | 8 (23) |
|  | Histological type Intestinal | 28 (84) |
|  |  Signet ring cells | 5 (16) |
|  |  HER2-overexpressing | 5 (16) |

\**n* = 33. Data are presented as *n* (%).

**Table 2** **Neoadjuvant chemotherapy adverse events**

| **Maximal toxicity**  | **All**  |  | **Grade 3/4**  |
| --- | --- | --- | --- |
| All  | 31 (92) |  | 10 (30) |
| Neutropenia  | 3 (10) |  | 1(3) |
| Febrile neutropenia  | 1 (3) |  | 1 (3) |
| Anaemia  | 2 (6) |  | 0% |
| Thrombocytopenia  | 2 (6) |  | 0% |
| Neurotoxicity  | 21 (63) |  | 7 (21) |
| Nausea  | 7 (21) |  | 0% |
| Asthenia  | 12 (36) |  | 6 (19) |
| Vomiting  | 2 (6) |  | 0% |
| Mucositis  | 4 (12) |  | 2 (6) |
| Diarrhoea  | 12 (36) |  | 3 (10) |
| Allergic reaction  | 1(3) |  | 1 (3) |

**Table 3 Serious adverse events during perioperative time**

|  |  |
| --- | --- |
| Patients\* with at least one grade 3-4 adverse event during perioperative time | 6 (18) |
|  | Medical complication | 7 (21) |
|  | Anastomotic leak | 2 (6) |
|  | Wound healing disorder | 1 (3) |
|  | Pneumonia | 7 (21) |
|  | Pleural complication | 1 (3) |
|  | Sepsis and infection | 5 (15) |
|  | Intestinal occlusion | 2 (6) |
|  | Bleeding | 1 |

\**n* = 33.

**Table 4 Surgical and pathological results of patients\***

|  |  |
| --- | --- |
| Type of surgery Subtotal gastrectomy Total gastrectomy Oesophagectomy | 11 (33)11 (33)11 (33) |
| Resection grade R0 R1 | 30 (90)3 (10) |
| Complete (TRG 1a)[†](https://www-sciencedirect-com.gate2.inist.fr/science/article/pii/S1470204516305319%22%20%5Cl%20%22tbl3fn2) | 12 (36) |
| Subtotal (TRG 1b) | 8 (24) |
| Partial (TRG 2) | 4 (13) |
| Minimal or none (TRG 3) | 9 (27) |
| yN0  | 21 (63) |
| yN1 | 6 (19) |
| yN2 | 6 (19) |

\**n* = 33.



**Figure 1 Time to relapse for all included patients.**



**Figure 2 Overall survival for all included patients.**