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Progress Report

Phase III randomized trial comparing 5-fluorouracil and oxaliplatin with or without docetaxel in first-line advanced gastric cancer chemotherapy (GASTFOX study)

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ABSTRACT

Introduction: In advanced gastric cancer, doublet regimen including platinum salts and fluoropyrimidine is considered as a standard first-line treatment. The addition of docetaxel (75 mg/m^2 q3w) to cisplatin (75 mg/m^2 q3w) and 5-fluorouracil has been shown to improve efficacy. However, this regimen (DCF) was associated with frequent severe toxicities (including more complicated neutropenia), limiting its use in clinical practice. Interesting alternative docetaxel-based regimens have been developed that need to be validated.

Aim: GASTFOX study is a randomized phase III trial comparing FOLFOX alone or with docetaxel at 50 mg/m^2 (TFOX regimen) in first-line treatment for advanced gastric cancer. In both arms, cycle is repeated every 2 weeks until disease progression or unacceptable toxicity.

Materials and methods: Main eligibility criteria: histologically proven locally advanced or metastatic gastric or esogastric junction adenocarcinoma, HER negative status, measurable disease, ECOG performance status 0 or 1, and adequate renal, hepatic and bone marrow functions.

Results: The primary endpoint is radiological/clinical progression-free survival (PFS). A difference of 2 months for the median PFS in favor of TFOX is expected (HR = 0.73) Based on a two-sided α risk of 5% and a power of 90%, 454 events are required to show this difference. Secondary endpoints included overall survival, overall response rate, safety, quality of life and the therapeutic index.

Conclusion: This study is planned to include 506 patients to demonstrate the superiority of TFOX over FOLFOX in first-line advanced gastric cancer treatment (NCT03006432).

1. Rationale and aims

Gastric cancer is the fifth-most-common cancer globally and the third leading cause of cancer deaths [1]. Systemic chemotherapy remains the standard palliative treatment for patients with advanced gastric or gastro-esophageal junction (GEJ) adenocarci-

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Table 1
5-Fluorouracil plus platinum salts with or without docetaxel regimens.

	Doublet			Triplet		
	CF [6]	FLO [10]	FOLFOX [14]	DCF [6]	FLOT [11]	TFOX [12]
Cycle	Every 4 weeks	Every 2 weeks	Every 2 weeks	Every 3 weeks	Every 2 weeks	Every 2 weeks
5FU bolus (D1)			400 mg/m^2			
5FU continuous	1000 mg/m^2/d (5 days)	2600 mg/m^2 (/24 h)	2400 mg/m^2 (/46 h)	750 mg/m^2/d (5 days)	2600 mg/m^2 (/24 h)	2400 mg/m^2 (/46 h)
Oxaliplatin (D1)		85 mg/m^2	85 mg/m^2		85 mg/m^2	85 mg/m^2
Cisplatin (D1)	100 mg/m^2			75 mg/m^2		
Docetaxel (D1)				75 mg/m^2	50 mg/m^2	50 mg/m^2
Main toxicities grade 3–4 (%)						
Neutropenia	57%	12%	29%	82%	48%	56%
Febrile neutropenia	12%	–	–	29%	2%	2%
Diarrhea	8%	6%	2%	19%	15%	11%
Vomiting	17%	3%	4%	14%	4%	3%
Neuropathy	3%	14%	2%	8%	9%	17%

Data of toxicities are reported from randomized phase III studies for CF, FLO, FOLFOX and DCF regimens, and from phase II studies for FLOT and TFOX regimens.
The comparison of doublet versus triplet regimens in randomized phase III study was performed only for CF versus DCF [6].

noma, leading to objective response, quality of life improvement, and survival increase [2]. Doublet regimen with cisplatin and fluoropyrimidine (CF regimen) is considered as a standard first-line treatment in advanced gastric cancer [3–5].

In a randomized phase III trial, the addition of docetaxel to CF (DCF regimen) demonstrated a significantly improvement of the tumor response rate, the time to tumor progression and overall survival (OS). However, the DCF regimen was associated with increased severe toxicities compared with CF (including more complicated neutropenia), and has not been used extensively in clinical practice or as the preferred chemotherapy backbone in clinical trials evaluating new targeted agents [6]. This prompted many investigators to explore alternative docetaxel-based regimens for advanced gastric cancer patients.

A first proposal was a split-dose of docetaxel, cisplatin, and 5-fluorouracil (5-FU) regimen suggesting a better safety profile in phase II studies [7,8]. Furthermore, oxaliplatin, a third generation platinum compound, has been shown to be at least as effective as cisplatin in the treatment of advanced gastric cancer [9,10]. A randomized phase III study comparing a biweekly combination of continuous 5-FU/leucovorin plus either cisplatin or oxaliplatin reported that efficacy was similar, and that the oxaliplatin-based regimen significantly reduced toxicity in comparison to the cisplatin-based regimen (leucopenia, anemia, nausea, vomiting, fatigue, renal toxicity, thromboembolic events) [10]. These results raised the question if the risk/benefit ratio of DCF could be improved by the use of 5FU/oxaliplatin as a backbone for docetaxel, instead of the classical 5FU/cisplatin regimen. Recently, phase II studies have evaluated the combination of 5FU/oxaliplatin (FOLFOX regimen in GATE study, and FLO regimen in AIO study) with docetaxel at 50 mg/m^2 every two weeks (TFOX regimen in GATE study, and FLOT regimen in AIO study) (see Table 1) [11,12]. These results suggested that this triplet regimen is as effective as triplet with cisplatin but with a more favorable safety profile deserving a prospective randomized validation. To our knowledge, there is no prior phase III study evaluating the 5-FU/oxaliplatin/docetaxel regimen in gastric cancer excepted in perioperative setting with the FLOT4 clinical trial demonstrating very recently that disease-free survival and OS were longer for patients treated with FLOT as compared with ECF/ECX regimen [13]. The combination of 5FU/oxaliplatin with docetaxel is nowadays the new standard of care for patients with resectable gastric cancer.

The aim of the GASTFOX study is to compare in a randomized phase III study the efficacy of 5FU/oxaliplatin (FOLFOX) alone or associated with docetaxel (TFOX regimen) in first-line treatment of advanced gastric cancer.

2. Study design

GASTFOX is a French academic, multi-center, randomized phase III study comparing FOLFOX alone (reference arm A) or with docetaxel (experimental arm B) in first-line treatment for advanced gastric cancer.

In arm A, patients receive FOLFOX regimen (every 2 weeks) consisting in folinic acid at 400 mg/m^2 (or elvorine 200 mg/m^2), oxaliplatin at 85 mg/m^2, 5-FU bolus at 400 mg/m^2 over 10 min followed by 5-FU continuous at 2.400 mg/m^2 as a 46-h infusion.

In arm B, patients receive TFOX regimen (every 2 weeks) consisting in docetaxel at 50 mg/m^2, folinic acid at 400 mg/m^2 (or elvorine 200 mg/m^2), oxaliplatin at 85 mg/m^2 followed by 5-FU continuous at 2.400 mg/m^2 as a 46-h infusion.

In both arms, treatment will be continued until disease progression, unacceptable toxicity or patient refusal.

Patients are randomized in a 1:1 ratio using minimization techniques with the following stratification factors: center, Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs 1), adjuvant chemotherapy or radio-chemotherapy (yes vs no), tumor stage (locally advanced vs metastatic), tumor location (stomach vs junction), and pathological type (signet ring cell adenocarcinoma (ADCI) vs non-ADCI).

Eligible patients were ≥18 years old with histologically proven locally advanced or metastatic gastric or GEJ adenocarcinoma (all Siewert stage) and HER negative status. Further criteria were measurable disease, ECOG PS 0 or 1, adequate renal, hepatic and bone marrow functions, no concurrent uncontrolled severe disease, and no other current or previous malignancy within the past 5 years (with the exception of carcinoma *in situ* of the cervix, basal or squamous cell carcinoma which is considered to be cured). Prior palliative chemotherapy was not permitted. Prior adjuvant (and/or neo-adjuvant) chemotherapy or radio-chemotherapy including 5-FU, with or without platinum salts and/or epirubicin were allowed if relapse occurred >12 months after the end of treatment. Major surgery or palliative radiotherapy was permitted if completed ≥4 weeks before random assignment. The main exclusion criteria were peripheral neuropathy of NCI-CTC 4.0 grade ≥2 at baseline, cerebral or meningeal metastases, known deficit of dihydropyrimidine dehydrogenase, prior docetaxel-based treatment (palliative or adjuvant setting), any contraindication or allergy to the treatments used in the study, and inability to submit to medical follow-up for geographical, social or psychological reasons.

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includes the following groups: FFCD, UNICANCER-GI and GERCOR. This protocol is registered on clinical-trials.gov (NCT03006432).

2.1. Trial endpoints

The primary end point is PFS defined as the time between randomization and the first radiological and/or clinical progression or the date of death from any cause, whichever occurred first. Secondary endpoints included OS, overall response rate (ORR), safety, quality of life and the therapeutic index. Overall survival is defined as the time between randomization and death for any cause. Tumor response assessments is performed every 8 weeks based on computed tomography and/or magnetic resonance imaging evaluation as defined by RECIST v1.1 criteria. Overall response rate include partial and complete responses. Safety is evaluated by adverse events classified and graded according to NCI-CTCAE v4.0, and quality of life is evaluated according to EORTC QLQ-C30 and STO-22 surveys. The therapeutic index evaluates the overall clinical benefit based on efficacy (PFS) and safety (febrile neutropenia rate) key parameters [11,12]. Median PFS is plotted against the incidence (%) of febrile neutropenia for each treatment arms and compared with the equivalent data reported previously for DCF and CF regimens [12]. The modalities of prescription for G-CSFs (granulocyte colony-stimulating factors) will be analyzed for the two treatment arms. The indication for primary prophylaxis with G-CSFs in arm B (TFOX) remains at the investigator's discretion.

After radiological or clinical progression, patients are followed every 6 months up to death and data from subsequent lines of chemotherapy are recorded in order to evaluate more accurately the impact of the first-line treatment in the OS.

A biological ancillary study on diagnostic tumor samples, circulating tumor DNA and constitutional genetic polymorphism is planned to identify prognostic and predictive biomarkers of efficacy and toxicity.

2.2. Statistical methods

Analyses are carried out on an intention to treat (ITT) basis on all randomized patients, whatever their eligibility and whatever treatment they have received. Each randomized patient is analyzed in the treatment arm to which he/she is allocated at randomization.

The hypotheses concerning the primary endpoint are:

H_0. The median PFS is not different between the two arms.

H_1. A difference of 2 months in the median PFS is hoped for (HR = 0.733, period of 5.5 months in arm A (FOLFOX) to 7.5 months in arm B (TFOX)).

Based on a two-sided α risk of 5% and a power of 90%, 454 events (radiological or clinical progression or death) are required to show this difference. With 24 months follow up, a recruitment rate of 11 patients per month and taking into account 10% of patients lost to follow-up, it will be necessary to randomize 506 patients overall (253 patients by arms).

An interim analysis is planned at 50% of events (227 events, radiological or clinical progression or death). The interim analysis is planned in order to evaluate efficacy (reject of H0) or futility (accept H0) at early stage. The *p*-values will be calculated using the O'Brien–Fleming function based on the number of events.

Survival analyses will be done using the Kaplan–Meier method and survival curves will be compared by log-rank test. Survival time will be described using medians and their 95% confidence intervals. Hazards ratios will be estimated by Cox model and all hypotheses linked to this method will be graphically tested.

Conflict of interest

None declared.

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