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Perioperative docetaxel, cisplatin, and 5-fluorouracil compared to standard chemotherapy for resectable gastroesophageal adenocarcinoma

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Abstract

Background: Even though the perioperative chemotherapy improves the overall survival (OS) compared to surgery alone in patients with a resectable gastroesophageal adenocarcinoma (GEA), prognosis of these patients remains poor. Docetaxel (D), cisplatin (C), and 5-fluorouracil (F) regimen improves OS compared to CF among patients with advanced GEA. We evaluated the potential interest of a perioperative DCF regimen, compared to standard (S) regimens, in resectable GEA patients.

Methods: We identified 459 patients treated with preoperative DCF or S regimens. The primary endpoint was OS. Propensity scores were estimated with a logistic regression model in which all baseline covariates were included. We then used two methods to take PS into account and thus make DCF and S patients comparable. OS analyses were performed with Kaplan–Meier and Cox models in propensity score matched samples, and inverse probability of treatment weighted (IPTW) samples.

Results: In the propensity score matched sample, the p-value from the log rank test for OS was 0.0961, and the 3-year OS rate was 73% and 55% in DCF and S groups, respectively. The multivariate Cox regression underlined a Hazard Ratio of 0.55 (95% CI 0.27–1.13) for DCF patients compared to S patients. The results from IPTW analyses showed that DCF was significantly and independently associated with OS (HR = 0.52; 95% CI 0.40–0.69).

Conclusions: In this retrospective multicenter, hypothesis-generating study, the propensity score analyses underlined encouraging results in favor of DCF compared to S regimens regarding OS. This promising result should be validated in a phase-3 trial.

Keywords: Gastric cancer; Gastroesophageal cancer; Preoperative; Neoadjuvant; Docetaxel; Taxane

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Introduction

Perioperative chemotherapy became standard of care in resectable gastroesophageal adenocarcinoma (GEA) patients since a significant increase in median overall survival (OS) was demonstrated over surgery alone. First, in the MAGIC trial, perioperative treatment with epirubicin (E), cisplatin (C), and 5-fluorouracil (F), provided an improved OS with a Hazard Ratio (HR) of 0.75 compared with surgery alone.[1] More recently, in the FFCD 9705 trial assessing the interest of perioperative CF regimen, the HR for death was 0.69 compared to surgery.[2] Despite these positive results, the long-term outcomes remain dismal, with less than 40% of patients alive at 5 years.[1,2] Hence, the development of a better treatment strategy in this setting is needed.

We live in an era of targeted therapies and immunotherapies, hence, room for a new chemotherapy agent remains uncertain in perioperative setting. Docetaxel, a potent microtubule-stabilizing agent, has demonstrated antitumor activity in advanced GEA.[3,4] Beyond the first line of chemotherapy, docetaxel in monotherapy improved OS and health related Quality of life (QoL) as compared to best supportive care alone.[4] In the first line setting, the addition of docetaxel to CF (DCF) demonstrated a better significant benefit for OS and a two-year survival rate over CF.[3] QoL assessed by global health status of QLQ-C30 and EQ-5D was also significantly improved in the DCF arm.[5] In a preoperative setting, encouraging results were observed with the same DCF regimen in a phase II trial. In this study, surgery was performed in 95% of patients and the complete resection (R0) was achieved in all patients, with a pathological complete response rate (pCR) of 9%. No treatment-related or surgical mortality was observed in this study.[6] A combined multicenter analysis of several modified DCF regimens revealed high histopathological response rates, and the pCR was found to be associated with better survival.[7]

To evaluate the potential interest of docetaxel before its further development in perioperative setting, we performed a retrospective multicenter study in real life to compare the DCF regimen with other chemotherapy regimens.

Patients and methods

Patient selection

Two French databases of consecutive resectable GEA patients were used. The first one was a national database of patients diagnosed from 1987 to 2010 among 21 centers, and the second one was a regional Franche-Comté database between 1999 and 2012 with patients among 5 centers that were not included in the first database. We excluded patients diagnosed at metastatic stage. We also excluded patients diagnosed before 2006 since only a few of these patients received preoperative treatment before that year (Supplementary Fig. 1).

Treatment

Preoperative treatments were classified as DCF regimen if patients received at least one cycle of this protocol, and standard (S) regimen if they received any preoperative treatment with the exclusion of taxanes. DCF regimen consisted of docetaxel (75 mg/m^2 on day 1), cisplatin (75 mg/m^2 on day 1), and 5-fluorouracil (750 mg/m^2/day on continuous perfusion on days 1−5), every 3 weeks as previously described by Van Cutsem et al.[3] The DCF treatment was recommended by a multidisciplinary oncologic board of some hospitals instead of CF due to an improvement on efficacy/toxicity ratio in metastatic patients.[8] Two clinicians, SK and FF, have independently checked the database to identify those patients that received DCF regimen, as well as those ones that received other chemotherapy regimens, and patients without preoperative treatment.

Definition of variables

The primary outcome was OS, defined as the time interval between diagnosis and death from any cause. Alive patients were censored on the last date of news. Clinical records were used to obtain baseline characteristics: gender, age at diagnosis, tumor localization, signet-ring cell histology, and clinical stage by the American Joint Committee on Cancer (AJCC) classification version 6. We also collected the type of surgery approach, the extension of lymph node dissection, number of dissected and metastatic lymph nodes, resectability and metastases at surgery, pathological stage, and pathological complete resection characteristics.

Statistical analysis

Qualitative variables were described using frequency and percentage, and continuous variables were described using mean (SD) and median (Min-Max). The differences in baseline characteristics between groups were tested using the Fisher *exact test* or Student *t* test for categorical and continuous variables, respectively.

Propensity score is a statistical method used in observational studies. Indeed, taking into account propensity score in the analyses allows to compare group characteristics even if the allocation treatment is not randomized, by controlling confounding factors in a non-parsimonious way.[9] Propensity score represents the probability of receiving a specific treatment for a patient, conditionally to baseline patient characteristics. Propensity scores were thus constructed and estimated using a univariate and then a final multivariate logistic regression model, in which the probability of receiving DCF was regressed on baseline covariates.