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Feasibility of preoperative and postoperative chemoradiotherapy in gastric adenocarcinoma. Two phase II studies done in parallel. Fédération Francophone de Cancérologie Digestive 0308 ☆

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Abstract ***Background:*** For resectable gastric cancer, both postoperative chemoradiotherapy and perioperative chemotherapy demonstrate high-level evidence for improved survival in Western populations. To evaluate the feasibility of pre- or postoperative chemoradiotherapy, we proposed two multicentre phase II studies.
Patients and methods: Patients with localised, histologically confirmed gastric cancer and Eastern Cooperative Oncology Group (ECOG) performance status <2 judged suitable for curative resection were eligible. Eligible patients were assigned to either preoperative chemo-

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radiotherapy followed by surgical resection or surgical resection followed by chemoradiotherapy depending on each centre. Chemoradiotherapy regimen included four courses of FOLFIRI (5 Fluorouracil, Leucovorin, Irinotecan) regimen then Concurrent fluorouracil at 200 mg/m^2/d by continuous infusion 5 days each week. A dose of 50 Gy in 25 fractions in the preoperative study, or 45 Gy in 25 fractions in the postoperative study, was delivered. The primary end-point for both studies was the proportion of patients, who completed the therapeutic sequence.

Results: Between September 2007 and January 2010, 63 patients were included in both studies. The postoperative study was stopped for futility at the first step. In the preoperative study, 31 patients (73.8%, confidence interval (CI) 95%: 65.8–90.1%) received complete therapeutic sequence. Serum albumin and dietary restriction evaluated by QLQ-STO22 (Quality of Life-Stomach module) score were significantly linked with chemoradiotherapy feasibility in univariate analysis with respectively Odds-ratio (OR) 1.16 [CI 95%: 1.01–1.33] and 0.17 [0.03–0.89], $p = 0.04$. Median overall survival time was 26.4 months in the preoperative study.

Conclusion: Feasibility of chemoradiotherapy was not achieved for these studies: 73.8% (CI 95%: 65.8–90.1) and 42.9% (CI 95%: 21.8–66%) in preoperative and postoperative settings respectively.

1. Introduction

For resectable gastric cancer, adjuvant treatment strategy remains debated [1]. Currently, both postoperative chemoradiotherapy and perioperative chemotherapy demonstrate high-level evidence for improved survival in Western populations [2–4]. Recent data from the INT-0116 trial, after a 10-year median follow-up, has confirmed benefits in both overall survival and recurrence free survival for patients treated by postoperative chemoradiotherapy [5]. Only one Asian trial has directly compared postoperative chemotherapy with chemoradiotherapy [6]. In this trial, disease free survival was significantly superior in node-positive patients receiving chemoradiotherapy ($p = 0.036$). In gastric cancer, several preoperative chemoradiotherapy regimens have been evaluated at phase II [8–13]. In cancer of the oesophagogastric junction (OGJ), preoperative chemoradiotherapy improved 3-year survival rate from 27.7% to 47.4% ($p = 0.07$) in comparison with chemotherapy alone [14]. These different studies argue in favour of radiotherapy associated with chemotherapy in adjuvant treatment of gastric cancer. However, the feasibility of postoperative and preoperative chemoradiotherapy has never been studied according to the same criteria. In preoperative chemoradiotherapy studies, feasibility was defined by intention-to-treat approach including for analysis, all patients before treatment [8–13]. However, in postoperative chemoradiotherapy studies, feasibility analysis was limited to selected patients, with good post operative nutritional status [5–7]. To evaluate the feasibility of pre- or postoperative chemoradiotherapy, in intent to treat approach, we proposed two parallel multicentre phase II studies. Each centre determined either a preoperative or postoperative strategy.

2. Patients and methods

2.1. Patient selection

Patients with localised, histologically confirmed gastric cancer or gastroesophageal junction Siewert III and Eastern Cooperative Oncology Group (ECOG) performance status <2 judged suitable for curative resection were eligible. Patients underwent the following investigations: computed tomography (CT) of the chest, abdomen and pelvis and blood tests (CBC Cell Blood Count, hepatic function, renal function and serum albumin). Oesophagogastroduodenoscopy with endoscopic ultrasonography (EUS) was performed only in patients with node size below 2 cm on CT scan. Only patients over 18 years of age and with adequate renal, haematological and hepatic functions were enrolled (creatinine <120 μmol/L, neutrophils $\geqslant 1500/mm^3$, platelets $\geqslant 100{,}000/mm^3$, serum albumin >30 g/L). Patients with $T > 2$ imaging (CT or EUS) or perigastric node involvement (CT or EUS) without detectable distant metastases or peritoneal carcinomatosis were included. Exclusion criteria were personal history of thoracic or abdominal radiation therapy, known pregnancy or total bilirubin >3 upper limit level. Local ethics committees approved the protocol and patients' written informed consent was obtained (N°EudraCT:2006-005576-40).

2.2. Study treatment

These phase II trials were initiated in 24 centres by the Fédération Francophone de Cancérologie Digestive (FFCD). Each centre selected preoperative study or postoperative study participation according to preference. Only one of the two studies was opened in each centre. Both studies were done in parallel.