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Exclusive neoadjuvant chemotherapy in locally advanced resectable gastric and gastro-esophageal junction adenocarcinoma

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ABSTRACT

Background: Perioperative chemotherapy improves the prognosis of patients with locoregionally advanced resectable gastric and gastro-esophageal junction adenocarcinoma. Nevertheless, only 50% of operated patients could receive the postoperative component chemotherapy. An exclusive preoperative chemotherapy is therefore an interesting strategy. We report the clinical course of patients with operable gastric and gastroesophageal junction adenocarcinoma treated with an intention of exclusive preoperative chemotherapy.
Methods: The medical records of all consecutive patients with an operable gastric or gastroesophageal junction adenocarcinoma and treated with an intention of exclusive preoperative chemotherapy were analysed.
Results: Between 1999 and 2014, 90 eligible patients were identified. Fifty-eight patients (64%) presented with clinical T3–T4 tumour and 63 (70%) had a lymph node involvement. Eighty (90%) patients were treated with 4 cycles of preoperative chemotherapy containing docetaxel, 5-fluorouracil (5FU) and a platinum salt. All patients had surgery with a D2 lymphatic dissection and R0 resection rates in 91% and 88% respectively. Median progression-free survival was 6.1 years (95% confidence intervals (CI): 1.6, NC) with median overall survival of 8.1 years (95% CI: 4.1, NC).
Conclusion: Our study suggests that an exclusive neoadjuvant approach when associated with a D2 lymph node dissection in resectable gastric and gastro-esophageal junction adenocarcinoma appears a feasible strategy with encouraging survival.

1. Introduction

In western countries, 50% of patients with gastric cancer are diagnosed with a localized or a regional lymph node spread stage [1]. For these patients, surgical resection is the main therapeutic modality. Nevertheless, the prognosis of patients with locally advanced gastric cancer after curative surgery is poor, with 5-year survival rates of 17–30% [2,3]. To decrease relapse rate after gastrectomy with a D2 lymph nodes dissection and improve survival, two different combined strategies using exclusively chemotherapy are used.

The first, adjuvant chemotherapy, was assessed in numerous trials with discordant results compared to surgery alone. Among those trials demonstrating a survival benefit, the majority were performed in Asia and a few in Western countries [4,5]. Due to discordance in survival, data were re-analysed in successive meta-analyses which concluded on a significantly slight overall survival (OS) benefit (HR, 0.82; CI 95%, 0.76 to 0.9) for adjuvant 5FU based chemotherapy compared to surgery alone in patients with gastric cancer [6–8].

The second strategy, mainly employed in European countries, is perioperative chemotherapy. Two randomized controlled trials (RCT) demonstrated an OS gain with perioperative chemotherapy. The MAGIC trial comparing the effect of a perioperative chemotherapy with surgery alone was the first to demonstrate an OS benefit

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(HR, 0.75; 95% CI, 0.6 to 0.93) of the perioperative treatment [2]. This result was confirmed by the "Fédération Francophone de Cancérologie Digestive" (FFCD) trial that reported also an OS gain (HR, 0.69; CI 95%, 0.5 to 0.95) [3]. In both trials, postoperative chemotherapy was started only in 50% of the patients in the perioperative arm.

Given the modest benefit of adjuvant chemotherapy and knowing that postoperative chemotherapy component can be performed only in 50% of the patients treated with a perioperative chemotherapy, an exclusive preoperative chemotherapy appeared as an interesting approach. On this basis, an exclusive preoperative chemotherapy strategy was adopted in our institution since 1999.

In this study, we are reporting the clinical course and the prognosis of patients with clinical T2-4N0 or TanyN+ gastric and gastro-esophageal junction adenocarcinoma treated with an intention of exclusive preoperative chemotherapy.

2. Material and methods

2.1. Patient selection

We retrospectively collected all consecutive patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma from 1999 to 2014 in our institution. Only patients treated with an intention of exclusive preoperative chemotherapy for clinical stage Ib to III were eligible. The few patients who received adjuvant treatment, decided after surgery because of pathologic very bad prognosis features, were kept in the cohort.

2.2. Clinical assessment

Radiological staging with computed tomography (CT) or fluorodeoxyglucose-positron emission tomography (FDG-PET), and endo-ultrasonography (EUS) was performed. To standardize the clinical stage, all EUS reports were reviewed and readjusted according to the 7th edition of the AJCC/UICC staging system [9].

2.3. Pathologic assessment

Hematoxylin and eosin-stained slides from surgical specimens for each case were retrieved. A pathologist (Dr G. Puppa) reviewed the slides of each patient. He defined the pathological stage according to the 7th edition of the AJCC/UICC staging system, the histologic subtype and determined the Becker tumour regression grade for each specimen [10,11].

2.4. Statistical analysis

Continuous variables were expressed as median and range. Categorical variables were reported as percentages. The progression-free survival (PFS) and OS distributions were estimated using the Kaplan–Meier method [12]. Progression-free survival was defined as the time between the first day of preoperative chemotherapy and the date of the first radiological or pathological documented event of local or metastatic relapse, incomplete surgery or death, whichever occurred first. OS was defined as the time between the first day of preoperative chemotherapy and the date of death from any cause. STATA statistical software version 13.1 (StataCorp LP, College Station, TX) was used for statistical analyses. This retrospective study was reviewed and approved by the Ethics Committee of the University Hospital of Geneva (Protocol No. 14-163).

Table 1
Clinico-pathological features in the 90 gastric or GEJ adenocarcinoma patients.

Total	n = 90
Median age at diagnosis (range):	57.5 years (24–76)
Gender:	
–Male	59 (66%)
–Female	31 (34%)
ECOG at diagnosis:	
–0	41 (45%)
–1	28 (31%)
–2	6 (7%)
–Unknown	15 (17%)
Tumor site:	
–GEJ	5 (6%)
–Stomach	85 (94%)
EUS staging (AJCC 2010):	
–T2N0	5 (6%)
–T1-2/N+	18 (20%)
–T3-4/N0	13 (14%)
–T3-4/N+	45 (50%)
–Unknown	9 (10%)

3. Results

3.1. Patients

A total of 90 patients with a clinical stage Ib to IIIc and histologically proven gastric or GEJ adenocarcinoma were identified for this study. There were 59 males (66%) and 31 females (34%). The median age at diagnosis was 57.5 years (range 24–76 years). Pretherapeutic staging procedures included endoscopy with biopsy, EUS, CT or FDG-PET of the chest and abdomen. Using the Lauren classification, 45 patients (50%) had a diffuse type adenocarcinoma. The EUS analysis was reviewed for 81 patients (90%). Fifty-eight patients (64%) had a T3–T4 tumour and 63 (70%) were lymph node positive at EUS staging. The characteristics of the patients are reported in Table 1. All of them were treated with neoadjuvant chemotherapy.

3.2. Preoperative treatment

For 80 patients (89%), 4 cycles of a docetaxel containing regimen were initially scheduled. Seventy-six patients (84%) received "TCF" regimen as 3 weekly regimen with docetaxel 75 mg/m^2 1-h intravenous (IV) infusion and cisplatin 75 mg/m^2 4-h IV infusion on day 1 plus 5FU 300 mg/m^2/day continuous IV infusion from day 1 to 14 [13]. Because of kidney function impairment or hearing problems 4 patients (4%) received a modified "FLOT" regimen as biweekly regimen with docetaxel 50 mg/m^2 1-h IV infusion on day 1 and oxaliplatin at a dose of 85 mg/m^2 2-h IV infusion plus 5FU 300 mg/m^2/day continuous IV infusion from day 1 to 14 [14]. Ten patients (11%) considered unable to receive a docetaxel and/or platin containing regimen were planned to be treated with 4 cycles of an anthracycline or an irinotecan containing regimen. Sixty-five patients (72%) received the 4 planned cycles of preoperative chemotherapy, 20 (22%) received less than the 4 planned cycles and 3 (3%) received more than 4 cycles. Thirty-three patients (37%) had complete treatment without dose reduction due to side effects. There was no toxic death. Characteristics of treatment are presented in Table 2.

3.3. Surgery

Surgery was carried out in all the patients and the characteristics of surgical procedures are described in Table 3. Seventy-nine patients (88%) had a complete tumour resection, 7 (8%) had

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