Perioperative chemotherapy in locally advanced gastric cancer. A retrospective study about 25 cases.

Chimiothérapie périopératoire dans le cancer gastrique localement avancé : Etude rétrospective à propos de 25 cas.

Ben Nasr Sonia, Ayadi Mouna, Bahloul Rim, Guesmi Sondes, Allani Bassem, Chrait Nesrine, Rifi Héla, Rais Henda, Mezlini Amel.

Service de carcinologie médicale- Institut Salah Azaiez

R É S U M É

Prérequis : La chimiothérapie néoadjuvante contenant 5FU, Cisplatine ± Docetaxel est l'un des moyens thérapeutiques les plus actifs dans le cancer gastrique localement avancé.

Objectif: Décrire le profil épidémiologique et clinique et les résultats thérapeutiques de la chimiothérapie périopératoire dans le cancer gastrique localement avancé en Tunisie.

Méthodes: Notre étude rétrospective a concerné les patients porteurs d'un cancer gastrique localement avancé confirmé histologiquement traités à l'institut Salah Azaiz de Tunis. Nos patients ont reçu 2-3 cycles/3semaines d'une chimiothérapie néoadjuvante basée sur les protocoles FP (5FU-Cisplatine) ou TPF (Docétaxel-Cisplatine-5FU).

Résultats: De 2010 à 2012, 25 patients avec un âge médian de 60 ans et un sex-ratio de 7,3 ont reçu une chimiothérapie néoadjuvante type TPF dans 20 cas et FP dans 5 cas. 17 patients (68%) ont reçu plus que 2 cycles. La toxicité était une mucite grade 3 dans 2 cas, une neutropénie grade 3/4 chez 3 patients et une insuffisance rénale chez 5 patients. Après chimiothérapie néoadjuvante, nous avons observé une réponse partielle chez 40% des patients et une stabilité chez 20%. Six patients (24%) ont été opérés. la chirurgie était curative chez 4 patients (R0 dans 3 cas) et palliative chez 2 patients à cause de la découverte per-opératoire d'une carcinose péritonéale. Après un délai médian de suivi de 16 mois, la survie globale médiane était de 16 mois (2-21 mois).

Conclusion: La chimiothérapie néoadjuvante n'a pas apporté de bénéfice dans le traitement du cancer gastrique localement avancé dans notre étude. Ceci pourrait être du à la forte masse tumorale et aux stades très avancés chez les patients tunisiens.

Mots-clés

Cancer gastrique, chimiothérapie néoadjuvante, chirurgie, réponse.

S U M M A R Y

Background: Perioperative chemotherapy containing 5FU, Cisplatin ± Docetaxel is one of the most active regimens in advanced gastric cancer.

Objective: To report epidemiological and clinical profile and therapeutic results of perioperative chemotherapy in locally advanced gastric cancer in Tunisia.

Methods: Our retrospective study concerned patients with histologically confirmed advanced gastric cancer treated at the institute Salah Azaiez of Tunis. They received 2-3 cycles / 3 weeks of neoadjuvant chemotherapy based on FP (5FU and Cisplatin) or TPF (Docetaxel-Cisplatin-5FU).

Results: From 2010 to 2012, 25 patients with a median age of 60 years and 7.3 sex-ratio received neoadjuvant chemotherapy. Protocols used were TFP in 20 and FP in 5 patients, 17 patients receiving more than 2 cycles. Side effects were represented by mucositis grade 3 in 2 patients, neutropenia grade ¾ in 3 patients and renal failure in 5 patients. After neoadjuvant chemotherapy, we observed 40% of partial response and 20% of stable disease. Six patients (24%) underwent surgery, curative in 4 (R0 in 3 cases) by total gastrectomy and D2 lymphadenectomy and palliative in 2 cases due to peritoneal carcinomatosis. With a median follow up of 16 months, median overall survival was 16 months (2-21 months).

Conclusion: Probably due to the very bulky and advanced stages of our gastric cancer cases, neoadjuvant chemotherapy using FP±T showed no benefit in the treatment of locally advanced gastric cancer in Tunisian patients.

K e y - w o r d s

Gastric cancer, neoadjuvant chemotherapy, surgery, response.

Although its incidence is decreasing in most countries, GC is common and represents the second leading cause of cancer death worldwide. The number of new cases is estimated at about 7000 per year and 5000 deaths in France in 2000 where it ranks third of digestive cancers in men after colorectal cancer and esophageal cancer and in second place in women after colorectal cancer. Five year Overall survival (OS) for patients with gastric cancer (GC) after curative surgery was low but seems to be improving in the last 20 years to reach a 45% rate. However it's lower in case of GC primitive invading lymph nodes, between 15 and 25%. Then cross the serosa (pT3), the risk of locoregional recurrence is about 50 to 60%, 20% of these recurrences being only locoregional. Poor prognosis in locally advanced gastric cancer (AGC) justified the development of several trials testing neoadjuvant chemotherapy (NACT) considered more effective and better tolerated than adjuvant chemotherapy (CT). Recently, MAGIC study tested perioperative chemotherapy (PECT) and showed benefit on OS and progression-free survival (PFS) [1-3]. The objective of our study was to evaluate tolerance/toxicity and therapeutic results of PECT with continuous infusion 5FU-Cisplatin (FP) ± Docetaxel (T) in AGC in Tunisia.

METHODS

This retrospective descriptive study was conducted at the medical oncology department of Salah Azaiz institute in Tunisia between 2010 and 2012. We collected patients with World Health Organization (WHO) performance status (PS) ≤ 2 and histologically proven AGC. Initial work up included clinical history, exam, gastric endoscopy and thoraco-abdominal (TA) CT Scan. CT included 2-3 cycles of P (80 mg/m2) and F (1000 mg/m2 d1-d5 continuous infusion using a double-lumen Hickman catheter and a portable infusion pump) if FP regimen was performed or P (75 mg/m2), T (75 mg/m2) and F (750 mg/m2 d1-d5 continuous infusion) if TPF regimen was done. In case of TPF, hematopoietic growth factors were administered at a dose of 5µg/kg/day for 5 to 10 days starting from day 5. CT cycles were repeated every 21 days. A fourth cycle of CT was done if it was judged necessary. Post-operative FP±T was recommended in case of response to NACT. Palliative CT if tumor was nonresponding consisted in Folfox, Folfiri or ELF. Folfox included F (Bolus of 400 mg/m2 on day 1 and 2400 mg/m2/day d1-d2 continuous infusion), Folinic acid (400 mg/m2 on day 1) and Eloxatine (85 mg/m2/day on day 1). Folfiri included F (Bolus of 400 mg/m2 on day 1 and 2400 mg/m2/day d1-d2 continuous infusion using), Folinic acid (400 mg/m2 on day 1) and Irinotecan (85 mg/m2/day on day 1). ELF included Etoposide (120 mg/m2/day d1-d3), Folinic acid (300 mg/m2/day d1-d3) and F (500 mg/m2/day d1-d3). Curative surgery was programmed three to six weeks after the last cycle of CT. The extent of the lymph node dissection was decided by the surgeon. Resection was considered curative as when all macroscopic and microscopic disease was removed. OS was calculated from diagnosis to death. The sites of relapse were classified as follows: the relapse was coded as local if tumor was detected in the surgical anastomosis, residual stomach, or gastric bed, as regional if tumor was detected in the peritoneal cavity (including intraabdominal lymph nodes, and peritoneum), and as distant if the metastases were elsewhere.

For statistical analysis, the data were analyzed using SPSS Version 18 software. We calculated simple frequencies and relative frequencies (percentages) for qualitative variables and means and medians for quantitative variables.

RESULTS

25 pts with AGC were included having median age of 60 years (32-83 years) and 7.3 sex-ratio. Five patients (20%) had a family history of cancer: gastric in 3 cases, colon in 1 case and both in 1 case. Epigastric pain was the most frequent symptom and occurred in 21 patients (84%) and weight loss averaged 9.18 ±6.84 kg (1- 20 kg). At diagnosis, PS was 0-1 in 23 patients (92%) and 2 in 2 patients (8%). Median body mass index was 22 (17-27.5). Median time to diagnosis was 2 months (1-45 months).

Tumor diameter in endoscopy averaged 3.7±1.7 cm (2-6 cm), localized in fundus in 40% or in antrum in 52% of cases. Histological examination of gastric biopsy showed an undifferentiated signet-ring cell carcinoma in 15 cases (60%).

In CT Scan, tumor size averaged 5.1±2.49 cm (2.5-9.5), gastric thickening observed in 20 patients (80%), perigastric fat, adjacent organ and Regional lymph node invasion were noted in 9 (36%), 4 (16%) and 16 cases (64%) respectively.

An average of 2.8 cycles were administered by TPF and FP in 20 (80%) and 5 cases (20%). After NACT, radiological response was partial in 10 cases (40%). Stability was observed in 5 cases (20%) and progression in 7 (28%) in peritonum in 2 cases, locoregional and pulmonary in 1 case, locoregional and bony in 1 case, hepatic and pulmonary in 2 cases and adrenal and pulmonary in 1 case. Twelve patients received palliative second line CT (Folfox in 5 cases and ELF in 7 cases) and 5 of progressed were treated by a third line treatment. NACT toxicity was mucositis grade 2-3 in 6 patients (24%), neutropenia in 13 patients (52%) (grade 1-2: 10 cases , grade 3-4: 3 cases), renal toxicity grade 3 in 5 cases (20%) requiring cisplatin dose reduction of 25%. Weight loss during NACT occurred in 8 (32%) patients and was estimated to 4kg (1-7 kg).

Surgery was performed in 6 of the responder patients. It was curative in 4 cases and palliative in 2 cases due to peritoneal carcinomatosis. Tumor staging after curative surgery according to American Joint Committee on Cancer (AJCC 2009) classification was as follow: IIIA in 2 cases, IIIB in 1 case and IIIC in 1 case. Median OS was 16 months (2-21 months).

DISCUSSION

In our study, we didn't find a clear benefit of NACT for AGC in Tunisian patients with a 40% overall response rate (ORR), 6 patients (24%) only reaching surgery. Our patients had an AGC due to a late time to diagnosis.

GC still represents a major clinical challenge due to its poor prognosis, a relative chemoresistance and late diagnosis at an advanced stage, which limits available therapeutic approaches in more than 50% of cases [4,5]. However, even after curative resection, more than half of T3 and T4 tumors recurred. OS varied between 15 to 30% if lymph nodes are invaded and 60 to 80% if not. Multiple studies have shown large benefit of NACT including tumor downstaging and thus providing curative surgery, elimination of micrometastases and improvement of

OS and PFS. UK MAGIC multicentre randomized study (N=503) [3] evaluated the interest of PECT including epirubicin-cisplatin-5-fluorouracil (ECF) against surgery alone in patients with resectable gastric cancer. the PECT group as compared with the surgery group, had a higher likelihood of OS (hazard ratio (HR) for death, 0.75; 95% confidence interval (CI), 0.60 to 0.93; p = 0.009; five-year OS, 36 % vs. 23 %) with an estimated improvement of 13 percentage points in the five-year OS, corresponding to a 25 percent reduction in the risk of death. A significant benefit in PFS was observed (HR for progression, 0.66; 95% CI, 0.53 to 0.81; P<0.001). Perioperative ECF also resulted in increasing the likelihood of curative resection by downstaging the tumor, eliminating micrometastases, rapidly improving tumor-related symptoms, and determining whether the tumor were sensitive to CT. The thesaurus of the French National Society of Gastroenterology (SNFGE) recommends a discussion of the patient record in consultative meeting before surgery and a proposal of a PECT for all cancer patients with stage greater than I (Grade A) of ECF (grade B) or PF (grade B) [3,6-8]. French multicenter randomized study compared the surgery alone with surgery flanked by two cycles of CT (FP) in locally AGC. The risk of recurrence and death were significantly lower in the CT group, the hazard ratios were respectively 0.65 (95% 0.48 to 0.89) and 0.69 (95% CI: 0.50 to 0.95). The PFS at five years was significantly higher in the CT group (34 against 17%, p = 0.018) [7,9]. TPF regimen (N=221 patients) was compared to FP (N=224 patients) in metastatic or recurrant GC and did an improvement in time to progression (5.6 months versus 3.7 months, p <0.001, reducing the risk of 32%), OS (9.2 months vs. 8.6 months, p = 0.02, decreased risk of 23%) and ORR (37% versus 25%, p = 0.01) [10].

In our study, patients were diagnosed at advanced non resectable stage. Tumor diameter in endoscopy averaged 3.7 cm (2-6 cm) and was estimated to 5.1 cm (2.5-9.5 cm) in CT Scan. Our tumor features could be a reason for poor response to NACT in our study compared to MAGIC. As a consequence, only 4 pts (16%) of our study reached complete surgery versus 81% in MAGIC study. In other studies, ORR for NACT was only about 30-40% for locally advanced tumors and reached 50-60% in others [9,11].

CONCLUSION

Probably due to the very bulky and advanced stages of our gastric cancer cases, NACT using FP±T showed no benefit in the treatment of AGC. Early and frequent use of endoscopy when gastric symptoms are reported could help to discover gastric cancer at earlier stage and improve response to treatment.

Abbreviation:

OS: Overall survival
PFS: progression free survival
GC: gastric cancer
AGC: locally advanced gastric cancer
NACT: neoadjuvant chemotherapy
CT: chemotherapy
PECT: perioperative chemotherapy
ORR: overall response rate
ECF: epirubicin-cisplatin-5-fluorouracil
FP : 5FU-Cisplatine
TPF : Docétaxel-Cisplatine-5FU
Folfox: 5FU- folinic acid -Eloxatine
Folfiri: 5FU-folinic-Irinotecan
ELF: Etoposide-folinic acid-5FU.

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