Postoperative Adjuvant Radiochemotherapy for Patients with Stage III or IV Gastric Cancer

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Abstract: *Background and Purpose:* It is known that radiotherapy or chemotherapy alone don't represent a standard of care as adjuvant treatment for patients with advanced gastric cancer that underwent surgical resection. The purpose in the approach of this cancer is to find an adjuvant treatment that can affect overall survival. Phase 2 studies and randomized trials suggest that a multimodal approach with chemo radiotherapy (CT-RT) can improve overall survival. We analyze the feasibility and toxic effects of chemo radiotherapy (CT-RT) as a post surgical adjuvant treatment in a cohort of patients with high risk gastric cancer.

Methods: We enrolled 48 patients with advanced gastric cancer (Stage III and IV, M0). These patients were submitted to surgical resection and all of them, within 6 weeks, underwent adjuvant chemotherapy with FOLFOX-4 (ie, a combination of folinic acid, fluorouracil, and oxaliplatin) for 8 cycles and concomitant radiotherapy (45 Gy in 25 daily fractions over 5 weeks). Radiotherapy started after the first 2 cycles of FOLFOX-4. Chemotherapy schedule was reduced by 25% during the period of the contemporary radiotherapy treatment.

Results: All patients except one ended the combined adjuvant treatment. We observed severe hematologic adverse effects only in less than 10% of patients (4 patients); regarding gastrointestinal toxic effects they occurred in 33% of patients and specifically we noted G1-G3 grade toxicity and no G4 toxicity . Disease-free and overall survival at 1, 2, and 3 years was superior to in untreated patients. One to 3-years Median disease–free and overall survival rates were 27 months and 15 months respectively.

Conclusions: A combined trial with chemo radiotherapy **(**CT-RT) as adjuvant treatment represents an effective approach for patients with resected advanced gastric cancer.

Keywords: Chemotherapy, Radiotherapy, Gastric cancer.

INTRODUCTION

Gastric Cancer is the second leading cause of cancer death worldwide, although its incidence is decreasing [1]. Complete surgical resection remains the only curative treatment option for patients affected by a gastric cancer. Even after complete surgical resection with negative margins (i.e. R0 resection) plus D1 or D2 lymphoadenectomy (i.e. systematic lymphoadenectomy of compartments 1 e 2) many patients, particularly those with stage III and IV (with M0 disease) will eventually relapse [2]. Studies have revealed a high rate of distant failure and also of loco regional relapses even after R0 resection [3,4]. Long-term survival is only achieved in 8% - 40% of patients with loco regionally advanced disease, which makes the evaluation of an adjuvant or neoadjuvant treatment option a priority for these patients [5]. According to the results of the Magic (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial [6] the common approach for resectable gastric cancers is, in Europe, constituted by a perioperative chemotherapy. Post-operative fluorouracile-based CT-RT is, instead, the recommended treatment for PT3 and N+ gastric cancers in the United States [7]. In our study obtained on selected patients (stages III or IV, Mo) we want to demonstrate the tolerance and the efficacy of post-operative chemo radiotherapy **(**CT-RT) as an adjuvant treatment.

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MATERIALS AND METHODS

Between January 2006 and June 2010 patients, a cohort of forty-eight patients, were enrolled. According to our in-

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clusion criteria we selected patients older than 18 years and younger than 75 years, all of them underwent a R0 surgical resection that is a complete removal of all macroscopic tumor masses and absence of microscopic residual tumor, negative margins, lymphoadenectomy extended beyond involved nodes with negative more distant lymph nodes (D2 lymphodenectomy). Anyone of them had an histologically confirmed diagnosis of gastric cancer. Patients were submitted to specific examinations to prove their adequate bone marrow, hepatic and renal function. Performance-Status was of 1 or less. Baseline characteristics of the enrolled population are depicted in Table **1**.

Median age was 54 (34-75), 34 patients were men and 17 women; most of them had a performance status of 0. The

Table 1. Patients' Characteristics (48ptz) and their Influence on the 3 Years Survival

	Patients (No)	3-y Survival (%)
Age,≤51y/>51y	24/24	62/47
Sex,M/F	32/16	45/80
Performance Status, 0/1	46/2	50/50
Pathologic Grading		
G1	1	100
G2	16	38
G3	31	38
Serum CEA level,≤3.5/>3.5ng/mL	39/9	60/15
Serum CA19-9 level,≤40/>40ng/mL	38/10	67/13
Site		
Antrum	36	65
Fundus	3	100
Corpus	5	0
Cardias	4	60
Size ≤4/>4 cm^2	29/19	67/29
Tumor		
T2	2	100
T3	42	44
T4	4	100
Nodes		
N1	7	80
N2	26	39
N3	15	50
UICC stage		
IIIA	9	100
IIIB	22	53
IV(M0)	17	40
Bormann classification		
I	1	0
II	12	100
III	22	32
IV	13	20
Lauren classification, intestinal/diffuse	8/40	67/30
Ming classification,expansive/infiltrative	10/38	63/42
Vascular-lymphatic invasion, no/yes	31/9	58/44
Resected nodes,≤26/>26	34/14	37/73
Metastatic nodes,≤9/9	35/13	55/38

64.6 % of the patients had stage III cancer and the 35.4% had stage IV cancer. Overall, 781 LNs were removed (mean [SD],26 [10]; range 15-59; median 26) and 305 turned out to be metastatic (LN +).

Chemotherapy-Radiotherapy (CT-RT) schedule consisted on 2 cycles of CT at full dose, followed by contemporary CT-RT (with a CT dose reduced by 25 %), and then by two more cycles of CT at full dose for a total of eight courses. CT treatment started within 6 weeks of surgery and consisted on oxaliplatin, 85 mg/m^2 on day 1; folinic acid, 200 mg/m^2 as a 2-hour infusion, followed by bolus fluorouracil, 400 mg/m^2; and a 22-hour infusion of fluorouracil, 600 mg/m^2 on days 1 and 2 every 2 weeks (FOLFOX-4). CT-RT treatment started two weeks after the second cycle of Folofox-4. Totally 45 Gy were delivered in 25 fractions, five days per week, with a 3D conformal technique. Computed tomography–based 3-dimensional RT planning was previously performed and radiotherapy was delivered with 18-MV photons in all the patients, generally by means of a 3-field technique.

The Clinical Target Volume (CTV) was defined using preoperative computed tomographs, endoscopic findings, surgical clips, and all other available information and included the gastric bed, the draining LNs as described in the Intergroup 0116 study [8,9], the anastomotic region, and a safety margin around the former tumor involving all mucosal cavity walls for at least 3 cm. The PTV (Planning Target Volume) was calculated with an expansion of 1cm over the CTV. So the 45 Gy were delivered in 25 fractions, to the tumor bed, anastomoses and stumps, and regional lymphatics. The design of the radiation treatment fields for postoperative treatment was individualized according to tumor stage and location in the stomach and the type of surgery performed. Lymph node stations included in the radiation fields were perigastric, celiac, splenic hilar, suprapancreatic, porta hepatis, pancreaticoduodenal, and local paraaortic nodes. For proximal lesions involving the gastroesophageal junction, the paraesophageal nodes were also included in the radiation fields. In patients with tumors confined to the proximal third of the stomach or gastroesophageal junction with limited lymphatic invasion (fewer than three nodes positive) treatment of the pancreaticoduodenal nodes and porta hepatis nodes was omitted. Similarly, treatment of the splenic hilar nodes was omitted in patients with tumors of the antrum/lower third of the stomach with limited lymphatic invasion. Clinical target volumes (CTV) and dose-limiting normal tissues for radiotherapy were defined on axial CT slices according to detailed and illustrated CTV delineation guidelines. These guidelines were produced thanks to a multimodal approach between oncologists, radiation oncologists, gastric surgeons, and diagnostic radiologists, and they comprise illustrative CT scans and diagrams that are designed to show practical examples of the CTV contouring process. Dose–volume histograms (DVHs) were recorded for the kidneys, liver and spinal cord in all patients. Baseline hepatic and renal function were evaluated prior to starting chemotherapy and also radiotherapy. During radiotherapy the Folfox-4 was contemporary applied biweekly at a reduced dose of 25%.

Concerning Chemotherapy (CT) treatment toxic effects were determinate before starting and at each 2-week cycle using the National Cancer Institute Common Toxicity Criteria [10]. Treatment delays and dose modifications were based on the results of a complete hematologic evaluation performed on the day of the planned treatment. When thrombocytopenia or neutropenia grade (G>2) or other significant non hematologic toxic effects developed, CT recycle was delayed for up to 2 weeks. The fluorouracil dose was reduced in cases of severe Gastro-intestinal toxicity (G3 – 15 patients totally).

During the RT-CT treatment patients were submitted to clinical examination once a week to assess the effect and the toxicity of the treatment. Hematologic parameters were evaluated each 7-10 days. Patient's weight was acquired before starting RT treatment, at half of the treatment and at the end of the treatment. A specific attention was directed to patient nutrition. Most of the patients had no severe symptoms and or major problems in feeding. Enteral or parenteral nutrition was added in seven patients when inadequate intake of energy caused weight loss or body mass index modification.

The primary study end points were determination of toxic effects and the safety profile of the treatment. Secondary end points included DFS and OS rates, calculated from the time of surgery to evidence of relapse or the date of the last evaluation and death, respectively. No patient was lost to follow-up.

RESULTS

All patients, except one, completed the treatment that was well tolerated. Common adverse effects were gastrointestinal such as nausea, vomiting, abdominal pain, and dyspepsia that were recorded respectively in 35 patients (74%), 18 patients (38%), 11 patients (24%) and 8 patients (17%). We didn't record any G4 gastrointestinal toxic effect. Biochemistry parameters did not have significant variations , only two patients needed growth factors and only one patient needed a nutritional supplementation. No treatment-related deaths were reported. Toxic effects and their recurrence are resumed in Table **2**.

During the first evaluation period of this study (i.e in the period including the start of chemotherapy treatment, the concomitant chemo-radiotherapy treatment and the first 19 months of Follow-UP) 10 patients (34%) died for reasons linked to the disease and cancer recurrence was observed in 16 patients (55%). Eighty percent of cancer recurrences occurred in the first 18 months, and no cancer relapse was observed after 2 years. Median disease–free and overall survival rates were 35% and 60% respectively. One-to 3-year OS was 85.0%, 62.6%, and 50.1%, respectively. Mean SD survival time was 27 months. One-to 3-year DFS survival was 79%,35%, and 35%, respectively . Mean and median DFS times were 21 months and 15 months , respectively. We observed a direct connection between male sex, worsening TNM stage, reduction of resected nodes and the presence of high number of metastatic lymph nodes and a worst prognosis that impressed the OS [7]. The peritoneum was the main site of relapse. As a single site of progression, it was shown to be involved in 6 patients (12,5%), and 1 patient had simultaneous dissemination to lumboaortic LNs. Ovarian metastases were discovered in 3 women, 1 of whom underwent radi-

Table 2. Main Toxic Effects Registred in the Study

Toxic effect	Grades 1-2, No.(%)	Grades 3 No.(%)	Grades 4 No.(%)
Hematologic			
Neutropenya	23	3	0
Thrombocytopenia	13	1	0
Anemia	10	0	0
Febrile neutropenia	0	0	0
Gastrointestinal			
Nausea	25	11	0
Vomiting	15	3	0
Abdominal Pain	10	1	0
Dispepsya	8	0	0
Hepatic	0	0	0
Neurologic	16	1	0
Others			
Asthenia	11	7	0
Allergic	0	0	0

cal resection. One patient developed a single-site metastasis in supraclavicular nodes that was treated with RT.One patient developed multiple liver metastases and anastomotic recurrence. Other single sites of disease progression were bone (2 patients), pleura (1 patient), and lumboaortic LNs (1 patient). Seven of the progressed patients were treated with CT for advanced disease [7].

We observed a correlation between the preoperative serum CEA levels and the 3-years survival (60% of surviving patients with CEA level ≤ 3,5ng/mL vs 15% with CEA level > 3,5ng/mL; p<0,01) and with the serum CA-19-9 levels (67% of surviving patients with CA19-9 ≤ 40ng/mL vs 13% with > 40ng/mL p= .0003) [7].

Considering the lymph nodes dissection we found that the number of resected nodes (≤ 26 vs > 26) and the number of metastatic lymph nodes (≤ 9 vs > 9) had some influence on the 3-years survival: 37% vs 73% (p= .08) and 55% vs 38% (p= .22) respectively.

DISCUSSION

Gastric Cancer remains a major cause of cancer-related death in most Western countries. Surgery is the only proven effective therapy, but overall 5-year survival rates remain low after resection.

For patients who underwent surgery, prognosis is determined by a series of factors [24,25] among which depth of invasion [11,12], nodal status [12-14], and metastasis [15-17] are the most important recognized system to predict prognosis.

Recently, adjuvant therapies after gastric carcinoma resection have become a matter of discussion [9,18] .The trials in question, however, included a wide variety of different tumor stages, so that adjuvant treatment was administered no matter how advanced the tumor was. Future studies in this field should be stratified on the basis of predicted individual risk to later on select those patients who benefit the most from an adjuvant treatment [19].

Many studies and meta- analysis showed that chemotherapy alone, as adjuvant treatment, does not modify the surgical benefit [20-23], but surely improves the OS and relapse-free survival [24, 25].

In the study by the Italian Trials in Medical Oncology (ITMO) Group, Bajetta *et al*.[20] used a EAP regimen (etoposide,adriamycin and cisplatin) followed by the Machover schedule (fluorouracil and folinic acid) given as adjuvant treatment to patients with poor prognostic factors (N+ or T3/4) finding a drug-related grade 3/4 WHO toxicities that included leukopenia (21%), nausea and vomiting (14%), mucositis (9%), neutropenia (3%) and thrombocytopenia (2%). They concluded that there was a limited relative risk reduction in the patients receiving adjuvant therapy (17% in DFS and 7% in OS).

The Italian Group for the Study of Digestive Tract Cancer (GISCAD) using the PELFw regimen, consisting of eight weekly administrations of cisplatin, LV, epidoxorubicin, 5-FU and glutathione with the support of filgrastim, or a regimen consisting of six monthly administrations of a 5-day course of 5-FU and LV, daily, 5-FU/LV, found no benefit from an intensive weekly chemotherapy in gastric cancer, with only 19 patients (9.4%) that completed the treatment in the PELFw arm and 85 (43%) patients that completed the treatment in the 5-FU/LV arm [21].

In the GOIM 9602 Study De Vita *et al*. [26] in radically resected IB–IIIB gastric cancers patients, with an adjuvant chemotherapy regimen called ELFE (epirubicin, leucovorin, fluorouracil, etoposide) didn't find any improvement in OS over surgery alone.

The role of RT alone as adjuvant treatment was reported in a randomized trial [27] in which 145 patients received surgery alone, 138 were administered postoperative CT, and 153 were given postoperative RT. No survival differences were reported, but RT offered an advantage in terms of reduction in local recurrence (27% with surgery alone vs 10% with surgery and RT). Forty percent of patients had gross or microscopic residual disease after surgery, and 24% of patients initially enrolled in the RT arm finally did not receive any treatment with radiation. In fact 19 of 153 patients enrolled to be submitted to post–operative RT didn't begin the treatment with radiations due to death or bad Performance Status; 13 patients refused to be submitted to RT treatment and, moreover, 4 of 153 patients didn't satisfied the entry criteria to start treatment.

So it was concluded that a feasible solution can be founded in a well balanced combination of CT plus RT.

The largest trial evaluating the role of CT-RT as adjuvant treatment was the US Intergroup 0116[9] In this study, 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomized to receive surgery alone or surgery plus postoperative CT-RT. Survival at 3 years was 50% vs 40% in favor of postoperatively treated patients. After 5 years of follow-up, OS was shown to improve by 11.6% (28.4% vs 40%; $P < .001$) and relapse-free survival to increase from 25% to 31%, both in favor of pa-

tients treated with postoperative CT-RT as opposed to surgery alone. Loco regional relapse was shown to decrease from 29% to 19%, CT-RT arm vs surgery alone. However, toxic effects were significantly higher with CT-RT, whereas treatment-related mortality was acceptable (1% in the CT-RT arm vs 0% in the surgery alone arm) [9].

Given these data however, there remain concerns regarding the toxicity of this combined treatment, the optimal chemotherapy regimen and the optimal method of radiotherapy delivery in patients treated previously with surgery.

In our study the aim is to demonstrate that an adequate adjuvant treatment is important for patient's survival and to avoid relapses. RT treatment associated to CT helps the local control of the disease. It's known that Folfox-4 is not the more common regimen used in gastric cancer. Post-operative fluorouracil–based CT represent indeed the standard of care for pT3 and N+ Gastric Cancer in the United States [9], moreover it was recently demonstrated by several phase 2 studies that the bolus of fluorouracil can be substituted with a continuous infusion of fluorouracil and the addition of cisplatin or paclitaxel and this schedule seems to be much more tolerated [2,28]. FOLFOX-4 schedule, including continuous fluorouracil infusion and oxaliplatin, used at full dose after surgery and at reduced dose during concomitant RT, can be considered the most active, and recently widely investigated, CT regimen for Gastric Cancer treatment [26]. Therefore his benefit is mainly evident only after adequate surgery. It is also true that this schedule may cause side effects such as stomatitis, nausea, vomiting, and also neurological toxicity but all these effects are treatable with common drugs. Moreover we didn't have evidence of G4 toxicity. Our experience didn't show the occurrence of particularly side effects RT–related. The most common are nausea, dyspepsia and vomiting, but it must be said that these symptoms are generally amplified by the concomitant CT treatment.

We observed Grade 2 neutropenia in 23% of patients and Grade 3 in 3%. Gastrointestinal toxicity evidenced a Grade 2 nausea in 25% of patients and Grade 3 in 11%, Grade 2 vomiting in 15% and Grade 3 in 3%. Moreover we found Grade 2 Neurologic side-effects in 16% (Grade 3 in 1%).

We also observed a correlation between the preoperative serum CEA levels and the 3-years survival (60% of surviving patients with CEA level ≤ 3,5ng/mL vs 15% with CEA level > 3,5ng/mL ; p<0,01) and with the serum CA-19-9 levels (67% of surviving patients with CA19-9 ≤ 40ng/mL vs 13% with > 40ng/mL p= .0003) [7].

Considering the lymph nodes dissection we found that the number of resected nodes (≤ 26 vs > 26) and the number of metastatic lymph nodes (≤ 9 vs > 9) had some influence on the 3-years survival: 37% vs 73% (p= .08) and 55% vs 38% (p= .22) respectively. Also the presence of advanced Bormann grade was significantly associated with a worse DFS rate[7].

Patients underwent first follow-up 3-4 months after RT treatment. No significant symptoms related to previous RT were referred, late gastrointestinal and hematologic toxicity were G0; nutrition was almost regular and body weight increased. Mean (SD) Follow-Up was 19 months (range 5-36 months).

Given that the CT regimen used in our study is not considered the more active in gastric cancer; we can conclude that the final therapeutic benefit is mainly evident only if adequate surgery can be performed.

As regards radiotherapy, a 3D-conformal therapy can be still considered the "gold standard". Anyway a 3D planning with the respect of the dose-constraints as recently described in an AIRO – Associazione Italiana di Radioterapia Oncologica – publication [29] for liver, kidneys and spinal cord, is of fundamental importance.

In conclusion, we can say that adjuvant CT-RT treatment with FOLFOX-4 and 25 daily fractions of 3D conformal radiotherapy at 1.8 Gy per fraction, totally 45Gy, were shown to be well tolerated and safe in fit patients with locally advanced gastric cancer after potentially curative surgery.

ACKNOWLEDGEMENTS

None declared.

COMPETING INTERESTS

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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Received: January 12, 2012 Revised: January 16, 2012 Accepted: January 18, 2012