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Response to neoadjuvant chemotherapy in locally advanced gastric and gastroesophageal cancer: Phase II clinical trial

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► ***Short report***

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ABSTRACT

Background: Gastric cancer is an important health problem across the world. Chemotherapy in combination with local treatment is standard treatment for locally advanced gastroesophageal cancers. The purpose of this investigation was evaluation of response and tolerability to neoadjuvant EOX regimen in locoregionally advanced gastric cancer. ***Materials and Methods:*** patients with locoregionally advanced gastric or EG junction adenocarcinoma enrolled in this study. Staging workup including chest and abdominal computed tomography (CT) scan, upper GI endoscopy, endoscopic ultrasonography (EUS), CEA, CBC, liver and renal function test were done. After treatment with 3 cycles of EOX regimen, endoscopic ultrasonography (EUS) and chest and abdominal CT scan was done to evaluate the response to neoadjuant chemotherapy. ***Results:*** The age of patients ranged from 37 to 78 years, with a mean age of 56.6 (SD=11.8). before chemotherapy, most patients were classified as stage III (98.8%) and after chemotherapy, most patients were classified as stage II (57.14%). only 28.5% of tumors were resectable before chemotherapy, but after chemotherapy 82.1% of tumors were resectable. 75% of tumors were downstaged after chemotherapy. ***Conclusion:*** With regard to acceptable response and downstaging of tumors and less toxicity with EOX regimen in locoregionally advanced gastric cancer, it seems that evaluation of this regimen as neoadjuvant chemotherapy in more advanced phase III clinical trial is necessary and logical.

Keywords: *Gastric cancer, gastroesophageal cancer, neoadjuvant chemotherapy, EOX regimen, ECF regimen.*

INTRODUCTION

Gastric cancer is an important health problem across the world, 930000 new cases and 700000 deaths are related to gastric cancer each year [1]. During the years 1996 through 2002, the 5-year survival rate for patients with gastric cancer was just 24% in the U.S. 31% and 33% of gastric cancer cases are in locally advanced and metastatic stages in the USA and 5-year survival rate is 22% and 3% at these stages respectively [2]. chemotherapy is the standard treatment for advanced gastroesophageal cancer; a systematic review and meta-analysis based on aggregate data in 2005 proved that chemotherapy improves survival versus best supportive care[3].

Neoadjuvant chemotherapy was firstly described for locally advanced nonresectable gastric cancer in 1989 [4]. In Europe, pre and perioperative chemotherapy became an acceptable treatment regarding the results of MAGIC trial in UK and ACCORD in France [5, 6]. Recently, studies showed that neoadjuvant chemotherapy increases the quality of life and decreases cancer related symptoms in unrespectable gastric cancers [7].

A recent systematic review indicate that

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treatment with systemic chemotherapy is associated with increasing quality of life, symptomatic relief and improve performance in many patients with inoperable gastric and gastroesophageal cancer [8]. In the MAGIC trial, three cycles of pre and postoperative chemotherapy of ECF (epirubicine, cisplatin and 5-FU) improved survival in contrast to surgery alone [5]. In another French trial, two or three cycles of preoperative and three or four cycles of postoperative cisplatin and 5-FU improved survival[6]. Neoadjuvant protocols including docetaxel, cisplatin and 5-FU (TCF); etoposide, cisplatin and 5-FU (EFP); etoposide, doxorubicine and cisplatin (EAP) have been studied in different clinical trials [7,8]. The randomized REAL-2 study for advanced and locally advanced gastroesophageal cancer, investigated the potential for substituting oral capecitabine for infusional 5-FU and oxaliplatin for cisplatin, in the classic ECF regimen. Data obtained from this study, demonstrated that the 5-FU and cisplatin components of ECF regimen maybe substitutable with capecitabin and oxaliplatin, without any decrease in efficacy [9].
since infusion of 5-FU for 21 days in ECF regimen has psychological and financial costs, we have decided to evaluate response and adverse effects of EOX regimen, a one day regimen with lower costs and psychological stress, in locally advanced gastric and esophagogastric cancer patients.

MATERIALS AND METHODS

This is a phase II clinical trial study (approved as assistant period thesis in Tehran university of medical sciences, research department in 10.09.2009 with number 88/21783) on patients with locally advanced gastric or gastroesophageal cancer, referred to our Cancer Institute during 2009-2010. Locally advanced disease was defined as T_3 and T_4 adenocarcinoma with or without lymph node involvement and also patients with T_{1-2} node positive disease.

Patient selection

Inclusion criteria includes histologically confirmed gastric or gastroesophageal adenocarcinoma, performance status ≥ 70 with Karnofsky score, normal kidney function (serum Cr ≤ 1.5 mg/dl), normal liver function (serum bilirubin ≤ 1.5 mg/dl) and normal bone marrow function (neutrophil count > 1500, platelet count > 100000 and hemoglobin > 10). Patients ineligible for inclusion in the clinical trial were those with M_1 or T_{1-2} N_0 carcinoma, peritoneal carcinomatosis (gross) or uncontrolled medical comorbidities and poor performance status (<70 with KPS).

Study was confirmed by medical ethics committee of the Tehran University of Medical Sciences and informed consent process was done. Staging workup includes chest and abdominal computed tomography (CT), upper gastrointestinal endoscopy with endoscopic ultrasonography (EUS), measurement of carcinoembryonic antigen (CEA), complete blood count, serum electrolytes, and liver and renal function tests. T and N classification was determined by EUS only. A surgical evaluation was performed before chemotherapy.

Chemotherapy

patients were treated with EOX regimen that consists of intravenous bolus epirubicin 50mg/m^2 on the first day, oxaliplatin 130mg/m^2 mixed in 500cc dextrose 5% water solution that be infused over 2 hours on the first day and capecitabine 625mg/m^2 orally twice daily, every day for 21 days. Antiemetic therapy includes intravenous granisetron and dexamethasone 3mg and 8mg respectively; oral vitamin B6 with dose of 100mg daily was also prescribed. The cycles repeated every 21 days on outpatient basis for 3 cycles. CBC was taken every week and biochemical profile was evaluated before each cycle of treatment. Granulocyte Colony Stimulating Factor (G-CSF) prescribed only as secondary prophylaxis in cases of neutropenia (neutrophil count <500). In cases of thrombocytopenia (platelet count < 100000) treatment was stopped and CBC was repeated every 48 hours. Doses of all drugs were

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diminished by 25% in cases of neutropenic fever, grade4 thrombocytopenia (platelet count <25000) or neutropenia (neutrophil count <500), grade 3-4 mucositis and refractory diarrhea or vomiting.

Response and toxicity evaluation

According to WHO criteria for Response, three weeks after third cycle of chemotherapy, response was evaluated by endoscopic ultrasonography (EUS) and chest and abdominal computed tomography (CT).

Toxicity including Anemia,thrombocytopenia, neutropenia, neutropenic fever, diarrhea, hand-foot syndrome and neuropathy also was evaluated according to NCI-CTC (National Cancer Institute Common Toxicity Criteria) during treatment.

After treatment with three cycles of chemotherapy non-responders who were free of metastases and peritoneal involvement, received chemoradiation. Palliative chemotherapy or supportive care was given to metastatic patients and patients who could not tolerate chemoradiotherapy.

Treatment after chemotherapy

Surgery was done four weeks after completion of neoadjuvant chemotherapy; eligible patients for surgery that were selected by physical exam, EUS and CT scan, underwent surgical gasterectomy with paragasteric (D1) lymphadenectomy. Curative resection was defined as removal of all gross disease and negative surgical margins. All surgical specimens underwent gross and microscopic examination for evidence of response to chemotherapy.

Postoperative chemoradiation was performed for margin positive, disease beyond T_2 or lymph node positive patients. Patients were received external beam radiation therapy with linac machine using 2D technique with one AP and one lateral field. radiation dose of 5040cGy in 28 days with concurrent bolus injection of 5-FU (400mg/m^2 daily on the first 4 days and last 3 days of radiation period) with leucovorin (30mg/m^2) was prescribed.

Statistical analysis

Data were analyzed with SPSS for Windows (version 13). For all analysis, $P < 0.05$ was considered statistically significant. Comparisons of preoperative characteristics, including tumor grade and tumor location for responders versus non responders were performed using Fisher`s exact test. Acturial survival was calculated using Kaplan-Meier method.

RESULTS

Between the years 2010 to 2011, 28 patients were enrolled in this phase II trial. Age of study group ranged from 37 to 78 years (mean 56.64, SD = 11.8). The majority of patients were male (n=22, 78.57%). 21.4% of patients revealed poorly differentiated adenocarcinoma (n=6) and in 67.8% of cases, tumors were in proximal location.

Table 1 shows patient characteristics before chemotherapy. Before chemotherapy, most patients were classified as stage III (92.8%) and only 28.5% of them were operable. All patients completed 3 cycles of neoadjuvant chemotherapy.

Table 2 shows patient characteristics after chemotherapy. After chemotherapy, most patients had stage II disease (57.14%) and 82.1% of them, were considered operable.

Table 1. patient characteristics before chemotherapy.

Patient characteristic	No.	Percentage %
Sex		
Male	22	78.57
Female	6	21.43
Pathologic differentiation		
Well	5	17.9
Moderately	3	10.7
Poorly	15	53.6
Signet ring	5	17.9
Tumor location		
Proximal	19	67.85
Distal	4	14.28
Diffuse	5	17.9
Baseline T classification		
T_2	1	3.6
T_3	10	35.7
T_4	17	60.7
Baseline N classification		
N_0	3	10.7
N_1	24	85.7
N_2	1	3.6

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Table 2. patient characteristics after chemotherapy.

Patients characteristics	No.	Percentage(%)
Postchemotherapy T classification by EUS		
T_2	5	18.52
T_3	18	66.66
T_4	4	14.81
Postchemotherapy N classification by EUS		
N_0	16	57.2
N_1	10	35.7
N_2	2	7.1
Pathological T classification		
T_1	1	7.6
T_2	2	15.38
T_3	10	76.92
pathological N classification		
N_0	9	69.2
N_1	4	30.8
N_2	0	0

After chemotherapy, EUS findings demonstrated downstaging of disease in 75% of the patients (21 patients) but 14.3% and 10.7% of patients had stable and progressive disease respectively (non responders). Non responders received chemoradiation and if they had metastasis or could not tolerate chemoradiation, received chemotherapy; 7 patients (60.7%) underwent chemoradiation. 10 of patients that underwent surgery, received adjuvant chemoradiation for different indications. Mean Radiation dose was 50.05 ± 0.14 Gy.

Table 3 shows correlations between disease characteristics and response to neoadjuvant chemotherapy. There are some disease characteristics that were correlated with a better response such as T or N stage, tumor grade, tumor location and level of serum CEA. Patients with serum CEA <5µg/l, T3N1, T4N1, distal tumors or tumors limited to cardia had a better response ($p < .005$).

Four weeks after chemotherapy, operable patients were determined by physical exam, laboratory tests, EUS and CT scan. 82.2% of the patients had resectable tumors (23 patients); of which 2 refused surgery, 5 were medically inoperable and 18 patients underwent surgery. At surgery, 5 were determined to be unresectable and 13 underwent curative surgery (46.4% of all patients). Of patients that underwent curative surgery, 10 had surgical involved margin or were T3 or T4 on pathologic exam and received adjuvant chemoradiation (50.4 Gy in 28 fractions with concurrent 5-FU and leucovorine).

During chemotherapy, 42.8% of the patients (12 patients) developed anemia, 7% of them had grade 3-4 anemia (2 patients) and received packed blood cell; 35.7% of the patients (10 patients) developed neutropenia, 25% grade 3-4 neutropenia (7 patients) and received G-CSF; 28.5% of the patients (8 patients) developed diarrhea, 10.7% grade 3-4 diarrhea (3 patients) and 32.1% of the patients (9 patients) developed nausea and vomiting, 7.1% grade 3-4 (9 patients). Because of these adverse effects, 21.4% of the patients had a pause in chemotherapy (6 patients).

During 9 months follow up, 64.2% of patients (18 patients) were disease free, 14.2% of them (18 patients) died because of the cancer and 14.2% of patients (4 patients) experienced recurrence and received palliative chemotherapy.

Table 3. Response to chemotherapy according to disease characteristics.

Disease characteristics	Responders	Non responders	P value
TN stage			
T_3N_1	87.5%	12.5%	P < 0.05
T_4N_1	71.4%	28.6%	P < 0.05
Others	50%	50%	P > 0.05
CEA level			
< 5	75%	25%	P < 0.05
> 5	63%	37%	P > 0.05
Location			
Cardia and proximal	68.4%	31.6%	P > 0.05
Others	75%	25%	P < 0.05

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DISCUSSION

Neoadjuvant chemotherapy offers a theoretical advantage over adjuvant chemotherapy. Chemotherapy maybe more efficient if given prior to surgical disruption of vasculature, tumor down staging may increase surgical successful resection, and it allows evaluation of the tumor chemo-sensitivity to cytotoxic drugs. Furthermore, patients may tolerate preoperative cytotoxic treatment better than post operative therapy, as performance status is usually negatively impacted by surgery. However, lack of response to neoadjuvant chemotherapy is the most important disadvantage of treatment.

Based on MAGIC and ACCORD trial that mentioned above, peri-operative chemotherapy for operable gastric and gastro esophageal cancer has became standard of clinical practice in many parts of Europe. However, it is clear that considerably more investigations are still required to improve pre and peri-operative chemotherapy with new chemotherapy regimens with regard to efficacy and toxicity. A recent systematic review indicate that treatment with systemic chemotherapy is associated with increasing quality of life, symptomatic relief and improve performance in many patients with inoperable gastric and gastro esophageal cancer [10]. Therefore, in terms of chemotherapy, there is no internationally accepted standard of care and significant therapeutic breakthroughs have not been achieved yet. However, in the past five years, new cytotoxic agents such as docetaxel, oxaliplatin, irinotecan, and capecitabine are utilized. In Japan, S_1 with or without a platinum compound has became the first-line therapy for advanced gastric cancer [12]. In many parts of Europe and Canada epirubicine is incorporated with 5-FU and a platinum compound (e.g. ECF). In Germany, colon- like regimens like biweekly cisplatin plus weekly leucovorin and 5FU (PLF) or biweekly oxaliplatin, leucovorin and 5FU (FLO) are used because they are considered to be more tolerable than cisplatin and 5FU that given every three weeks [13,14].

An algorithm of therapeutic strategies and their response for gastric and gastro esophageal cancer is shown in table 3. The only phase III trial that have evaluated EOX regimen in patients with advanced gastric cancer is Cunningham trial.

Although there is increasing evidence about EOX regimen in advanced gastric cancer, to the best our knowledge, this study is the first phase II Trial that have evaluated this regimen in locally advanced, not advanced, gastric cancer; so we have to compare our results with the results of phase III trials in advanced gastric and gastro esophageal cancer. Comparison between non-homogeneous groups may cause different results about response rate. As it is clear in table 4, response rate is highest in this trial (75%) which may be due to non-homogenous comparison groups. Therefore, our results must be supported with phase III trial that will compare EOX regimen with other regimens as neoadjuvant chemotherapy in locally advanced gastric cancer.

Table 5 shows a comparison of toxicity profiles between our study and Cunningham trial in term of EOX regimen toxicity. This table shows that we had less toxicity with EOX regimen in comparison to Cunningham study. Hand and foot syndrome and complicated neutropenia were observed only in 7.1% and 0% respectively. Utilizing vitamin B6 and monitoring of patients during therapy, may explain more favorable complications.

Table 4. Results of this trial in comparison with other related trials [11, 12, 9].

Therapy scheme	XP	FP	FLO	PLF	EOX	ECF	EOF	ECX	EOX
No. patients	166	150	112	108	244	263	245	250	28
Author	Kang		Al-Batran		Cunningham				this study
Percentage of LA	?	?	2.7	9.3	24.3	20.5	23	23.2	92.8
Response rate %	41	29	35	24.5	47.9	40.7	42.4	46	75
MOS (month)	10.5	9.3	10.7	8.8	11.2	9.9	9.3	9.9	

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Table 5. Adverse effects of EOX regimen in comparison with Cunningham study [9].

	Cunningham study		Current study	
Toxicity	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)	All grades (%)
Anemia	8.6	64.2	7	40.7
Thrombocytopenia	5.2	21.1	0	10.7
Neutropenia	27.6	62.6	25	35.7
Febrile neutropenia	7.8	9.8	0	0
Diarrhea	11.9	61.7	10.7	28.5
Nausea and vomiting	11.4	78.9	7.1	32.14
Hand and foot syndrome	3.1	39.3	0	7.1
Peripheral neuropathy	4.4	83.7		

CONCLUSION

With regard to feasibility to use EOX regimen on outpatient basis and acceptable response and downstaging of tumors and less toxicity with this regimen in locoregionally advanced gastric cancer, it seems that evaluation of this regimen as neoadjuvant chemotherapy in more advanced phase III clinical trial in non metastatic gastric cancer is necessary and logical.

Conflicts of interest: *none to declare.*

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