The Phase 2 Study of "(TOX) Preoperative Chemotherapy" Response Rate and Side Effects in [Locally Advanced Operable Gastric Adenocarcinoma] Patients With Docetaxel, Oxaliplatin and Capcitabine

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Abstract

Background: Early stage gastric cancer diagnosis has ensued different approaches in resection strategies. In order to increase the proportion of cases which have undergone radical resection or have reduced the recurrence rate, different pre-operative treatments have introduced. Here, we have verified an active preoperative chemotherapeutic regimen in locally advanced gastric cancer patients.

Methods: Forty nine patients who have found eligible to enter this phase 2 trial have treated with oxaliplatin 100 mg/m^2 IV, docetaxel 50 mg/m^2 IV, plus capecitabine 625 mg/m^2 PO (TOX). Clinical staging has been following the first 2 cycles of induction chemotherapy. Patients that have further undergone radical surgery, have evaluated for pathological response rate.

Results: Anemia (10.2%), nausea (10.2%) and vomiting (6.1%) were the most frequent grade 3 or 4 adverse effects. Regarding the pathologic staging, 6 patients (12.2%) had complete response (95% CI 3% to 21.4%), 18 of them (36.7%) had partial response (95% CI 23.2% to 50.2%), then 3 patients (6.1%) had stable disease (95% CI 0%-12.8%). Among the patients who had surgery, 22% had pathologic complete response.

Conclusion: Preoperative chemotherapeutic regimen of TOX seems to be an active and safe neoadjuvant therapy in non metastatic gastric cancer. It should further be considered with concurrent radiotherapy.

Keywords: Preoperative period; Chemotherapy; Neoadjuvant Therapy; Stomach neoplasm

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Introduction

More than 70% of new cases in Gastric Cancer (GC) have found in the developing countries, causing 10% mortality of global cancer mortality rate [1]. It counts as the 1st common cancer in Iranian male, but the 3rd in Iranian female population respectively [2]. Nowadays, more cases of early stage GCs have diagnosed; and this has raised therapeutic challenges among the oncologists [3]. Postoperative chemotherapy could not be qualified for all cases, while more than 50% of these patients have experienced recurrence or metastasis after primary treatment [4].

In order to decrease this recurrence, after radical resection at early stages, preoperative chemotherapy regimens have introduced. They have revealed advantages of such treatments in comparison to surgery [5-6]. Regarding to high locoregional relapse of GC, a sufficient regimen would decline the relapse rate and improve the survival.

Several studies have demonstrated better clinical and pathologic responses in locally advanced GCs recruiting preoperative chemoradiotherapy with experienced doses [4, 7, 8]. Neoadjuvant chemotherapy has considered as potential treatment opportunity for not only resectable GCs but also

particularly eliminate micrometastases [9]. Cisplatin plus S1 [9] or irinotecan [10] are among the evaluated regimens. Docetaxel in combination with cisplatin showed additive effects in treatment of GC despite its increased toxicities [11]. If oxaliplatin has replaced with cisplatin in combination with docetaxel, it has shown promising results with lower toxicity [12]. Also capecitabine plus docetaxel substituted for 5-FU, has shown well experienced active regimen for advanced GC treatment [13].

We investigate an active preoperative regimen to combine more aggressive induction chemotherapy among the non-metastatic GC patients, that at least these patients do not need night admission or hospitalization. Our primary objective is describing the adverse effects occurring through the treatment courses. The secondary objective is evaluation of the response rate in such regimens (clinically and pathologically).

Materials and Methods

This phase 2 trial has initiated in June 2008 with both "Fayyazbakhsh Hospital" and "Dr Yahyazadeh's Oncology Clinic" participation, Tehran, Iran. It has continued till March 2011. This trial was registered at ClinicalTrials.gov with identifier number of NCT01672333.

Patients:

Patients with histological diagnosis of gastric adenocarcinoma or Gastroesophageal Junction (GEJ) adenocarcinoma without any previous treatment have selected to enter the study. Other inclusion criteria were: T1 or T2 with N+, T3 or T4 with any N and non metastatic condition (M0) (according to the American Joint Committee on cancer TNM system 6th edition), age between 18-70 years, performance status 0-1 (according to Eastern Cooperative Oncology Group (ECOG) criteria), adequate bone marrow, liver and renal function (hemoglobin≥11 g/dl, platelets ≥100000/mm^3, absolute neutrophil count≥1500/mm^3, normal bilirubin, normal transaminases, normal creatinine), absence of active co-morbid illness (uncontrolled infection, uncontrolled diabetes mellitus, cardiopulmonary disease). Patients have excluded if they had any other malignant diseases within the past 5 years or if they were pregnant or breast feeding.

This study was in accordance with the declaration of Helsinki. All the patients have provided informed consent prior to any treatment and have fully described about the study purpose. The protocol has reviewed and approved by Milad Hospital review board.

Pretreatment Evaluation:

Complete initial work up within 2 weeks prior to first infusion has done. Medical history and physical examination has evaluated. Baseline laboratory tests and imaging have carried out that included: pregnancy test if applicable, CBC, AST, ALT, total bilirubine, creatinine, total protein, albumin, CEA, CA19-9, chest X-ray for gastric and chest CT scan for GEJ, abdominopelvic spiral triphasic CT scan, upper GI endoscopy and Endosonography (EUS). Neurology and cardiology consult has also done. Clinical and paraclinical staging has conducted considering imaging evaluations.

Study Procedures:

Treatment Plan

Two courses of chemotherapy have initiated three weeks apart with following doses: oxaliplatin 100 mg/m^2 IV over 2 hours at 1st day, docetaxel 50 mg/m^2 IV over 1 hour at 1st day, plus capecitabine 625 mg/m^2 PO for 14 days. Patients have evaluated after 2 courses and those with the progressive disease have proceeded to immediate surgery. Otherwise, treatment has continued for a total 4 courses in absence of unacceptable toxicity or disease progress. These patients have undergone gastric resection within 3-5 weeks, after the last course of chemotherapy patients have evaluated on following variables every week during chemotherapy:

ECOG Performance Status (PS), physical examination, CBC, AST, ALT, total Bilirubin, creatanin (only during induction chemotherapy), neurologic examination and weight.

Premedications

Anti emetics, consisted of granisetron 3 mg and dexamethason 20 mg IV, has prescribed 30 minutes before chemotherapy. G-CSF as prophylaxis or as curative therapy has considered optional. Erythropoietin alpha administration considered at physician's prescription. Also blood transfusion has considered if Hb≤10g/dl.

Surgery

If patients would be suitable for surgery (without any exclusion, or prohibited criteria), they should undergone a radical total or subtotal D1 gaseterctomy.

These patients have undergone gastric resection within 3-5 weeks, after the last course of chemotherapy, and of course after side effects healing.

Patients with persistent local tumor, or who experienced poor performance status or other medical problems, have referred for further non-surgical treatment.

Safety Evaluation

All patients who have received at least one dose of this study medication, and the group that their follow-up data was available, have considered as evaluable for safety. CBC, renal and liver functions' toxicities have recorded on first day of each cycle. Maximum grade (severity) has reported by cycle and by patient. Non hematological toxicities have recorded frequently, in each cycle. Maximum grade or severity has reported by cycle and by patient. Toxicity has graded according to WHO criteria. No dose reduction has allowed.

Clinical Response

Clinical response based on RECIST criteria. Accuracy of response has evaluated by CT scan and endosonography. Each patient with more than 2 weeks delay within the induction chemotherapy has not included in response evaluation and has sent off from the study.

If the clinical evaluations after induction chemotherapy have shown no evidence of disease involvement, or decreased level of involvement, or without change, it has respectively considered as Complete Response (CR), Partial Response (PR) and Stable Disease (SD). If the level of involvement has increased, it has considered as Progressive Disease (PD).

Statistical Methods

Regarding the pathological complete response rate of more than 35% (null hypothesis, 20%), 49 patients have required with a power of 81% and α=0.05. Our primary outcome was to determine the clinical response rate after induction chemotherapy. Our secondary outcome was to determine the pathological response rate after 4 total cycles of chemotherapy. Related toxicity and adverse effects have followed. Descriptive data have reported as frequencies and median.

Results

Several patients have assessed for eligibility to enter our study from June 2008 to March 2011. Forty nine have found to adjust our criteria. The remaining were not eligible due to the following reasons: advanced disease, gastrointestinal obstruction, comorbid cardiopulmonary insufficiency, comorbid renal insufficiency, performance status greater than" 1".

The characteristics of eligible patients have summarized in Table1and their flow chart is shown in Figure 1. The median age was 61 years (range: 27-69). Most of the patients had PS of 0.

Distribution of adverse effects during all the chemotherapy cycles has reported in details in Table 2. The most common grade 3 or 4 toxicity were anemia and nausea followed by vomiting, hand-foot syndrome and dysuria. There were several cases of adverse effects that occurred in lower grades (<3) which have treated with antiemetics, G-CSF, erythropoietin alpha and blood transfusion if needed. One of our patients experienced Cerebro-Vascular Accident (CVA) during the treatment time, then died unfortunately.

After the first two courses of chemotherapy (induction chemotherapy) patients have clinically assessed for staging. Eight patients (16%) have found with Progressive Disease (PD), 30 of them (61%) had Partial Response (PR) and 11 patients (23%) had Stable Disease (SD). Forty one cases who did not experience PD, received the full chemotherapeutic cycles with the median number of 4 (range: 4-6). There was no Dose Limiting Toxicity (DLT) experienced during the study. All adverse effects with a grade greater than "2" could be successfully treated. Among the 41 patients, 14 of them could not undergone surgery due to the following reasons: patients' inappropriate medical state (n=8), death (n=3), and withdrawal of consent (n=3).

The pathologic stage of 27 patients with CR, PR and SD who undergone surgery has shown in Table 3 (compared with their primary clinical stage).

Regarding the pathologic staging; 6 patients (12.2%) had complete response (CR, 95% CI 3% to 21.4%), 18 of them (36.7%) had PR (95% CI 23.2% to 50.2%), and 3 patients (6.1%) had SD (95% CI 0%-12.8%). Among those patients who had surgery, 22% had pathologic complete response.

Table 1. Patients overall characteristics

		Number	Percentage
Gender			
	Male	37	24.5
	Female	12	75.5
Performance status			
	0	38	77.5
	1	11	22.5
Site of tumor			
	Antrum	7	14.3
	Body	11	22.4
	Cardia	25	51.0
	Fundus	5	10.2
	Pyloris	1	2.0
Clinical stages			
	T3N0	1	2.0
	T3N1	24	49.0
	T3N2	7	14.3
	T3Nx	3	6.1
	T4N0	0	0.0
	T4N1	8	16.3
	T4N2	3	6.1
	T4Nx	3	6.1

T3, The tumor is growing into the subserosa layer; **T4,** The tumor has grown into the serosa and may be growing into a nearby organ or other structures; **NX,** Nearby (regional) lymph nodes cannot be assessed; **N0,** No spread to nearby lymph nodes; **N1,** The cancer has spread to 1 to 2 nearby lymph nodes; **N2,** The cancer has spread to 3 to 6 nearby lymph nodes.

Table 2. Grade 3 or 4 adverse effects

		Number (49)	Percentage
Hematologic			
	Anemia	5	10.2
	Leukopenia	-	-
	Thrombocytopenia	-	-
Non-hematologic			
	Nausea	5	10.2
	Vomiting	3	6.1
	Anorexia	-	-
	Stomatitis	-	-
	Diarrhea	-	-
	Abdominal pain	-	-
	Neuropathy	-	-
	Fatigue	-	-
	Dysuria	1	2
	Hand–foot syndrome	2	4.1
	Dysphagia	-	-
	Cerebrovascular accident	1	-

Table 3. Pathologic staging in patients who underwent surgery

Clinical Stage	Pathologic Stage						Total Surgery	Total Non-Surgery
	T0	T1	T2	T3	T4	Tx		
T3	7	1	6	10	-	-	24	11
T4	-	-	-	3	-	-	3	11
Total							27	22
	N0	N1	N2	Nx				
N0	-	-	-	-			0	1
N1	12	4	-	1			17	15
N2	4	2	1	-			7	3
Nx	1	2	-	-			3	3
Total							27	22

TX, The main (primary) tumor cannot be assessed; **T0,** No signs of a main tumor can be found;**T1,** The tumor has grown from the top layer of cells of the mucosa into the next layers below such as the lamina propria, the muscularis mucosa, or submucosa; **T2,** The tumor is growing into the muscularispropria layer; **T3,** The tumor is growing into the subserosa layer; **T4,** The tumor has grown into the serosa and may be growing into a nearby organ or other structures; **NX,** Nearby (regional) lymph nodes cannot be assessed; **N0,** No spread to nearby lymph nodes; **N1,** The cancer has spread to 1 to 2 nearby lymph nodes; **N2,** The cancer has spread to 3 to 6 nearby lymph nodes.

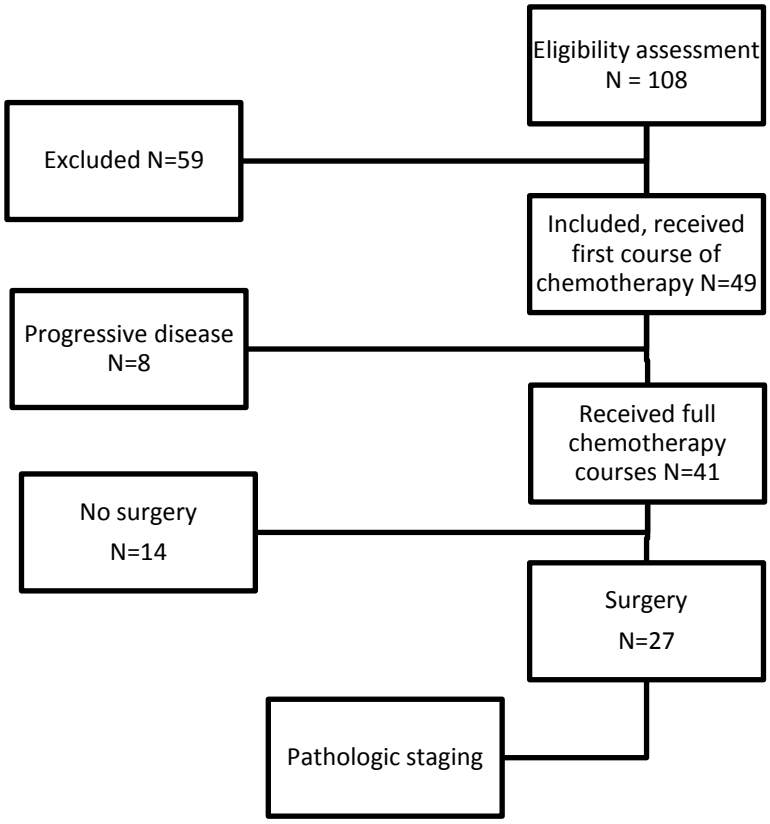

Figure 1. It is the flow chart of participants over the course of the trial.

Discussion

We have conducted a single center phase 2 study to evaluate the response rate and safety profile of a combination of docetaxel, oxaliplatin and capecitabine (TOX). This neoadjuvant regimen along with surgery has tested in 49 locally advanced GCs as a preoperative treatment. Combination modalities, with preoperative or postoperative chemotherapy, used for the minority of patients with locally advanced cancers have revealed better prognosis in comparison with tumor resection [5, 6, 14]. These studies have suggested new care standards for such above patients. However, it seems that postoperative approaches could be applied in cases that undergo radical gastrectomy, although in most of them it has not performed at quality optimum levels.

We have prescribed the chemotherapeutic agents at recommended doses, in which other studies have not found any limiting toxicity (DLT) [3, 15, 16]. Higher doses, however, at 75 mg/m^2 of docetaxel and 130 mg/m^2 of oxaliplatin, have revealed 16% DLT [3]. In explained doses of TOX regimen, have shown promising results, with 12.2% and 36.7% of pathological CR and PR in respect. TOX regimen has well experienced by the patients, noticing that there was no treatment associated deaths.

Among the other trials, this study has tried to establish a standard preoperative chemotherapy regimen, could be applicable in most of the cases. Staging methods has considered here, by employing EUS and CT-scan, have been reported helpful for predicting the outcome of neoadjuvant chemotherapy in locally advanced GCs [17, 18].

In 2002, a study on 12 patients has reported the advantages from replacement of oxaliplatin with 5-FU/Leucovorin in colorectal cancers, not only providing an active treatment but also reducing the side effects [19]. Kang et al. [20] has found that capecitabine could efficiently replaced 5FU in GCs. Its oral rout prescription has caused its participation among a plenty of trials thereafter. Docetaxel in combination with oxaliplatin has usually used in a plenty of GC treatments, in early or advanced levels, with or without radiotherapy [3, 13, 15, 16].

The most frequent adverse effects in our study, have reported as: anemia and nausea vomiting, that were in concordance with previous studies recruiting similar regimens [13, 15, 16] and studies which prescribed neoadjuvant preoperative chemotherapy [4]. Hand-foot syndrome occurred in 2 patients as we have included oxaliplatin in our regimen. Our pathological CR rate (12.2%) has found to be comparable with several similar studies in preoperative chemoradiation therapies in esophageal cancer (pathological CR of 21%) [21]. Treatment with the same regimen plus radiation in Spigel et al's study [22] have shown better results (pathological CR 49%) in esophageal cancer, however, concurrent radiation seems to influence the results.

Neoadjuvant chemotherapy in locally advanced GCs has found to notably increase the rate R0 resection, however could not improve the overall survival rate if has not accompanied by adjuvant therapies [23]. In locally advanced GCs ,"tumor size and differentiation" have reported as the main tumor predictor factors response to neoadjuvant chemotherapy [24].

However, in gastric adenocarcinoma, after neoadjuvant chemotherapy and resection, the risk of recurrence and cancer specific death in patients with pathological complete response stays high. Almost one third have symptomatic CNS recurrence. This indicates the necessity of follow-up studies in such patients [25].

The results of this study should be carefully interpreted due to small number of patients investigated and wide CIs found. Forty five percent of all eligible patients could not make it to surgery due to several causes including disease progress, inappropriate medical status, early death and withdrawal of consent. However, noticeable numbers (55%) could undergone surgery.

In conclusion, preoperative chemotherapeutic regimen of oxaliplatin 100 mg/m^2 IV, docetaxel 50 mg/m^2 IV, plus capecitabine 625 mg/m^2 PO seems to be an active and safe treatment. It could considered to be evaluated in other phase 2 trials. It could be also considered for phase 1 trials with concurrent radiotherapy.

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Conflict of Interest

The authors have no conflict of interest to declare.

Authors' Contribution

Seyyed-Hossein Yahyazadeh-Jabbari contributed in conception and design, data collection, analysis and interpretation of data and writing the manuscript. Nasser Malekpour contributed in conception and design, data collection and critical

revision of the manuscript. Bahram Salmanian contributed in conception and design, data collection, statistical analysis and writing the manuscript. Hossein Foodazi contributed in conception and design, data collection, analysis and interpretation of data and writing the manuscript. Masoud Salehi contributed in data collection, statistical analysis and critical revision of the manuscript. Farsad Noorizadeh contributed in data collection, analysis and interpretation of data and critical revision of the manuscript.

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