

## **Comparative analysis of integrated chemotherapy regimens in treatment of end-stage gastric cancer.**

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### **Abstract**

**Objective:** To compare the clinical efficacy and safety between doublet and triplet neo-adjuvant chemotherapy regimens for patients with unresectable advanced gastric cancer.

**Methods:** All patients diagnosed with unresectable advanced gastric cancer were randomly divided into doublet (group A) and triplet groups (group B). In group A, patients received two kinds of chemotherapy drugs and their counterparts in group B were administered with three kinds of chemotherapy drugs. The primary-endpoint was the rate of patients converted to resection for unresectable advanced gastric cancer. The secondary-end points included the response rate of the neo-adjuvant chemotherapy, survival and adverse events.

**Results:** In total, 288 patients admitted to the Affiliated Hospital of Changchun University of Traditional Chinese Medicine were recruited in this study and divided into group A (n=140) and B (n=148). The response rate after preoperative chemotherapy between two groups were 48.6% and 48.7% respectively (P=0.981). After 4 rounds of chemotherapy, 78 patients (55.7%) in group A received R0 surgery and 62.1% patients (92/148) in group B underwent radical operation. The median duration of follow-up was 17.5 months (range 3.3 to 71.5 months). The median progression-free survival (PFS) of two groups were 15.0 months and 14.0 months (P=0.442). The Overall Survival (OS) between groups A and B was the same (29.1 months and 30.0 months, P=0.144). Group B had more serious adverse effect in leukopenia, fatigue and vomiting, etc.

**Conclusions:** For unresectable advanced gastric cancer, more effective interventions including triple chemotherapy drugs did not produce more benefit on survival and other clinically relevant outcomes, and had more toxic effect.

**Keywords:** Locally advanced gastric cancer, Chemotherapy, Doublet, Triplet.

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### **Introduction**

Recently, the prevalence of gastric cancer decreases and it is still among the highest mortality rate. Generally, gastric cancer patients are diagnosed with advanced stage involved with adjacent structures [1]. For those fail to tolerate radical surgery during initial diagnosis due to advanced stage, their clinical prognosis is relatively poor [2].

Previous investigators have found that treatable gastric cancer can be effectively managed with neoadjuvant chemotherapy [3]. Multiple chemotherapy regimens have been applied to decrease the tumor staging and increase their survival [4,5]. In a trial from the UK, three courses of pre-operative chemotherapy using epirubicin, cisplatin and 5-Fluorouracil (5-Fu) improve the survival compared with surgery alone [6]. In recent years, supplement of docetaxel to 5-Fu and cisplatin has

been proven to enhance clinical prognosis of such population in the Europe, USA, and other countries. [3,7]. Though the response rate of these combined regimes consisting of three drugs was alarmingly high, the risk of neutropenia and febrile neutropenia was significantly increased. Doublet regimen such as capecitabine+oxaliplatin and S-1+cisplatin [8,9] yields a high response rate and slight adverse events. The clinical efficacy of treatment consisting of three chemotherapy drugs remains to be elucidated in clinical settings [10].

The goal of this clinical trial is to compare the clinical efficacy and safety between the doublet and triplet neoadjuvant chemotherapy regimens in the treatment of resectable advanced gastric tumors following radical surgery.

## Materials and Methods

### Baseline data

During January 2013 and December 2014, clinical data of patients diagnosed with topically advanced gastric cancer were prospectively analysed during the initial diagnosis in our institution. Inclusion criteria: Those with gastric or gastroesophageal adenocarcinoma validated by histochemical staining; (2) Bulky lymph nodes ( $\geq 3 \text{ cm} \times 1$  or  $\geq 1.5 \text{ cm} \times 2$ ) along with the splenic, celiac, the superior mesenteric vein, and common/proper hepatic artery; The macroscopic tumor type is neither the Borrmann type 4 nor large (8 cm or more) type 3. Tumors invade into surrounding structures (T4b); those received at least 1 cycle of chemotherapy and at least one Computed Tomography (CT) scans evaluation. Exclusion criteria: Peritoneal metastasis (gross or microscopic); Tumor metastatic to the lung, liver or other sites, with pleural effusion; Serious uncontrolled co-morbid conditions; No target lesion; No CT evaluation; Multidisciplinary evaluation was performed prior to patient enrolment. Written informed consents were obtained from all participants. The study procedures were approved by the ethics committee of our hospital.

### Chemotherapy schedule

Chemotherapy was administered as the first-line treatment. The chemotherapy regimen was determined by the surgeons and oncologists. The regimens of chemotherapy for the two groups were listed in Table 1. The primary regimen consisted of capecitabine was orally administered at a dose of 1000 mg/m<sup>2</sup> twice daily from 1-14 d followed by resting for 1 w, and intravenous administration of oxaliplatin at a dose of 130 mg/m<sup>2</sup> on 1 d (XELOX). Alternative regimens consisted of mFolfox6 (intravenous infusion of oxaliplatin at a dose of 130 mg/m<sup>2</sup> on d 1 and intravenous infusion of leucovorin 400 mg/m<sup>2</sup> on d 1 followed by continuous intravenous infusion of 5-fluorouracil 2,400 mg/m<sup>2</sup> for 46 h repeated every 2 w, S-1+docetaxel (docetaxel 40 mg/m<sup>2</sup> on d 1, given by intravenous infusion, S-1: 40 mg, bid when the Body Surface Area (BSA) was  $<1.25 \text{ m}^2$ ; 50 mg, bid when the BSA was between  $1.25 \text{ m}^2$  and  $1.5 \text{ m}^2$ ; 60 mg, bid when the BSA was  $>1.5 \text{ m}^2$ , repeated every 3 w), EOX regimen (epirubicin 50 mg/m<sup>2</sup> on d 1, given by intravenous infusion; oxaliplatin, 130 mg/m<sup>2</sup> on d 1, given by intravenous infusion; capecitabine, 625 mg/m<sup>2</sup> orally administered twice a day on d 1-14 followed by 1 w rest; repeated every 3 w), DOF (docetaxel 50 mg/m<sup>2</sup> on d 1, given by intravenous infusion; intravenous infusion of oxaliplatin at a dose of 85 mg/m<sup>2</sup> on d 1; intravenous infusion of leucovorin 400 mg/m<sup>2</sup> on d 1 followed by continuous intravenous infusion of 5-fluorouracil 2,400 mg/m<sup>2</sup> for 46 h, repeated every 2 w. The chemotherapy endured until patients could undergo radical operation, disease progression or non-tolerable adverse events. Patients presenting with disease progression were treated after the surgeons achieved consensus.

### Response rate and toxicity assessment

Following different cycles of chemotherapy, patients received abdominal CT scan to assess the response rate and determine whether radical surgery is necessary. Tumor response rate was assessed based upon the assessment criteria of RESIST 1.1 [11]. An absence of carcinoma cells in the primary site was defined as path CR (pathologic complete response), and  $<10\%$  residual carcinoma cells in the specimen was defined as path PR (pathologic partial response) [12]. The severity of adverse events was evaluated based upon NCI-CTC 3.0 [13].

### Surgical procedures

According to the site and severity of the gastric cancer, the choice of operation can be determined. The malignant tumor was removed with  $\geq 5 \text{ cm}$  from the stomach margin. Subtotal gastrectomy was conducted for those with distal metastasis. Total esophagogastrectomy or gastrectomy was considered for adjacent malignant tumors. D2-type nodal dissection was also performed when necessary.

### Postoperative interventions

After R0 resection, adjuvant chemotherapy with original regimen was performed within postoperative 40 d. Six cycles of chemotherapies were delivered perioperatively. Palliative chemotherapy was performed for those failing to tolerate radical surgery until disease progression. If adjuvant radiotherapy should be administered after R0 resection was decided by the physicians. Postoperative follow-up was performed on a regular basis. Physical examination was delivered with a time interval of 3 months. Abdominal CT was performed once half a year. Chest CT scan and endoscopy of the upper gastrointestinal were performed each year.

### Statistical analysis

Conversion rate to radical resection in unresectable patients was considered as the primary end-point event evaluated after two or three cycles of chemotherapy. The response rate, Progression-Free Survival (PFS), Overall Survival (OS) and adverse events were defined as the secondary end-point events. Baseline data and relevant factors were analysed by descriptive statistical method. Categorical parameters were statistically compared using Fisher's exact test. The mean values of PFS and OS were compared by log-rank test. SPSS statistical software 19.0 was utilized for statistical analysis (SPSS, Chicago, IL). A P value of  $<0.05$  was considered as statistically significant.

## Results

### Baseline characteristics

During November 2012 and January 2015, 288 patients were enrolled in the study. All patients had full information of follow-up. The baseline characteristics of the patients are shown in Table 1. The two groups had good balance in the

items of gender, age, KPS status, site of location, histologic subtype, causes of unresectable reason, clinical stage.

### Chemotherapy response

After a median of 4 cycles and 12 w of chemotherapy, 283 patients had response evaluations (one did not because of acute perforation of stomach five days after the first regimen of chemotherapy). There was no difference in two groups. In group A, one person had a Complete Response (CR), 66 had Partial Responses (PR), 50 had Stable Disease (SD), and 20 had Progression of Disease (PD). The Response Rate (RR) was 48.6% and Disease Control Rate (DCR) was 84.3% (Table 2).

### Surgical findings and pathological staging

As illustrated in Table 3, after evaluation of resectability by multidisciplinary team, 90 patients in group A and 106 in group B could receive operation. However, R0 resection could not be obtained at exploration for 72 patients (24 in group A; 48 in group B). Ultimately, 78 patients in group A and 92 in group B achieved an R0 resection. Nevertheless, the rate of resection with curative intent was similarly in two groups (55.7% vs. 62.1%, P=0.061). The median time from end of chemotherapy to surgery was 30 d (range 16 to 37) and 28 d (range 16 to 45), which was similar in two groups (P=0.561).

In the patients who had radical operation, 96 cases in group A (96/156, 61.5%) had pathological responses and 8 (8/156, 5.1%) had complete pathological responses (pCR). While 120 in group B (120/184, 65.2%) had pathological response and 4 of them (4.3%) had pCR. Down-staging effect could be observed similarly between two groups regarding the ypT (43.6% vs. 52.2%, P=0.430) and N-categories (41.0% vs. 50.0%, P=0.408). The median time from surgery to discharge was 11 d (8-72 d) and 10 d (7-25 d) respectively. Two cases in group A and 6 in group B had postoperative complications described as lung infection and pancreatic fistula after surgery. A proportion of 74.3% (58/78) and 82.6% (76/92) patients who got radical surgery had D2 lymphadenectomy respectively. The median number of dissected lymph nodes (72 in group A; range 14 to 61, vs. 68 in group B, range 9 to 56) was similar in both groups. Lymph nodes metastasis was also the same in

group A (48/78, 61.5%) and group B (62/92, 67.4%; P=0.819). The median number of positive lymph nodes was 6 (range from 0 to 28) in group A and 4 (range from 0 to 26) in group B.

### Patients' survival

After postoperative 17 month-follow-up (range 3.3-71.5 months), a total of 196 cases presented with disease progression or recurrence, and 142 cases died. The median survival rate in both arms was reliable due to the <50<sup>th</sup> percentile. Patients in group A experienced similar PFS (15.0 vs. 14.0 months, P=0.442) and OS (29.1 vs. 30.0 months, P=0.144) with those in group B.

### Subgroup analysis

Patients who could not have radical surgery in two groups had similar PFS (5.6 vs. 4.4 months, P=0.338) and OS (13.3 vs. 11.5 months, P=0.69). The survival of patients undergoing radical operation had not reached in group B, while the PFS and OS in group A were 23.7 months and 39.0 months. There was not significant survival difference in two groups regard to PFS (P=0.314) and OS (P=0.336). XELOX (98/140, 70.0%) and EOX regimens (110/148, 74.3%) were the most commonly used doublet and triplet regimen for gastric cancer in our study. Regardless of whether the combined chemotherapy regimen was XELOX or EOX, neither treatment regimen yielded a significant PFS (10.7 months vs. 14.0 months, P=0.38) and OS (27.0 months vs. not reached, P=0.71).

### Adverse events

Mild adverse events occurred in both groups, as illustrated in Table 4. No case died from chemotherapy or surgery. Gastrointestinal symptoms and leukocytopenia were the primary adverse events. Triplet group had more serious adverse effect in leucopenia (8.6% vs. 20.3%, P=0.047), fatigue (2.9% vs. 12.2%, P=0.036) and vomiting (1.4% vs. 9.5%, P=0.035). One patient presented with acute gastric 5 d after the first cycle of chemotherapy. Four postoperative complications occurred in patients undergoing surgery perioperatively.

**Table 1.** Baseline data of the enrolled patients.

Baseline parameters	Group A: with two drugs (N=140)	Group B : with three drugs (N=148 )	P value
Gender (N)			
Male	49/70.0%	57/77.0%	
Female	21/30.0%	17/23.0%	0.339
Age (median year, range)			
Median	58	56	0.321
Range	18-77	30-75	
>60	34/48.6%	29/39.2%	0.257

Location (N)			
Gastroesophageal junction	34/24.3%	24/16.2%	
Stomach	106/75.7%	124/83.8%	0.382
Lauren type (N)			
Intestinal type	82/58.6%	70/47.3%	
Diffuse type	20/28.6%	30/40.5%	
Mixed type	9/12.8%	9/12.2%	0.307
Median cycles of treatment	4 (1-6)	4 (2-6)	0.865
CEA (N)			
Normal	48/34.3%	46/31.1%	
Elevated	92/65.7	102/68.9%	0.682
Causes of unresection			
T4b	26/18.6%	38/25.7%	
Borrmann type 4 or large type 3	28/20.0%	34/23.0%	
Bulky lymph nodes	86/61.4%	76/51.3%	0.446
Clinical T stage			
cT3	14/10.0%	22/14.9%	
cT4	126/90.0%%	126/85.1%	0.378
Clinical N stage			
cN1	46/32.9%	58/39.2%	
cN2	40/28.6%	30/20.3%	
cN3	54/38.5%	60/40.5%	0.483

**Table 2.** Comparison of response rate between two groups.

	Group A: with two drugs (N=140)		Group B : with three drugs (N=148 )		P value
	No.	%	No.	%	
Response evaluation					0.981
CR	2	1.4	2	1.4	
PR	66	47.2	70	47.3	
SD	50	35.7	58	39.2	
PD	20	14.3	18	12.1	
Not assessable	2*	1.4	0	0	
ORR (CR plus PR)	68	48.6	52	48.7	0.102
DCR (CR plus RR plus SD)	118	84.3	130	87.9	0.538
Patients received surgery					0.061
Radical surgery	78	55.7	92	62.2	
Palliative surgery	12	8.6	24	16.2	

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**Table 3.** Comparison of surgical efficacy between two groups.

	Patients received radical surgery in group A (n=78)		Patients received radical surgery in group B (n=92)		
Pathological response					0.725
Responders	46	61.5	60	65.2	
pCR	4	5.1	4	4.3	
Patients received D2 lymphadenectomy	58	74.4	76	82.6	0.233
Median total nodes	36 (14-61)		34(9-56)		0.754
Median positive nodes	6 (0-28)		4(0-26)		0.421
Median time from end of treatment to surgery	30 (16-37)		28(16-45)		0.561
Median time from surgery to discharge	11 (8-72)		10(7-25)		0.752
Pathological T stage					0.547
pT0	4	5.1	6	6.5	
pT1	6	7.7	6	6.5	
pT2	8	10.3	22	23.9	
pT3	20	25.6	22	23.9	
pT4	40	51.3	36	39.2	
Pathological N stage					0.819
pN0	30	38.5	30	32.6	
pN1	10	12.8	20	21.7	
pN2	12	15.4	10	10.9	
pN3a	14	17.9	16	17.4	
pN3b	12	15.4	16	17.4	
Patients with T downstage	34	43.6	48	52.2	0.43
Patients with N downstage	32	41	46	50	0.408

\*One did not have response evaluation because of acute perforation of stomach five days after the first regimen of chemotherapy.

**Table 4.** Comparison of grade 3/4 adverse events between two groups.

Toxicities	Group A: with two drugs (N=140)		Group B: with three drugs (N=148 )		P value
	No.	%	No.	%	
Leukocytopenia	12	8.6	30	20.3	0.047
Febrile neutropenia	0	0	6	4	0.089
Thrombocytopenia	2	1.4	6	4.1	0.338
Anemia	2	1.4	4	2.7	0.593
Nausea	4	2.9	18	12.2	0.036
Vomiting	2	1.4	14	9.5	0.035
Diarrhea	0	0	4	2.7	0.116
Hand-foot skin reaction	4	2.9	6	4.1	0.695
Hepatic dysfunction	8	5.7	10	6.8	0.796

Neuropathy	4	2.9	4	2.7	0.955
Mucositis	2	1.4	6	4.1	0.338
Cardiac side effect	0	0	2	1.4	0.329

## Discussion

Surgery has been the mainstay of treatment for primary gastric cancer, and good results with gastrectomy have been reported in early gastric cancer, but the prognosis of advanced gastric cancer was not improved with surgery therapy. In the present investigation, patients receiving preoperative chemotherapy followed by radical gastrectomy obtained longer survival. Nevertheless, the optimal neoadjuvant chemotherapy regimen for resectable advanced gastric tumors remained debated. A concurrent triplet regimen is attractive as the neoadjuvant (preoperative) chemotherapy because a triplet regimen may have a high response rate. Considering the outcomes of the MAGIC trial [3] and Real-2 trial [14], epirubicin, cisplatin and 5-Fu (ECF) and epirubicin, cisplatin and capecitabine (EOX) are regarded as the standard perioperative chemotherapy. In Japan, an S1/cisplatin/paclitaxel combination regimen showed 63.5% and 59.1% in two Phase II studies [15,16]. However, phase II studies have demonstrated that doublet regimen such as XELOX and SP regimen produces a favorable tumor response rate with a relatively mild toxicity profile [8,9]. These results suggested that regimen including three key drugs do not have more benefit in terms of response rate as neoadjuvant chemotherapy than doublet regimen. Not just more that, it had been showed that more adverse effects occurred in triplet regimen and the tolerability was not acceptable. In the MAGIC trial, severe adverse events sometimes occurred during the first course of chemotherapy just after gastrectomy. It is challenging to finish intensive chemotherapy postoperatively. In current study, the clinical outcome difference between preoperative doublet and triplet chemotherapy regimens has been analysed for the first time in China. We confirmed that doublet regimens have similar response rate (48.6% and 48.7%) and conversion rate to radical resection (55.7% and 62.1%) with triplet regimens, and are more tolerate. Meanwhile, the PFS and OS in two groups did not significantly differ (15.0 vs. 14.0 months and 29.1 vs. 30.0 months).

In our study, the most generally used doublet regimen was XELOX (70.0%) and EOX regimen (74.0%) was the mostly used triplet regimen for gastric cancer. In spite of the chemotherapy consisting of XELOX or EOX, no statistical significance was identified in terms of survival. Similarly, no matter what the patients had radical surgery or not, the PFS and OS in two groups were the same. The patients who had curable operation could benefit more from transformable chemotherapy than these received palliative treatment, and the benefit was not affected by the choice of chemotherapy regimen.

Gastrectomy combined with D2 lymphadenectomy is an efficacious intervention for curable gastric tumors, whereas the safety of D2 resection lymphadenectomy remains to be

elucidated. In the present study, a majority of patients in group A (74.4%) and group B (82.6%) received R0 resection in combination with D2 lymphadenectomy with a median discharge time of 11 and 10 d, which did not differ from those untreated with neoadjuvant chemotherapy [14]. Eight among 206 patients undergoing palliative and radical surgery yielded surgical complications of pulmonary infection and pancreatic fistula.

Previous investigations have demonstrated that patients who achieved a complete response (pCR) with no residual microscopic tumor obtained the most benefits from neoadjuvant chemotherapy. Nevertheless, merely 5%-10% of patients obtained pCR, which is uncommon in clinical practice. In this investigation, the CR rates were 5.1% in group A and 4.3% in group B, which is consistent with the previous findings [17-21]. In current research, 3 cases obtained who stable disease after obtaining pCR. CT scan findings are not constantly consistent with the histological results.

In addition, our data indicate that chemotherapy related toxicity effects tended to be more frequent in Group B (triplet therapy) than Group A (doublet therapy), especially in leucopenia, fatigue and vomiting. In addition, the perioperative complication in triplet group was more than doublet group, three and one respectively. More aggressive treatment including three chemotherapy drugs had more toxicity effect, but did not produce more benefit on survival and other clinically relevant outcomes as expected.

The limitation of current study is in non-randomized and non-blinded setting. The chemotherapy regimens are not consistent which might produce selection bias. Moreover, the follow-up time is short and the 5 y OS rate has not yet been reached.

To conclude, patients diagnosed with topically advanced unresectable gastric tumors can obtain identical benefits after doublet and triplet chemotherapy regimens. Chemotherapy consisting of three chemotherapy drugs would yield a higher risk of adverse events. Thus, doublet chemotherapy is recommended to minimize the adverse events.

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