Journal of
Carcinogenesis & Mutagenesis

Sun et al., J Carcinog Mutagen 2017, 8:5
DOI: 10.4172/2157-2518.1000306

Research Article Open Access

Adjuvant Capecitabine and Oxaliplatin *vs.* Capecitabine and Paclitaxel in Gastric Cancer Patients after D2 Gastrectomy

Jing Sun[1], Shaohua He[2], Peinan Lin[1], Ping Li[1], Xiaomin Cai[1], Lele Li[1], Jing Qian[1], Chong Liu[3] ,Xiao Li[3], Yiqian liu[1], Oluf Dimitri Røe[4,5], Yongqian Shu[1], Yanhong Gu[1*] and Xiaofeng Chen[1*]

[1]Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing 210029, PR China

[2]Department of Oncology, Tumor Hospital of Huaihua, Lulin Road, Huaihua 418000, PR China

[3]Department of Pathology, the First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing 210029, PR China

[4]Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[5]Cancer Clinic, Levanger Hospital, Nord-Trøndelag Health Trust, Levanger, Norway

Jing Sun and Shaohua He have contributed equally to this article.

**Corresponding author: Yanhong Gu, Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing 210029, PR China; Email: guluer@163.com*

Xiaofeng Chen, Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing 210029, PR China, Tel: +8615720802922; E-mail: Xiaofengchen915@126.com

Received date: July 24, 2017; **Accepted date:** September 14, 2017; **Published date:** September 19, 2017

Abstract

Objective: This retrospective study was carried out to compare the safety and efficacy of adjuvant capecitabine/oxaliplatin (XELOX) versus capecitabine/paclitaxel (XP) in gastric cancer patients after D2 gastrectomy.

Methods: The hospital records of the First Affiliated Hospital of Nanjing Medical University from 2008-2012 were searched to identify patients treated with adjuvant XELOX or XP after D2 gastrectomy and their clinicopathological data were retrieved. Disease-free survival (DFS) and overall survival (OS) were analyzed by Kaplan-Meier method with log-rank test.

Results: A total of 144 stage I-III patients who received adjuvant XELOX (n=89) or XP (n=55) after D2 gastrectomy were identified. The median follow-up time was 47.0 (25.0-80.0) months. The 3-year DFS and OS rate was 67.0% versus 50.8% (p=0.047) and 74.8% versus 63.5% (p=0.184) in the XELOX and XP group respectively. XELOX significantly reduced the risk of relapse at three years (HR 0.60, 95% CI 0.36-0.99) but did not reduced the risk of death at the third year (HR 0.66, 95% CI 0.36-1.22) compared with that treated with XP.

Conclusions: These results indicate that adjuvant XELOX after D2 gastrectomy has a clinical advantage over XP; however, prospective studies are needed to verify this finding.

Keywords: Adjuvant chemotherapy; Capecitabine; Gastric cancer; Oxaliplatin; Paclitaxel

Introduction

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of tumor-related death worldwide [1,2]. However, the largest burden is in East Asia, including Japan, Korea and China with60% of the global incidence of GC [3,4]. The 5-year overall survival (OS) is approximately 20% and has not improved significantly over the last decade, but several studies have shown positive effects of peri-operative treatment. However, due to different types of neo-adjuvant and adjuvant regimens as well as surgical methods [5] the results have not been consistent [6]. Post-operative chemoradiation was recommended as a standard of care after gastrectomy in the USA based on the INT-0116 study [7]. Perioperative chemotherapy with epirubicin, cisplatin, and infused fluorouracil (ECF) had been recommended based on the MAGIC trial [8], in which three preoperative and three postoperative cycles of ECF decreased tumor size and significantly improved progression-free (PFS) and OS compared to surgery alone in patients with operable gastric or lower esophageal adenocarcinoma. In Asia, The ACTS-GC trail conducted in Japan was the first study which showed a 3-year survival benefit (80.1% versus 70.1%) by adjuvant treatment of 1-year oral S-1, compared with surgery alone [9]. In 2011, results from the planned interim analysis of the CLASSIC study indicated that adjuvant chemotherapy with capecitabine plus oxaliplatin (XELOX) significantly prolonged disease-free survival (DFS) in patients with curative D2 gastrectomy with stage II-IIIB [10]. Consequently, both XELOX and oral S-1 are now recommended for adjuvant chemotherapy in Asia [11]. However, the outcome results have in general been moderate and new active regimens should be explored.

Paclitaxel has shown encouraging efficacy in the treatment of advanced gastric cancer [12], and has also been tested in the adjuvant setting in a series of trials [13-15]. Considering the efficacy of paclitaxel in advanced gastric cancer and the moderate effective of current regimens in adjuvant treatment, paclitaxel containing regimens are also recommended in China in the adjuvant setting [16].

This retrospective study was conducted to compare the efficacy and safety of adjuvant XELOX and XP regimens in gastric cancer patient.

Materials and Methods

Patient selection

Retrospective search of the medical records of the Department of Oncology of the First Affiliated Hospital of Nanjing Medical University from Jan 1st, 2008 to Aug 31st, 2012 was conducted. Cases were included when they fulfilled the following criteria: 1) patients with pathologically verified gastric cancer treated with D2 gastrectomy (R0,R1); 2) patients who received either XELOX (capecitabine/oxaliplatin) or XP (capecitabine/paclitaxel) as adjuvant chemotherapy; 3) adequate hematological and organ function: white blood cell count >4.0 × 10^9/L, neutrophil granulocyte >1.5 × 10^9/L, platelet count >100 × 10^9/L, liver and renal function (aspartate aminotransferase, alanine transaminase, serum total bilirubin and creatinine) <1.5 × normal upper limit; 4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 5) age range 18-80 years; 6) available clinicopathological and survival data.

Exclusion criteria were: 1) patients with synchronous malignancies; 2) patients with neo-adjuvant treatment or chemoradiation; 3) patients with synchronous metastasis.

This protocol was approved by the First Affiliated Hospital of Nanjing Medical University Ethics Committee prior to study start.

Data collection and follow-up

The histopathological diagnosis and grading of selected objects from surgical specimens were confirmed according to the World Health Organization (WHO) classification of malignant gastric tumors and the Elston and Ellis grading scheme, respectively [17]. Stage, tumor size, invasion depth, primary tumor location, positive lymph node number, metastasis, vascular and perineural involvement was determined retrospectively according to the 2010 UICC-pTNM stage on the basis of postoperative histological findings by CW and XL (Department of Pathology, the First Affiliated Hospital of Nanjing Medical University). Patient records and operation notes were reviewed for detailed clinicopathologic data.

Adverse events were evaluated according to the CTCAE3.0 (Common Terminology Criteria for Adverse Events v3.0). Only objective events were included as hematologic toxicity retrieved from the patient records. The subjective adverse events, such as nausea and neurotoxicity were not included due to lack of accuracy in a retrospective setting.

The date of chemotherapy beginning was regarded as the starting point of the survival follow-up until August 31, 2014. The OS was defined as period from the first chemotherapy to death or the last follow-up and DFS was defined as the span between the start of chemotherapy to the date of confirmed recurrence or death from any cause.

The patients were routinely monitored every 3 months for the first 2 years, then every 6 months until 5 years after surgery. After 5 year, the patients were visited every year. Follow-up data were acquired from patient records, death certificates or patients and their families by telephone calls.

Chemotherapy regimens

The XELOX regimen consisted of intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle) combined with oral capecitabine (1000 mg/m^2, bid, day 1-14) every 3 weeks/cycle. The XP regimen was composed of intravenous paclitaxel (150mg/m^2 on day 1) plus capecitabine (1000 mg/m^2, bid, day 1-14) every 3 weeks/cycle. Dose reductions or interruptions were decided by the oncologists who were in charge of the patients. Informed consents for the chemotherapy schedule and possible adverse effects of each patient were obtained in written form before treatment.

Statistical analysis

Three-year disease free survival was used for the primary endpoint of this study because most relapses occur within 3 years after surgery [18]. Secondary end points included 3-year OS and toxicity. The survival curves were produced by the Kaplan-Meier method and tested with the log–rank test. Fisher exact test was used for basic characteristics analysis. The Cox proportional-hazards model was used to calculate the hazard ratios. All P values calculated in the subgroup analysis were two-sided [9,19]. Statistical analyses were done with SPSS version 18.0 (Chicago, IL, USA) and a two-sided $P<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 144 cases (89 and 55 in the XELOX and XP group, respectively) were eligible for this retrospective study. The median age in this cohort was 61 year (range 19-78). Baseline characteristics were comparable between the two groups (Table 1). Most of the patients had adenocarcinoma (82.0% *vs.* 89.1%) and ulcerative cancer (86.5% *vs.* 90.9%) and the majority of the patients had Stage II and III disease (95.5% *vs.* 87.3% in the XELOX and XP group, respectively).

Characteristics	XELOX, n (%)	XP, n (%)	P value
All cases	89	55	
Age	19-77 (61.4)	32-78 (60.7)	
Male/Female	66/23	41/14	1
Mean cycles	5.4 (3-8)	5.8 (2-9)	
Primary tumor site			0.259
Esophagogastric junction	21 (23.6%)	14 (25.6%)	
Antrum	30 (33.7%)	21 (38.1%)	
Body	38 (42.7%)	18 (32.7%)	
Others	0 (0%)	2 (3. 6%)	
Histology			0.595
Adenocarcinoma	73 (82.0%)	49 (89.1%)	
Signet ring cell carcinoma	6 (6.7%)	1 (1.8%)	
Mucinous adenocarcinoma	7 (7.9%)	3 (5.5%)	
Others	3 (3.4%)	2 (3.6%)	

Bomman classification			0.695
Ulceration	77 (86.5%)	50 (91.0%)	
Infiltrative	2 (2.2%)	2 (3.6%)	
Diffuse	4 (4.5%)	1 (1.8%)	
Others	6 (6.8%)	2 (3.6%)	
Tumor size(cm)			0. 566
≤ 6	67 (75.3%)	39 (70.9%)	
>6	22 (24.7%)	16 (29.1%)	
Pathologic T stage			0.388
T1	6 (6.7%)	4 (7.3%)	
T2	8 (9.0%)	10 (18.2%)	
T3	16 (18.0%)	7 (12.7%)	
T4	59 (66.3%)	34 (61.8%)	
Pathologic N stage			0.439
N0	26 (29.2%)	19 (34.5%)	
N1	23 (25.8%)	10 (18.2%)	
N2	20 (22.5%)	17 (30.9%)	
N3	20 (22.5%)	9 (16.4%)	
TNM stage			0.159
I	4 (4.5%)	7 (12.7%)	
II	20 (22.5%)	14 (25.5%)	
III	65 (73.0%)	34 (61.8%)	
Vascular invasion			0.167
Yes	26 (29.2%)	10 (18.2%)	
No	63 (70.8%)	45 (81.8%)	
Perineural invasion			0.325
Yes	25 (28.1%)	11 (20.0%)	
No	64 (71.9%)	44 (80.0%)	
Margins			0.167
R0	57 (64.0%)	45 (81.8%)	
R1	32 (36.0%)	10 (18.2%)	
Type of surgery			0.857
Total gastrectomy	32 (36.0%)	19 (34.5%)	
Subtotal gastrectomy	57 (61.3%)	36 (65.5%)	

Table 1: Baseline characteristics of gastric cancer patients.

Survival

The median follow-up time was 47.5 months (25.0-80.0 months) and 46.3 months (30.0-69.0 months) in XELOX and XP group, respectively. At the cutoff for the analysis, 61 patients (68.5%) in the XELOX group survived without relapse, compared with 28 patients (50.9%) in the XP group. Median DFS was not reached in both XP and XELOX group (Figure 1).

The 3-year disease-free survival was 67.0% (95% CI 61.8-72.2) in the XELOX and 50.8% (95% CI 44-57.6) in the XP group (p=0.047). XELOX significantly reduced the risk of relapse at 3 years (HR 0.60, 95% CI 0.36-0.99).

Three-year disease-free survival was significantly higher in XELOX than in the XP group in patients with gender male (p=0.046), no perineural invasion (p=0.031), no vascular invasion (p=0.029) and those who were younger than 61 years old (p=0.026) (Figure 2).

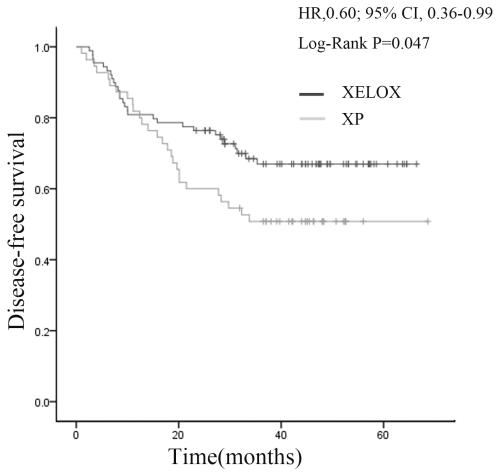

Figure 1: Kaplan-Meier curves of disease-free survival. P value was calculated by log-rank method. XELOX: Capecitabine plus oxaliplatin; XP: Capecitabine plus paclitaxel. The 3-year disease-free survival was 67.0% and 50.8% in the XELOX and XP group (p=0.047), and 3-year overall survival rate was 74.8% in the XELOX group and 63.5% in the XP group. The hazard ratio for 3 year relapse in the XELOX group was 0.60 (95% CI 0.36-0.99).

Median OS has not been reached in either group. The 3-year OS rate was 74.8% (95% CI 60.1-79.5) in the XELOX and 63.5% (95% CI 57.0-70.0) in XP group (p=0.184). The XELOX group tended to reduced risk of death compared with XP group (HR 0.66, 95% CI 0.36-1.22) (Figure 1).

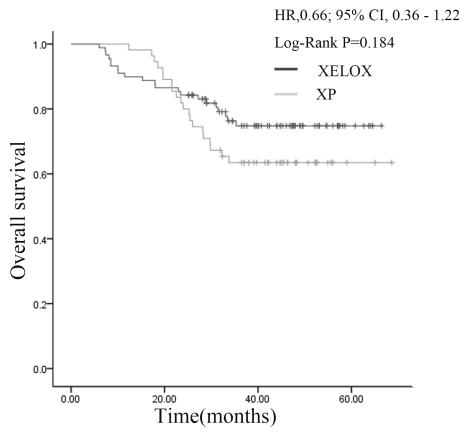

Figure 2: Subgroup analysis for 3-year DFS. XELOX: Capecitabine plus oxaliplatin; XP: Capecitabine plus paclitaxel; HR: Hazard ratio; CI: Confidence interval.

Adverse effects

No patient died due to severe toxicity. Twelve (21.9%) patients in the XP group had to reduce dosage by 15%-30% of the starting dose due to grade 3-4 toxicity, and 5 (5.6%) cases had to decrease the dose of oxaliplatin or capecitabine in the XELOX group. Two (2.2%) patients discontinued oxaliplatin and used capecitabine alone from the fifth cycle. The incidence of all grade thrombocytopenia was significantly higher (p=0.005) in XELOX group while there was no significant difference in grade 3-4 thrombocytopenia between the two groups. The XP group had more grade 3-4 leucopenia than the XELOX group (p=0.003). No significant difference regarding the liver and renal function was observed.

Discussion

Our study showed that adjuvant XELOX chemotherapy after D2 gastrectomy improved 3-year disease-free survival compared with adjuvant XP chemotherapy. Moreover, subgroup analysis of negative prognostic markers showed consistent benefit for adjuvant XELOX chemotherapy compared with XP chemotherapy. The OS data from our study are not mature. However, the data indicated that XELOX group had a higher 3-year DFS rate compared with XP group (67.0% *vs.* 50.8% P=0.047).To the best of our knowledge, this is the first study comparing the adjuvant XELOX and XP regimen in gastric cancer patients that underwent D2 resection.

Three-year DFS was used for the primary endpoint of this study because most relapses occur within 3 years after surgery and is strongly correlated with 5-year OS [18]. A meta-analysis of individual patient data collected in randomized clinical trials found that DFS is an acceptable surrogate for OS in trials of cytotoxic agents for gastric cancer in the adjuvant setting and has been widely used in many trials, including the CLASSIC and SAMIT trial [20].

The CLASSIC study was a phase III trial that randomized 1035 patients with stage or gastric cancer following D2 gastrectomy to observation or eight cycles of capecitabine and oxaliplatin (XELOX). Patients in the XELOX arm had improved 3-year DFS (74% *vs.* 59%, P0.0001) and OS (83% *vs.* 78% P=0.0493) [21]. After 5 years follow up, the XELOX arm had significantly better 5-year DFS (68% *vs.* 53%, P<0.0001) and 5-year OS (78% *vs.* 69%, p=0.0029) [22].

In our study, the 3-year disease free survival in XELOX group was 67.0%, which was lower than that in the CLASSIC study. Although our patient population had D2 resection, we had more stage III patients (73.0% in our study and 51.0% in CLASSIC), which may be an important reason why our 3-year DFS was lower. The other factor is that we had approximately 36% R1 resection in XELOX group, while in CLASSIC trial, all the patients were R0 resection.

Paclitaxel was demonstrated as effective against gastric cancer by exerting a unique mechanism of anticancer action and show no cross-resistance with fluoropyrimidine [23-25]. Paclitaxel-based regimens had been recommended in NCCN guideline (Chinese version) for preoperative chemoradiation, first and second line in palliative chemotherapy [16]. Recently, a multicenter, phase II prospective study conducted in China indicated that paclitaxel plus capecitabine as first-line chemotherapy in advanced gastric carcinoma showed promising efficacy and a phase III study had been launched for further investigation [12]. Considering the encouraging efficacy in palliative treatment, paclitaxel had also been tested in adjuvant setting for long time [14,26]. However, so far no trial with high level of evidence has shown encouraging efficacy of paclitaxel in adjuvant setting. Most recently, Tsuburaya et al. reported the results of SAMIT trial in which sequential paclitaxel followed by tegafur and uracil (UFT) or S-1 versus UFT or S-1 monotherapy were tested as adjuvant chemotherapy for T4a/b gastric cancer [15]. The results showed that the 3-year disease-free survival for sequential treatment was not significantly better than that in monotherapy (57.2% *vs.* 54.0%, p=0.273). Thus, adding paclitaxel before S-1 or UFT is not recommended.

The key weakness of this report is its retrospective nature. The evaluation of relapse and toxicity was not predefined. The data of the subjective adverse events such as the neurotoxicity couldn't be determined. Moreover the sample size was relatively small.

In conclusion, our results showed that the efficacy of adjuvant capecitabine plus oxaliplatin was superior to the capecitabine plus paclitaxel after D2 gastrectomy, which supports the use of capecitabine and oxaliplatin regimen in this setting. The use of adjuvant paclitaxel could be restricted to patients with unacceptable neurotoxicity of oxaliplatin and for advanced stage IV disease.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC) (81301896), Natural Science Foundation of the Colleges and Universities in Jiangsu Province (13KJB320011), Program for Development of Innovative Research Teams, by Jiangsu Province Clinical Science and Technology Projects (clinical research centre, BL2012008), and by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and by Provincial Initiative Program.

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