

Efficacy and safety of capecitabine as maintenance therapy after capecitabine-based combination chemotherapy for patients with advanced esophagogastric junction adenocarcinoma

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Abstract. – OBJECTIVE: The aim of the present study was to investigate the efficacy and safety of single-agent capecitabine therapy after capecitabine-based combination chemotherapy for patients with advanced adenocarcinoma of the esophagogastric junction (EGJ).

PATIENTS AND METHODS: Seventy-two patients with pathologically proven advanced EGJ adenocarcinoma underwent 2-6 cycles of capecitabine-based first-line combination chemotherapy between January 2010 and October 2014. When initial disease control had been achieved, 60 patients were randomly assigned to receive the capecitabine treatment (oral capecitabine 1,250 mg/m² twice daily on days 1-14 every 3 weeks) to see whether it is involved in maintenance regimen or not, while 12 patients were excluded. The primary endpoint of this study was progression-free survival (PFS). Secondary endpoints were overall survival (OS) and major adverse events were monitored.

RESULTS: The median PFS was 11.0 months (95% confidence interval [CI], 0-23.2 months) and OS was 17.0 months (95% CI, 2.1-31.9 months) for the maintenance group. In contrast, median PFS was 7.0 months (95% CI, 5.8-8.2 months) and OS was 11.0 months (95% CI, 2.07-31.9 months) for the control group. Compared to controls, patients who received capecitabine maintenance therapy showed significantly prolonged PFS and OS. The capecitabine-related adverse events included leukopenia, anemia, and thrombocytopenia, hand-foot syndrome, nausea/vomiting, neuropathy, and liver dysfunction. Treatment-related adverse events were tolerable, and there were no significant differences in the prevalence of adverse events between patients who received maintenance therapy and controls.

CONCLUSIONS: Our finding shows that single-agent capecitabine maintenance therapy was effective, well-tolerated and safe after first-line capecitabine-based combination chemotherapy in patients with advanced EGJ adenocarcinoma.

Key Words:

Advanced esophagogastric junction (EGJ) adenocarcinoma, Capecitabine, Maintenance therapy.

Introduction

In 2012, an estimated 951,600 new cases of gastric cancer and 723,100 deaths occurred which makes it the third most common cancer and third leading cause of cancer-related mortality worldwide¹. Also, it is the third most frequent malignancy in China¹. In the last two decades, a steady decline in gastric carcinoma incidence and mortality rates has been reported². In contrast to the declining trends for gastric carcinoma, however, the incidence rates of adenocarcinoma of the esophagogastric junction (EGJ) have shown a significant increase in China³⁻⁷.

Some previous studies have shown that EGJ adenocarcinoma was different from distal gastric carcinoma in several clinicopathological features, such as the differentiation degree was inferior to that of distal gastric carcinoma, the tumor size was larger than that of distal gastric carcinoma⁶, and the prognosis of patients with EGJ adenocarcinoma was also extremely poor

compared to that of those with distal gastric carcinoma⁸. Therefore, EGJ adenocarcinoma has been granted a specific classification to distinguish these cancers from carcinoma of the rest of the stomach^{9,10}. According to topographic anatomical criteria, the EGJ cancers were categorized into three subtypes: adenocarcinoma of the distal esophagus (AEG I), true carcinoma of the cardia (AEG II), and subcardial gastric carcinoma (AEG III)^{11,12}. However, despite these molecular and clinical differences, patients with EGJ cancers and those with distal gastric carcinoma were often treated identically with systemic fluoropyrimidine-based chemotherapy¹³.

A prospective randomized trial has confirmed higher response rates, survival, and quality of life (QOL) benefits with the regimen of epirubicin, cisplatin, and protracted venous-infusion fluorouracil (FU; ECF regimen)¹⁴. The efficacy and tolerability of three-drug regimens containing FU, anthracycline, and cisplatin has also been demonstrated by a systematic review and meta-analysis¹⁵. Cunningham et al¹⁶ demonstrated that capecitabine and oxaliplatin may become a promising treatment with superiority to the ECF regimen in median overall survival (OS) for advanced esophagogastric cancer. However, there was still no definite chemotherapy regimen for patients with advanced EGJ cancer.

The advanced EGJ cancer still cannot be cured. Therefore, the aim of combination chemotherapy treatment are to prolong survival, relieve symptoms, and improve the QOL. However, the OPTIMOX2 study¹⁷ showed that complete discontinuation of chemotherapy had a negative effect on progression-free survival (PFS) compared with the continuation of maintenance therapy in metastatic colorectal cancer. Subsequently, the feasibility of maintenance therapy has been proven in numerous cancers; for example, the benefits of single-agent capecitabine maintenance therapy have been shown in patients with metastatic breast cancer¹⁸⁻²⁰, metastatic colorectal cancer^{21,22}, non-small cell lung cancer^{23,24}, and metastatic breast cancer^{25,26}. A prospective observational study demonstrated that capecitabine maintenance therapy was an independent prognostic factor in advanced gastric adenocarcinoma patients²⁷. To the our best knowledge, the role of capecitabine maintenance therapy in adenocarcinoma of the EGJ has not been explored. Capecitabine is an oral fluoropyrimidine agent which is desirable on the basis of

several features such as tolerability, inexpensive, convenience, non-invasive delivery, and effectiveness²⁸. Therefore, based on the above findings, we designed the present study to further determine the efficacy and safety of single-agent capecitabine treatment in patients with adenocarcinoma of the EGJ.

Patients and Methods

Ethics Statement

The informed consent were taken from all the patients participated in the present study. The study was approved from the local ethics committee of YangZhong Peoples' Hospital in Jiangsu Province and it was performed in accordance with the ethical standards of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients

All the EGJ adenocarcinoma patients were enrolled between January 2010 and October 2014 in the Department of Oncology, YangZhong Peoples' Hospital, and had never previously received combination chemotherapy with paclitaxel and capecitabine. Patients were enrolled according to the following inclusion criteria: (1) histologically confirmed locally advanced EGJ adenocarcinoma; (2) complete follow-up information was available; (3) received 2-6 cycles of capecitabine-based chemotherapy as first-line chemotherapy; (4) ≥ 18 years of age; (5) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ; (6) life expectancy of at least 3 months; and (7) presence of at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines. The major exclusion criteria were as follows: (1) never accepted previous systemic therapy (chemotherapy or biologic therapy); (2) pregnant or lactating women or women of childbearing potential who had not been surgically sterilized or did not employ adequate contraceptive measures; (3) clinically significant co-morbidities such as cardiac disease, hematological disease, liver dysfunction, and peripheral neuropathy; (4) subjects with persistent gastric outlet obstruction, complete dysphagia or feeding jejunostomy; (5) no target lesion; (6) history of other malignancy and some central nervous system diseases; (7) disease progression or relapse during the first-line chemotherapy; (8) complete follow-up infor-

mation was unavailable. Sixty patients who completed combination therapy were recruited in the present study according to the above standards. Out of 60 patients, 30 patients received capecitabine as maintenance treatment (group A) and 30 patients without maintenance therapy (group B) i.e. control group.

Treatment

All patients received 2-6 cycles of the combination regimen of paclitaxel and capecitabine with oxaliplatin (paclitaxel 145 mg/m² intravenous on day 1, capecitabine 1,250 mg/m² oral twice daily on days 1-14, and oxaliplatin 85 mg/m² intravenous on day 1 every month) or without oxaliplatin (paclitaxel 145 mg/m² intravenous on day 1, capecitabine 1,250 mg/m² oral twice daily on days 1-14 every 3 weeks). After responding to chemotherapy, 30 patients continued to receive maintenance treatment with capecitabine at the same dosage until disease progression or intolerable toxicity, and another 30 patients were followed up without receiving any treatment.

Efficacy and Safety Assessments

The primary endpoint was median PFS, which was defined as the interval from the first-line treatment to disease progression or death. Secondary endpoints were OS, defined as the interval from treatment to death or the termination of follow-up, for patients either receiving capecitabine maintenance or not, and major adverse events (AEs). Clinical therapeutic efficacy was assessed every 2 cycles using the RECIST version 1.1. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0).

Statistical Analysis

All the data were analyzed using SPSS version 16.0 software package (SPSS Inc., Chicago, IL, USA). The Kaplan-Meier analysis was used to estimate the PFS and OS, and the log-rank test was used to compare the differences in PFS and OS between the two groups. The chi-square test, Fisher's exact test, and the *t*-test were used to compare the baseline characteristics and disease response rates. All tests were two-tailed, and a value of *p* < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 72 patients who were enrolled between January 2010 and October 2014 were treated with the first-line combination chemotherapy of paclitaxel and capecitabine with or without oxaliplatin. Of these, 12 patients developed disease progression and could not continue the study, while 60 patients were recruited for randomization into the capecitabine maintenance group (group A) or the control group (group B). The baseline characteristics of these 60 patients are listed in Table I. A total of 60 patients with a performance status of 0-1 consisted of 30 women and 30 men, with a median age of 63 years (range, 49-73 years) for group A and 68 years (range, 61-75 years) for group B. There were no significant differences between the maintenance and control groups in gender, age, sites of metastasis, or response to first-line chemotherapy, while there was a statistical difference in the numbers of metastatic sites between the groups (Table I).

Efficacy

After the first-line chemotherapy treatment, 2 patients received a complete response (CR), where as 5 patients received partial response (PR), while 23 patients achieved stable disease (SD) in the capecitabine maintenance group. In

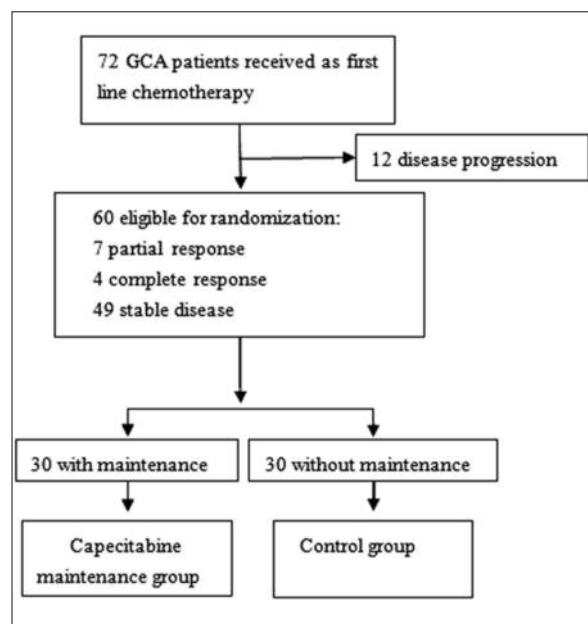


Figure 1. Schematic diagram.

Table I. Baseline characteristic of the study patients.

	Control group	Capecitabine group	<i>p</i> -value
Gender			0.781
Female	20	21	
Male	10	9	
Age, years			0.326
Range	34-74	44-75	
Median	59.3	61.8	
Sites of Metastasis			0.501
Liver	8	3	
Pelvic cavity	12	11	
Distant lymph nodes	28	19	
Bone	5	4	
Lung	6	6	
Others	0	2	
Number of metastasis site			0.000
One sites	3	20	
Two sites	18	10	
Three sites	10	5	
Histology subtype			0.301
Well or moderate	12	18	
Poor	16	14	
Response to chemotherapy			0.480
CR	2	2	
PR	5	2	
SD	23	26	

the control group, 2 patients achieved a CR, 2 achieved PR, and 26 achieved SD. Subsequently, 60 patients received either the single-agent capecitabine regimen or no capecitabine maintenance. The median PFS was 11.0 months (95% confidence interval [CI], 0-23.2 months) in the capecitabine maintenance group and 7.0 months (95% CI, 5.8-8.2 months) in the control group, $p < 0.05$ (Figure 2A). The median OS was 17.0 months (95% CI, 2.1-31.9 months) in the capecitabine maintenance group and 11.0 months (95% CI, 2.07-31.9 months) for patients in the control group, $p < 0.05$ (Figure 2B). In terms of PFS and OS, the efficacy was higher in patients who received maintenance treatment compare to those who did not.

Safety

The major AEs for maintenance treatment are summarized in Table II. The common AEs of capecitabine included hematologic AEs (leukopenia, anemia, and thrombocytopenia) and non-hematologic AEs (hand-foot syndrome, nausea/vomiting, neuropathy, and liver dysfunction). Among the 30 patients who received maintenance treatment, 6 patients had grade 3 AEs (1 patient had leukopenia and nausea/vomiting, 2 patients had leukopenia, 1 had nausea/vomiting, and 1 had neuropathy). Other AEs observed in

this study were of mild to moderate intensity (grade 1/2). There were no grade 4 AEs were observed, and no toxicity-associated deaths occurred. Our data showed that the incidence of AEs did not significantly differ between the capecitabine maintenance group and the control group.

Discussion

In this open-label phase 2 study initiated from 2010, the primary endpoint and secondary endpoints were all met. In the present study, 60 patients with EGJ adenocarcinoma who achieved disease control through the administration of first-line capecitabine-based chemotherapy followed by single-agent capecitabine were recruited. PFS and OS were 11.0 and 17.0 months for the capecitabine maintenance group respectively, while they were only 7.0 and 11.0 months for the control group. The incidence of therapy-related toxicity was generally mild; the common AEs were leukopenia, nausea/vomiting, and neuropathy in our study, and there were no significant differences in the AEs between the capecitabine maintenance group and the control group.

Almost all the previous research treated patients with EGJ cancers and those with distal

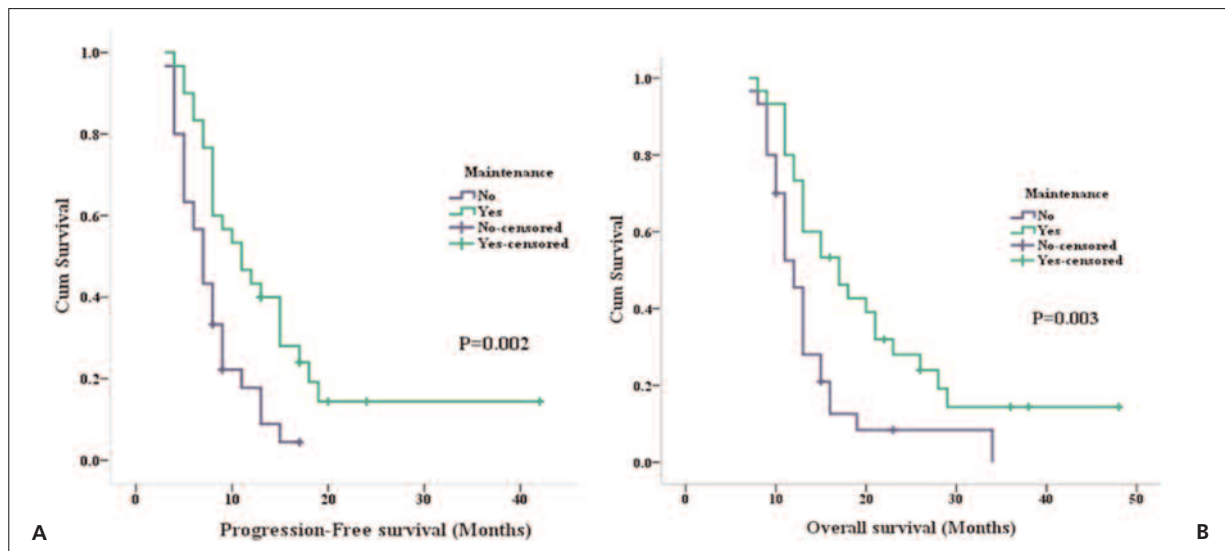


Figure 2. **A**, Kaplan-Meier analysis of progression-free survival from randomization. The median progression-free survival (PFS) was 11.0 months (95% confidence interval [CI], 0-23.2 months) for patients in group A, while it was 7.0 months (95% CI, 5.8-8.2 months) for patients in group B, $p < 0.05$. **B**, Kaplan-Meier analysis of overall survival from randomization. The median overall survival (OS) was 17.0 months (95% confidence interval [CI], 2.1-31.9 months) for patients in group A, while it was 11.0 months (95% CI, 2.07-31.9 months) for patients in group B, $p < 0.05$.

gastric carcinoma identically, and surgical resection is also typically the initial management strategy²⁹. Furthermore, many clinical trials have been employed to evaluate perioperative and neoadjuvant chemotherapy and have shown a survival advantage in gastric cancer^{30,31}. In contrast, the adjuvant chemotherapy regimens have delivered the best survival results to patients with advanced EGJ cancers and distal gastric carcinoma¹⁵.

All the patients participated/enrolled in our study had advanced EGJ adenocarcinoma. At present, there remains no evidence available for the optimal duration of first-line chemotherapy

for adenocarcinoma of the EGJ. With the exception of those already mentioned above. The NCT00477711 trial³² demonstrated that cetuximab combined with cisplatin and capecitabine was well-tolerated and effective in advanced gastric or EGJ adenocarcinoma in China. A randomized multicenter phase II study established capecitabine with irinotecan as a relevant platinum-free first-line chemotherapy regimen in patients with metastatic adenocarcinoma of the stomach or EGJ³³. In addition, Zhang et al³⁴ evaluated the efficacy and toxicity of the combination regimen of cisplatin, 5-FU, and paclitaxel (PCF) for patients with advanced EGJ adenocarcinoma.

Table II. Incidence of adverse events in the study patients.

Adverse events	Group A			Group B		
	All grade	Grade 3	Grade 4	All grade	Grade 3	Grade 4
Hematologic AEs						
Leukopenia	18	0	0	20	3	0
Anemia	18	0	0	15	0	0
Thrombocytopenia	10	1	0	18	0	0
Non-Hematologic AEs						
Hand-foot syndrome	18	0	0	10	0	0
Nausea/Vomitin	8	0	0	21	2	0
Neuropathy	18	1	0	25	0	0
Liver dysfunction	10	0	0	13	0	0

They found that the median OS and PFS were 12.0 and 5.7 months, respectively. Those patients receiving first-line treatment showed, the response rate (CR+PR) was about 40%, and that the major AEs included neutropenia, nausea/anorexia, and vomiting. These results demonstrated that the combination regimen with PCF was effective and tolerable as first-line therapy in Chinese patients with advanced gastric and EGJ adenocarcinoma. In our study, we administered the chemotherapy regimen strictly according to the common malignant tumor chemotherapy clinical guideline (version 2004, Nanjing) of Jiangsu Province Anticancer Association Professional Committee of Chemotherapy.

Nowadays, a growing body of research evidence supports the use of maintenance therapy after the first-line chemotherapy in several kinds of solid tumors. Capecitabine is a newer cell-cycle S-phase-specific fluoropyrimidine carbamate formulated as an oral agent²⁸. However, capecitabine involved the requirement of three steps of specific cellular enzymes to convert it for activation and the activation was mediated by thymidine phosphorylase, which is expressed at much higher concentrations in gastric cancers than in the adjacent normal tissues²⁸. Furthermore, the side effects of capecitabine were usually not deadly but rather influenced the QOL²⁸. Therefore, numerous relevant studies were performed to explore the activity and toxicity of capecitabine monotherapy. As mentioned above, metastatic breast cancer¹⁸⁻²⁰ and metastatic colorectal cancer^{21,22} patients could achieve benefits from single-agent capecitabine maintenance treatment. Moreover, a cohort study²⁷ verified the value of capecitabine maintenance therapy in advanced gastric cancer patients; the median PFS reached 11.4 months in the maintenance group, which was much higher than the 7.1 months reached in the control group. Additionally, this study also showed that maintenance therapy was an independent prognostic factor in advanced gastric carcinoma²⁷. Furthermore, several giant clinical trials are underway to further explore capecitabine-based first-line chemotherapy and maintenance treatment in EGJ adenocarcinoma patients, such as NCT00719550, NCT00891878, NCT00583674, NCT00084617, and others (ClinicalTrials.gov).

This clinical study was an attempt to analyze the importance of capecitabine monotherapy after capecitabine-based combination therapy for the better quality of life. It is well known that the

incidence rates of EGJ adenocarcinoma are highly distributed in northern China such as in Linzhou and the central part such as Henan Province³⁵. The total 72 specimens were collected from Jiangsu Province which was also a high-risk field for gastric carcinoma and esophageal cancer. All the data we obtained was representative and complete. More than that, all the patients were enrolled with good compliance. Here, we observed that single-agent capecitabine chemotherapy could significantly improve the PFS and OS in patients with EGJ adenocarcinoma compared with capecitabine-free patients. However, those results are preliminary and have to be confirmed in larger populations as well as in many other regions/parts of the country.

Conclusions

Capecitabine is an effective and well-tolerated maintenance therapy in patients with EGJ adenocarcinoma, and could be one of the manageable regimens for patients treated with first-line capecitabine-based chemotherapy. Further study is required in the larger population.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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