

## RESEARCH ARTICLE

# Retrospective Study of Gemcitabine Based Chemotherapy for Unresectable or Recurrent Esophagus Squamous Cell Carcinoma Refractory to First Line Chemotherapy

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### Abstract

**Purpose:** To investigate the efficacy and toxicity of a combination of gemcitabine with nedaplatin (GN) or cisplatin (GC) for patients with unresectable or recurrent esophagus squamous cell carcinoma. **Methods:** Gemcitabine was administered at 1 g/m<sup>2</sup> intravenously on days 1 and 8; and nedaplatin or cisplatin were administered at 80 mg/m<sup>2</sup> intravenously on day 1. We analyzed the response rate, overall survival time, progression-free survival time, and toxicity in 21 patients treated with GN and 27 patients treated with GC. **Results:** In patients treated with gemcitabine plus nedaplatin, the ORR was 47.6%, the median progression-free survival time was 4.1 months, and the median survival time was 9.3 months. In patients treated with gemcitabine plus cisplatin, the ORR was 48.2%, the median progression-free survival time was 3.9 months, and the median survival time was 9.1 months, respectively. There were no statistically significant differences in ORR, PFS and OS between the two groups. In both, the most commonly observed toxicities were thrombocytopenia and fatigue. Nausea and vomiting was more frequent in the GC group than in the GN group. **Conclusion:** Gemcitabine based chemotherapy was effective and tolerable for patients with unresectable or recurrent esophagus squamous cell carcinoma refractory to first line chemotherapy.

**Keywords:** Esophageal cancer - gemcitabine - nedaplatin - cisplatin

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### Introduction

Esophageal cancer (EC) is one of the most common malignancies in China, Iran, South Africa, Uruguay, France and Italy. Among these countries, China has almost half of the total cases with the highest mortality rate. Massive epidemiological studies revealed the prevalence of this disease in China, especially in the Taihang Mountain range areas in the North. Moldy food, pickled vegetables, nitrosamines and their precursors, trace element deficiencies in the soil, nutritional deficiencies, fungal infection, polycyclic hydrocarbons, and other factors may contributed to the high cancer incidence. Squamous cell carcinoma is the most common histological type of esophageal cancer in China. Although with appropriate prevention strategies, early detection, and early treatment of this cancer have been pursued vigorously in many areas of China, the prognosis remains poor. The overall survival rate of 5 years was less than 30% because most patients had advanced diseases because of lacking symptoms in early state. The medium survival time was 4-8 months in advanced esophageal cancer. (Hou et al., 2008) The combination of 5-Fu plus cisplatin with or without radiotherapy is regarded as the standard first-line treatment. However; there have been few reports

of systemic chemotherapy for esophageal cancer in the second-line setting. In this study, we investigated the efficacy and toxicity of GC/GN to treat unresectable or recurrent esophageal cancer patients who refractory to first-line chemotherapy.

### Materials and Methods

#### Patients

From all patients with recurrent esophageal cancer receiving Gemcitabine based chemotherapy at Changhai Hospital between April 2008 and April 2011, following criteria were used for our study: (1) Confirmed esophagus squamous cell carcinoma by histology; (2) Progression after 5-FU/or Doxetaxol plus platinum-based chemotherapy; (3) Age from 18-70 years old; (4) Eastern Cooperative Oncology Group performance status of 0-2; (5) No other active malignancies; (6) Adequate bone marrow, renal and hepatic function; (7) No other serious medical complications (8) No symptomatic brain metastasis; (9) Written informed consent.

#### Treatment

The treatment was performed according to the following schedule: gemcitabine was administered at 1

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**Table 1. Patients Baseline Characteristics**

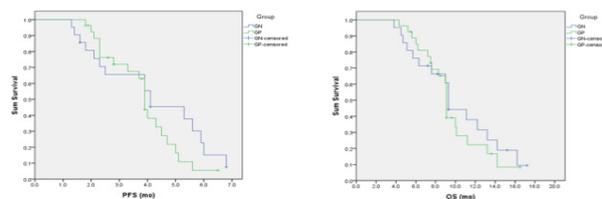
Parameter	GN	GC
Number of patients	21	27
Age		
Median	53	51
Range	35-70	41-70
Gender		
Male	16	20
Female	5	7
ECOG performance status		
0	9	11
1	6	9
2	6	7
Prior radiotherapy		
Yes	7	9
No	14	18
Prior chemotherapy		
T based	7	9
F based	14	18

g/m<sup>2</sup> intravenously on day 1 and 8; and nedaplatin or cisplatin was administered at 80 mg/m<sup>2</sup> intravenously on day 1. We choose nedaplatin or cisplatin according to the patient's chemotherapy regimen in the first-line, that is: if the patients had used cisplatin before, we choose nedaplatin, if nedaplatin, then cisplatin. When grade 4 hematological toxicity or grade 3 or 4 nonhematological toxicity or PS deterioration was observed, the dose was reduced by about 20% percent in the subsequent treatment course. The treatment kept going until tumor progression or until unacceptable toxicity or patient refused.

**Assessment**

Responses were assessed according to the Response Evaluation Criteria in Solid Tumors every 2 cycles of each regimen, in principle. Definitions of response were: complete response--the disappearance of all target lesions; partial response -at least a 30% decrease in the sum of the longest diameter of target lesion, taking as reference the baseline sum of the longest diameter; progressive disease -a 20% or greater increase in the sum of the longest diameter of target lesion, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of one or more new lesion; and stable disease -neither sufficient shrinkage to qualify for progressive disease, taking as reference the smallest sum of the longest diameter since the treatment started. The target lesions were determined from the measurable lesion localized outside the prior radiation field.

The overall survival time (OS) was calculated from the data of initiation of the second-line chemotherapy to the date of death of any cause or confirmed survival. The progression free survival (PFS) was calculated from the date of the first administration of the second-line chemotherapy to the date of disease progression or death of any cause. Overall and progression-free survivals were analyzed using the Kaplan-Meier method. Toxicity was assessed according to the common toxicity criteria of the National Cancer Institute Version 2.0, every 2 or 3 weeks, in principle. The worst grade of each toxicity from the initiation of the second-line chemotherapy to 30 days after the last administration of chemotherapy was documented.



**Figure 1. Progression Free Survival and Overall Survival**

**Table 2. Response**

	GN	GC	p-value
Total	21	27	
CR	0	0	
PR	2	2	
SD	8	11	
PD	11	14	
ORR	47.61%	48.15%	0.601(Wilcoxon 660.0Z-0.036)
PFS (mo)	4.1	3.9	0.349(log rankx2)
OS (mo)	9.3	9.1	0.614(log rankx2)

**Statistical Analyses**

Fisher's exact test was used in data numeration, F-test was used in data measurement. The basic significance level was at p < 0.05 and all data was analyzed using SPSS statistical software (Version 11.0; SPSS Inc., Chicago, IL).

**Results**

**Patients**

The baseline of patient characteristics was shown in Table 1. 21 patients received GN treatment while 27 patients underwent GC treatment. Two treatment groups were well balanced in terms of age, gender, ECOG performance status and previous treatment received.

**Treatment Responses**

There was no complete response in both groups and there was 2 cases of partial response, respectively. There were 8 cases of stable disease in GN group and 11 cases in GC group, while progressive disease occurred in 11 and 14 patients, respectively. The ORR rate was 47.61% in GN group and 48.15% in GC group (Table 2). The medium PFS and medium OS was 4.1 months and 9.3 months in GN group, and 3.9 months and 9.1 months in GC group (Figure 1). There was no significant differences in treatment outcomes between two groups.

**Toxicities**

The hematological and nonhematological toxicities are shown in Table 3. Grade 4 nonhematological toxicity was not observed in both groups. In both groups, the most commonly seen toxicities were thrombocytopenia and fatigue. Nausea and vomiting was more frequent in GC group than that in GN group. During the course of therapy, grade 3/4 anemia was detected in 1 (3.7%) patients, and grade 1/2 anemia in 8 (29.6%) patients in the GC group. In the GN group, the numbers were 0 and 7 (33.3%) respectively. Grade 3/4 leucopenia, neutropenia and thrombocytopenia were documented in 3 (10.1%), 2 (7.4%) and 0 patients in the GN group, and 2 (9.5%), 2 (9.5%) and 1 (4.7%) in the GC group, respectively. Grade

**Table 3. Toxicities**

	GC (n=27) Grade n(%)				GN (n=21) Grade n(%)			
	1	2	3	4	1	2	3	4
<b>Hematologic toxicity</b>								
Leukopenia	9(33.3)	5(18.5)	2(7.4)	1(3.7)	8(38.1)	5(23.8)	1(4.7)	1(4.7)
Neutropenia	8(29.6)	3(11.1)	2(7.4)	0	8(38.1)	3(14.3)	2(9.5)	0
Anemia	6(22.2)	2(7.4)	1(3.7)	0	5(23.8)	2(9.5)	0	0
Thrombocytopenia	11(40.7)	2(7.4)	0	0	7(33.3)	1(4.7)	1(4.7)	0
<b>Nonhematological toxicity</b>								
Anorexia	12(44.4)	3(11.1)	3(11.1)	0	7(33.3)	3(14.3)	1(4.7)	0
Fatigue	13(48.1)	2(7.4)	3(11.1)	0	10(47.6)	3(14.3)	2(9.5)	0
Nausea	11(40.7)	7(25.9)	4(14.8)	0	6(28.6)	6(28.6)	2(9.5)	0
Vomiting	11(40.7)	8(29.6)	4(14.8)	0	5(23.8)	4(19.0)	3(14.3)	0
Febrile neutropenia	6(22.2)	2(7.4)	1(3.7)	0	6(28.6)	1(4.7)	1(4.7)	0

3 nausea and vomiting were detected in 4 (9.5%) and 3 (14.3%) patients in the GC group, while in the GN group the number was 4 (14.8%) and 3 (14.3%) respectively. Grade 1 or 2 nausea and vomiting were detected in 18 (66.6%) and 19 (70.3%) in the GC group. In the GN group, the numbers were 12 (57.2%) and 9 (42.8%), respectively.

## Discussion

Esophageal cancer is the second leading cause of death in China. It has a high rate of local and distant recurrences after operation. The median survival time has being short at only 24 month, which results in a 5-year survival rate below 30%. More than 70% of patients present with unresectable or metastatic disease at time of diagnosis. Several palliative chemotherapy regimens have been shown to have some activity in the first-line setting, with response ranging from 20-48% and 5-year survival rate of approximately 15%. The combination of fluorouracil and cisplatin, either alone or in combination with a third drug such as epirubicin or taxane, constitutes the most effective treatment option. In case of relapse or refractory, however, data on application of second-line therapy are few, and there is no consensus on the optional second-line chemotherapy so far. Various chemotherapy combinations have been tested for second-line therapy of esophageal cancer (Grunberger et al., 2007; Yamazaki et al., 2008; Thallinger et al., 2011). Brutnsws B et al have assessed the efficiency of the combination of docetaxel and Irinotecan in cisplatin-pretreated esophageal cancer. 24 patients were given docetaxel 25 mg/m<sup>2</sup> plus Irinotecan 55 mg/m<sup>2</sup> on days 1, 8 and 15 every 4 weeks. The response rate was low at 12.5%, and the overall survival was 6 months (Brutnsws et al., 2009; Enzinger et al., 2009).

In a phase II trial, 35 patients with esophageal SCC who had previously been treated with fluorouracil and cisplatin chemotherapy or chemoradiotherapy were treated with docetaxel 70 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> on day 1, repeated every 3 weeks. ORR was 34.2% with one patients (2.6%) achieving CR, 12 (31.6%) achieving PR, and 12 (31.6%) achieving SD. Again, progression free survival and overall survival were short, 4.5 months and 7.4 months, respectively, WHO grade 3 to 4 hematologic toxicities were seen in half the patients (Shim et al., 2010).

Apart from response rates, the time to progression was short in most studies, being less than 4 months in

13 trials and being not stated in another five of 27 trials (Cunningham et al., 2008; Nakajima et al., 2008; Jin et al., 2009).

Gemcitabine is a member of a general group of chemotherapy drugs known as anti-metabolites. It prevents cells from making DNA and RNA, which stops cell growth and causes the cell to die. Gemcitabine has been used to treat pancreatic cancer, breast cancer, ovarian cancer, non-small cell lung cancer, bladder cancer and soft tissue sarcoma (Yao et al., 2010, Kaya et al., 2012). Prior studies had demonstrated potential synergistic antitumor activity of gemcitabine in combination with cisplatin. Huang Jing (Huang et al., 2011) studied the efficacy and tolerability of such combination for esophageal cancer. In his study, the overall response rate was 42.1% (95%CI, 25.5%-56.5%). Median progression-free survival and median survival for all patients were 4.1 months (95%CI, 3.0-5.7 months) and 10 months (95%CI, 7-12 months), respectively. Patients with a response had significantly longer median survival compared with the patients without a response (11 months vs. 7.5 months, P=0.0069). Overall survival at 1 year was 36.8%, at 2 years was 10.5%, and at 5 years was 5.3%. Furthermore, a small number of the patients with metastatic esophageal cancer were still alive in 5 years with this regimen.

Nedaplatin is a second-generation platinum that does not require hydration. Hirata et al. (2000) reported that using nedaplatin alone to treat esophageal squamous cell carcinoma, the response rate was 51.7% with five partial response in nine patients who had chemotherapy previously. A Phase II Study of Paclitaxel and Nedaplatin as First-line Chemotherapy in Patients with Advanced Esophageal Cancer revealed that the overall response rate was 41.7% (95% CI, 27.8-55.7%) with 2 complete responses and 18 partial responses. The median overall time to progression and overall survival (OS) were 6.1 months (95% CI, 4.8-7.4 months) and 11.5 months (95% CI, 9.1-13.9 months), respectively. The estimate of OS at 12 and 24 months was 43.8% (95% CI, 29.7-77.8%) and 10.4% (95% CI, 1.8-19.1%), respectively. Because no studies have compared second-line chemotherapy with best supportive care for patients with esophageal cancer, any benefit of second-line chemotherapy for survival times were remains unclear (Cao et al., 2009).

In our study, the median overall survival times were 9.1 month for patients treated with GC and 9.3 months

for those treated with GN. The median PFS times were 3.9 and 4.1 months respectively. The efficacy results in our study confirmed that gemcitabine provides survival benefits to patient refractory to first-line therapy. We also showed that additional cisplatin or nedaplatin provided comparable benefit to patients with advance esophagus cancer. Both GC and GN were tolerable. There was no Grade 4 nonhematological toxicity in both groups. There was one case of Grade 4 leukopenia in each group. The most frequent toxicity was thrombocytopenia and fatigue in both groups. Nausea and vomiting was more frequent in GC group than that in GN group.

Our study indicated that gemcitabine based chemotherapy for unresectable or recurrent esophagus squamous cell carcinoma that refractory to first-line chemotherapy was effective and tolerable. Prospective, randomized studies are warranted to further test the benefit of gemcitabine based chemotherapy strategy in the second-line setting in patients with advance esophagus cancer.

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