

CONTINUOUS ADMINISTRATION OF ENDOSTAR PLUS GP CHEMOTHERAPY IN LOCAL ADVANCED OR METASTATIC LUNG SQUAMOUS CELL CARCINOMA

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ABSTRACT

Introduction: In squamous cell lung cancer (SQCLC), the current first-line therapy is considered platinum-based doublet chemotherapy and the benefit is limited. Aim of our study is to compare the effect of patients with local advanced or metastatic SQCLC, in comparable groups of patients treated with systemic chemotherapy containing gemcitabine/cisplatin (GP) or GP+ Endostar.

Materials and methods: All patients with local advanced or metastatic SQCLC who had undergone GP+ continuous administration of Endostar from September 2009 to January 2014 were evaluated. The GP group was constituted by selecting patients with local advanced or metastatic SQCLC treated with GP chemotherapy during the same period.

Results: Fifty-two patients were retrospectively included in the GP group and were compared with 98 patients who had undergone continuous administration of Endostar +GP and were evaluated prospectively. All characteristics were comparable. Median follow-up was 60 months in the GP group versus 58 months in the Endostar +GP group. The response rate (RR) was 34.7% in Endostar +GP group and 34.6% in the GP group. The disease control rate (DCR) was 89.7% in Endostar +GP group and 80.8% in the GP group. Both the RR and DCR were not found to be significantly different with each other. Median progression free survival (PFS) was 5.56 months in the GP group versus 7.23 months in the Endostar +GP group.

Discussion: The combination of continuous infusion of Endostar with chemotherapy can improve the PFS in local advanced or metastatic SQCLC patients without increasing adverse events.

Key words: Endostar, lung squamous cell carcinoma, continuous administration, gemcitabine/cisplatin.

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Introduction

Lung cancer is one of the most common and aggressive malignancies in the world. More than million patients are newly diagnosed every year globally. The five-year survival rate is less than 15%⁽¹⁾. High incidence and poor prognosis made it the leading causes of cancer related mortality. Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of lung cancer cases⁽²⁾. 25% to 30% of patients with NSCLC are in locally advanced stage, 40% to 50% of patients have distant metastases when they were diagnosed which were unresectable⁽³⁾. In NSCLC, squamous cell lung cancer accounts for 29%⁽¹⁾.

Because of the low rate of epidermal growth factor receptor (EGFR) mutation⁽⁴⁾, The platinum-based doublet chemotherapy is considered as the first-line standard therapy, but the benefit is limited.

Novel regimens are needed urgently to improve outcome, such as the anti-angiogenesis therapy. Endostar (YH-16) is a novel recombinant human endostatin developed by China. Compared to the rh-endostatin reported previously, an additional nine-amino acid sequence (MGGSHHHHH) was added at the N-terminal of the protein, which simplified the purification and improved the stability of the protein⁽⁵⁾. In 2005, Wang et al. published the results of stage III clinical trial which showed the combination of Endostar with vinorelbine plus

cisplatin significantly improve the clinical benefit compared with vinorelbine plus cisplatin alone⁽⁶⁾. Then endostar was approved by the China's State Food and Drug Administration (SFDA). Some other studies also discussed the efficacy of Endostar in treating NSCLC⁽⁷⁻¹⁰⁾, which showed the similar results. In these researches, Endostar was administered as once per day over four hours on day 1 to 14. Some preclinical studies^(11,12) reported that continuous releasing rh-endostatin revealed more significant tumor regression than conventional intermittent intravenous infusion, which suggested the new schedule might augment the efficacy. Here, we investigated the efficacy of continuous administration of Endostar combined with chemotherapy and compared it to the chemotherapy alone in advanced or metastasis SQCLC patients.

Materials and methods

Patients

All patients were pathologically or cytologically confirmed unresectable stage IIIB and stage IV SQCLC, with an Eastern Cooperative Oncology Group performance status of 0 or 1, from September 2009 to January 2014 in the 2nd affiliated hospital, Zhejiang University school of medicine. This study was approved by the ethics committee of the 2nd affiliated hospital, Zhejiang University school of medicine. All 98 patients who had received GP+ continuous administration of Endostar were prospectively included. 52 patients with local advanced or metastatic SQCLC treated with GP chemotherapy during the same period in our hospital were retrospective included.

Treatment

For all the patients, the chemotherapy of gemcitabine/cisplatin was administered as follow: gemcitabine 1000 mg/m² on day 1 and 8, cisplatin 75 mg/m² divided into 3 days every 3 weeks for 4-6 cycles. In the Endostar +GP group, 15mg Endostar (diluted in 250 ml normal saline) was delivered by automatic drug infusion pump (ZZB-II, Nantong apon medical appliance co. ltd, China) via a central line in the speed of 11ml per hour from day 0 to, one day prior to the chemotherapy. Tumor response to the therapy was assessed according to the Response Evaluation Criteria In Solid Tumors 1.1 criteria⁽¹³⁾ every 2 cycles. Finally, all patients were eligible for efficacy and safety evaluation.

Administration of gemcitabine, cisplatin, and Endostar was held back if the neutrophil level dropped below 1000/uL or the patient experienced febrile neutropenia. Chemotherapy with gemcitabine and cisplatin was held back if the platelet count dropped below 100,000/uL. Treatment resumed once these parameters were back to acceptable levels. Gemcitabine and cisplatin were held back for grade 3 nonhematologic toxicities until the toxicity had resolved to grade ≤ 2 . Endostar was discontinued in patients with grade ≥ 3 hemorrhage, hypersensitivity, cardiac toxicity.

Assessment of the response and adverse events

The results of physical examination, complete blood count, comprehensive blood chemistries, tumor marker, the abdominal and chest computerised tomography(CT), brain magnetic resonance imaging (MRI), bone emission computed tomography (ECT) or positron emission tomography (PET-CT) at the baseline and duration of therapy were recorded. The tumor response to the chemotherapy was assessed according to the Response Evaluation Criteria In Solid Tumors 1.1 criteria every 2 cycles by the chest and upper abdomen CT. The objective response rate (RR), disease control rate (DCR), progression free survival (PFS) were evaluated. Assessments of toxic effects were made according to the National Cancer Institute Common Terminology Criteria for Adverse Events CTCAE(14).

Follow-up and statistics

Patients in the GP + Endostar group were recorded prospectively and patients in the GP group were recorded retrospectively. Follow-up was every 3 months, with the abdominal and chest CT and tumor marker measurements.

All categorical variables, objective RR, and incidences of adverse events were analyzed and compared between the continuous infusion group and control groups using the χ^2 test or Fisher's exact test, as appropriate. The distributions of PFS were estimated using the Kaplan-Meier method, and the GP+ Endostar group and GP groups were compared using the log-rank test. All p values were two-sided, and values less than 0.05 were considered statistically significant. All analyses were performed using statistical product and service solutions(SPSS) 20.0 software. The research was approved by the ethics committee of our hospital.

The authors report no conflicts of interest in this work.

Results

Baseline Characteristics of the Patients

Baseline characteristics of the patients are detailed in Table 1. All characteristics were comparable. In the Endostar +GP and GP groups, the median ages of patients were 64 and 63 years, respectively. 90 of 98 (92 %) patients in the Endostar +GP group and 46 of 52 (88%) patients in the GP group were men. The Endostar +GP group included 79 (81%) current or ever smokers, while the GP group included 44 (85%). The numbers of patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 were 91 in the Endostar +GP group and 52 in the GP group. 7 patients in Endostar +GP group and 2 in GP group had an ECOG PS of 2. The median chemotherapy cycles in both Endostar +GP and GP group are 4.

		Endostar+GP group	GP group	P-value
Number		98	52	
Age	Median (range)	64(32-79)	63(42-80)	0.747
Sex	M/f	90/8	46/6	0.184
Smoking	Yes/no	79/19	44/8	0.219
PS	0/1/2	69/22/7	40/12/2	0.22
Stage	IIIB/IV	29/69	16/36	0.769

Table 1: The baseline characteristics of the patients.

Toxicity efficacy

The median follow-up time for the patients was 60 months in the GP group versus 58 months in the Endostar +GP group. At the cut-off time (2014.12), one patients achieved complete response (CR) in Endostar +GP group. The partial response (PR) cases were recorded as 33 and 18 in Endostar and GP group, respectively. There were 53 cases of stable disease (SD) in Endostar +GP group, 24 in GP group. 11 cases in Endostar +GP group, 10 cases in GP group were evaluated as progressive disease (PD). The RR was 34.7% in Endostar +GP group, as compared with 34.6% in the GP group. The DCR was 89.7% in Endostar +GP group and 80.8% in the GP group. Both the RR and DCR were not found to be significantly different with each other.

The detailed data of efficacy was reported in table 2. The median PFS was significantly improved in the Endostar +GP group compared with that in GP group (7.23 vs. 5.56 months, p=0.033). The survival curves are shown in figure 1.

Best response	Endostar +GP group	GP group	P-value
CR	1(1%)	0	
PR	33(33.7%)	18(34.6%)	
SD	53(54.1%)	24(46.2%)	
PD	11(11.2%)	10(19.2%)	
RR	34(34.7%)	18(34.6%)	0.86
DCR	87(89.7%)	42(80.8%)	0.27

Table 2: Response and control rates for overall disease. CR complete response, PR partial response, SD stable disease, PD progressive disease, RR response rate, DCR disease control rate

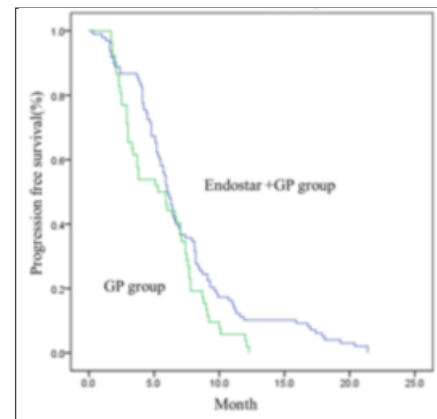


Figure 1: Progression-free survival of group receiving. Endostar +GP versus those receiving GP chemotherapy. GP, gemcitabine plus cisplatin; PFS, progression-free survival.

All patients (98 patients in the Endostar +GP group and 52 patients in the GP group) were included in the toxicity analysis, which is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. The patients in both groups were well tolerance. None of the patients died of adverse events. The detailed data of grade 3/4 events in each group are summarized in table 3.

In this study, Grade 3 or 4 of hematological toxicity consisted of neutropenia and anemia. Neutropenia was the predominant events in both groups, with 23 cases in Endostar +GP group vs. 10 cases in GP group, but there were no statistically significant difference between them. For the non-hematologic events, vomiting is relatively more often. 3 patients suffered from grade 3 or 4 of vom-

iting in Endostar +GP group, compared with 2 patients in GP group, which is not significantly different from each other. Other adverse events included dyspnea, allergic reaction, pneumonitis, headache, rash or desquamation, which are not found to be significantly different with each other. In Endostar +GP group, 2 patients had ST-segment and T wave changes, which were fully alleviated after suspending Endostar and chemotherapy, then the treatment continued.

Adverse Event	Endostar +GP group (N = 98) ≥Grade 3	GP group (N = 52) ≥Grade 3	P-Value
	number of patients (percent)		
Neutropenia	23(23.5%)	10(19.2%)	0.551
Thrombocytopenia	5(5.1%)	3(5.8%)	0.863
Anemia	2(2.0%)	1(1.9%)	0.961
Febrile neutropenia	2(2.0%)	1(1.9%)	0.961
Dyspnea	2(2.0%)	0	0.3
Allergic reaction	1(1.0%)	0	0.465
Pneumonitis	1(1.0%)	0	0.465
Vomiting	3(3.0%)	2(3.8%)	0.799
Headache	1(1.0%)	0	0.465
Rash or desquamation	2(2.0%)	1(1.9%)	0.961

Table 3: Treatment-related adverse events.

Discussion

SQCLC is a common and important subtype in NSCLC. The results from a retrospectively study of 12509 cases with NSCLC showed SQCLC comprises 29% of all patients⁽¹⁾. The mutation of EGFR in SQCLC is rare⁽¹⁵⁾. The meta-analysis⁽¹⁶⁾ showed the rate of EGFR mutation is only 10% in Asia and lower than 3% in the western country, which limits the application of target therapy such as tyrosine kinase inhibitors (TKIs). The anti-angiogenesis therapy might promise a new chance. But most of the clinical trials of anti-angiogenesis drugs in the advanced SQCLC are failed because of the toxicity. A phase II clinical trial of bevacizumab showed SQCLC was associated with high risk of severe pulmonary hemorrhage^(17,18). This subtype was excluded in the further studies about bevacizumab. Unfortunately, other anti-angiogenesis drugs such as sorafenib, motesanib and cediranib yet showed no benefits in the clinical trials⁽¹⁹⁻²¹⁾. Therefore, the survival and prognosis of SQCLC is worse than

adenocarcinoma due to lack of target and anti-angiogenesis therapy. The platinum-based doublet chemotherapy is still considered the fundamental regimen for the first-line therapy for SQCLC⁽²²⁻²⁵⁾.

In 2008, a stage III clinical trial (JMDB) showed in patients with SQCLC, the survival is significantly improved in cisplatin/gemcitabine than cisplatin/pemetrexed (10.8 v 9.4 months)⁽²⁶⁾. But the benefit is still limited. It seems that the therapy of SQCLC has achieved the “efficacy plateau”. Novel regimen urgently needed to make a breakthrough.

Endostatin (rh-endostatin) is a 20 kDa COOH-terminal fragment of collagen XVIII which was firstly identified by Folkman et al. in 1997. It has anti-angiogenesis properties and antitumor activities⁽²⁷⁾. Endostar (YH-16) is a novel recombinant human endostatin developed by China. The stage IV clinical trial of Endostar and standard chemotherapy regimens published on 2010th ASCO meeting showed Endostar could improve the median survival time and overall survival rate of patients with advanced NSCLC without significantly increasing adverse effects both in lung squamous and non-squamous cell cancer. The incidence of hemoptysis is 2-3% and no cerebral hemorrhage occurred in the patients with cerebral metastasis⁽²⁸⁾. Besides, A meta-analysis⁽¹⁶⁾ retrospectively researched the clinical trials about Endostar conducted recent years, and showed Endostar could significantly improve the clinical benefit without increasing the risk of hemorrhage in SQCLC. Based on these studies above, Endostar combined chemotherapy regimen could bring the clinical benefits significantly without increased adverse events both in lung squamous and non-squamous cell cancer.

In the previous clinical trials, Endostar is recommended as intravenous infusion over 4 hours once per day from day 1 to day 14 every 21 days treatment cycle^(6,8), in order to maintain therapeutic levels. In this schedule, Endostar is administered intermittent, which may cause fluctuation of plasma concentration but not a continuous level. The half-life of Endostar in vivo is short as 10 hours, which seems like the obstacle to maintain the stable and effective therapeutic plasma level. Continuous infusion might solve this problem and make the drug sufficient enough to combat the tumor growth, which might augment the efficacy of antitumor. The preclinical experiment have showed continuous infusion of endostatin could cause more significant tumor regression in mice model^(11,12). Kisker found that continuous administration results in more

effective tumor suppression at 5-fold reduced doses compared with bolus administration in mice model⁽¹¹⁾. Besides the animal experiments, a phase I clinical trial confirmed the 4-weeks continuous infusion of rh-Endostatin is safe⁽²⁹⁾, while the efficacy of continuous infusion of Endostar is unknown.

In this study, we compare the efficacy of continuous infusion of Endostar combined with chemotherapy to the chemotherapy alone in advanced lung squamous cell cancer patients. The use of Endostar significantly improved the PFS time from 5.56 to 7.23 months. The toxicity analysis showed patients in Endostar +GP group were well tolerated. There is no significant difference between two groups in the occurrence of grade 3/4 adverse events such as thrombocytopenia, neutropenia and vomiting. The major side effect of Endostar is supposed to be the cardiac toxicity. Our results showed the incidence of 3/4 grade cardiac toxicity is low (2%). The occurrence of hemoptysis is rare, no grade 3/4 hemoptysis happened, which demonstrates that the continuous infusion of Endostar in lung squamous cell cancer could improve the PFS time without increasing the side effects. Compared to other new chemotherapy regimen or target therapy in treatment of SQCLC, continuous infusion of Endostar might be suitable choice.

In conclusion, the combination of continuous infusion of Endostar with chemotherapy can improve the PFS time in local advanced or metastatic SQCLC patients without augmentation of adverse events. The cardiac toxicity is rare and controllable. This is a single center, nonrandom, retrospective research. The large sample prospective clinical trial is needed to confirm the efficacy and safety.

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