

Efficacy and safety of apatinib treatment for advanced esophageal squamous cell carcinoma

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Objective: No standard chemotherapy is available for patients with advanced esophageal squamous cell carcinoma (ESCC) who have failed prior first-line chemotherapy. The aim of this study was to evaluate the efficacy and safety of apatinib, an oral VEGFR-2 inhibitor, as salvage treatment for advanced ESCC.

Patients and methods: After apatinib dosing, the efficacy and toxicity were evaluated in 62 patients with pretreated advanced ESCC from 2014 to 2016 at Zhejiang Cancer Hospital. In addition, survival analysis was performed by the Kaplan–Meier method.

Results: Among the 62 patients, 15 achieved partial response while 31 had stable disease with a response rate of 24.2% and a disease control rate of 74.2%. Median progression-free survival (PFS) and overall survival were 115 and 209 days, respectively. Grade 3/4 toxicities (59.7%) were acceptable. Patients with grade 3/4 toxicities showed a longer PFS than those without (136 vs 63 days, $P=0.044$).

Conclusion: Apatinib is efficacious as second- or further-line treatment for advanced ESCC.

Keywords: esophageal squamous cell carcinoma, apatinib, vascular endothelial growth factor, toxicity

Introduction

Esophageal carcinoma is one of the leading causes of cancer-related death worldwide, especially in Asia.¹ Most Asian patients are diagnosed as having esophageal squamous cell carcinoma (ESCC), and the histology is somewhat different from non-Asian populations.^{2,3} Despite timely surgical interventions at an early stage, many cases tend to recur during the follow-ups.^{4,5} Currently, platinum-based regimens are a standard first-line treatment for advanced ESCC with a median progression-free survival (PFS) under 6 months.⁶ No definitive chemotherapeutic regimen has been properly established for those who have failed prior first-line chemotherapy.

Vascular endothelial growth factor (VEGF) could stimulate the growth of new blood vessels, regulate vascular permeability and exert anti-apoptotic effects in endothelial cells. It frequently becomes overexpressed in esophageal cancers.^{7,8} In addition, its overexpression was identified as a poor prognostic predictor for advanced ESCC.⁹

Previous studies have indicated that apatinib, a VEGFR-2 inhibitor, was potentially efficacious for solid carcinomas.¹⁰ As a small-molecule, VEGFR tyrosine kinase inhibitor improved PFS and overall survival (OS) in pretreated patients with advanced gastric cancer.^{11,12} However, no clinical studies have examined the efficacy and safety of apatinib treatment for advanced ESCC.

A retrospective study was conducted to evaluate the efficacy and safety of apatinib for advanced ESCC after failed prior first-/further-line treatment.

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Patients and methods

Patient eligibility

Patients with advanced ESCC receiving apatinib as second/ further-line treatment between March 2014 and June 2016 were included. All histological diagnoses of ESCC were made according to the histopathological criteria of WHO 2015 version. No local radiotherapy or interventional therapy was offered during apatinib dosing. The study protocol was approved by our institutional review board of Zhejiang Cancer Hospital. All participants provided informed consent prior to treatment.

Treatment regimen

Apatinib was administered at a daily dose of 500 mg, and one treatment cycle lasted 28 days. In addition, one dose reduction (500–250 mg) was allowed for drug-related toxicity.

Responses and toxicities

Tumor efficacy was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). In addition, toxicities were assessed by the National Cancer Institute Common Toxicity Criteria version 4.0 (CTC 4.0). Tumor responses were evaluated for every two cycles when no noticeable sign of progression was present.

Follow-ups and statistical analyses

PFS denoted the time from the first dosing day of apatinib to documented progression or mortality from any cause. In addition, OS was defined as the time from the first dosing day to mortality or the last follow-up. Survival analysis was conducted using the Kaplan–Meier method and compared using log-rank test. The survival curves were plotted according to the Kaplan–Meier method. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The median follow-up period was 10.2 (2.0–22) months. Follow-ups were conducted up to October 30, 2016.

Results

Patient characteristics

A total of 62 patients diagnosed with ESCC were included in the current study. Among them, 54 were male and eight were female with a median age of 60.5 years. In addition, 46 of them were previous or current smokers and 16 belonged to never smoker category. All of them received platinum-based first-line chemotherapy. Apatinib was prescribed as second-line (n=21) and further-line (n=41) treatments. Performance status (PS) was 0–1 in 52 patients and 2 in 10 patients. Patient characteristics are summarized in Table 1.

Table 1 Clinical characteristics of 62 patients

Variables	N (%)
Gender	
Male	54 (87.1)
Female	8 (12.9)
Age (years)	
Median (range)	60.5 (40–72)
>60	32 (51.6)
≤60	30 (48.4)
PS	
0–1	52 (83.9)
2	10 (16.1)
Smoking history	
Yes	46 (74.2)
No	16 (25.8)
Alcohol use	
Yes	49 (79.0)
No	13 (21.0)
Location of tumor	
Upper third	9 (14.5)
Middle third	24 (38.7)
Lower third	29 (46.8)
Line of apatinib therapy	
Second	21 (33.9)
Further	41 (66.1)
Prior therapies in advanced stage	
Chemotherapy	44 (71.0)
Chemoradiotherapy	18 (29.0)
Post-progression therapy after apatinib	
Chemotherapy	16 (25.8)
Palliative treatment	46 (74.2)

Abbreviation: PS, performance status.

Clinical efficacies

The clinical responses were as follows: CR (n=0), PR (n=15), SD (n=31) and PD (n=16). The values of objective response rate (ORR) and disease control rate (DCR) were 24.2% and 74.2%, respectively. The median PFS was 115 days (95% CI, 97–133; Figure 1), and the median OS was 209 days (95% CI, 165–253; Figure 2).

No significant correlation existed in PFS among gender ($P=0.51$), age ($P=0.43$), line of therapy ($P=0.43$), smoking history ($P=0.23$), location of tumor ($P=0.44$) and PS ($P=0.06$). Univariate analysis is detailed in Table 2. Patients with grade 3/4 toxicities showed a longer PFS than those without grade 3/4 toxicity (136 vs 63 days, $P=0.044$; Figure 3). Interestingly, PFS in individuals with grade 3/4 hypertension and hand-foot syndrome was longer than that in other patients (153 vs 112 days, $P=0.037$).

Among 46 SD patients, 13 had a PFS of >6 months, and the patient characteristics are summarized in Table 3.

Toxicity evaluations

The median dose of apatinib was 500 (250–500) mg. Ten dosage reductions were available. The rate of grade 3/4

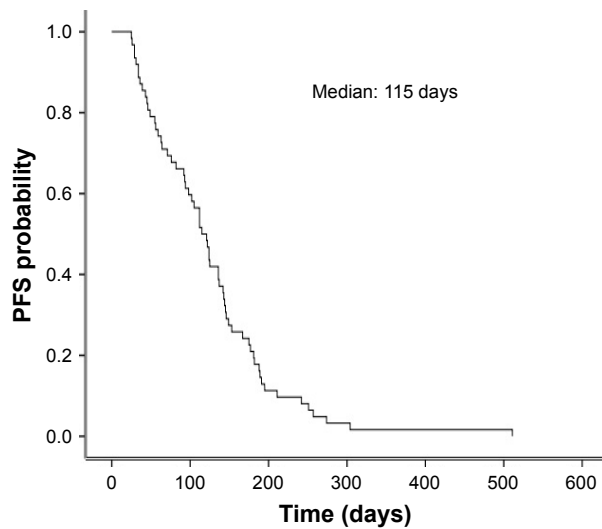


Figure 1 Kaplan-Meier curve of PFS after apatinib dosing.
Abbreviation: PFS, progression-free survival.

toxicities was 59.7% (37/62). Five patients presented with grade 4 toxicity, including worsening proteinuria (n=2), hypertension (n=2) and hand-foot syndrome (n=1). The most common grade 3/4 adverse events were as follows: hand-foot syndrome (n=10), hypertension (n=7), proteinuria (n=7), hepatic injury (n=5), fatigue (n=3), esophagitis (n=3) and nausea/vomiting (n=2; Table 4).

Discussion

To sum up, apatinib had some potential efficacy as a salvage treatment for advanced ESCC therapy. To the best of our knowledge, it represented the first-ever attempt of examining the efficacy and safety of apatinib for advanced ESCC.

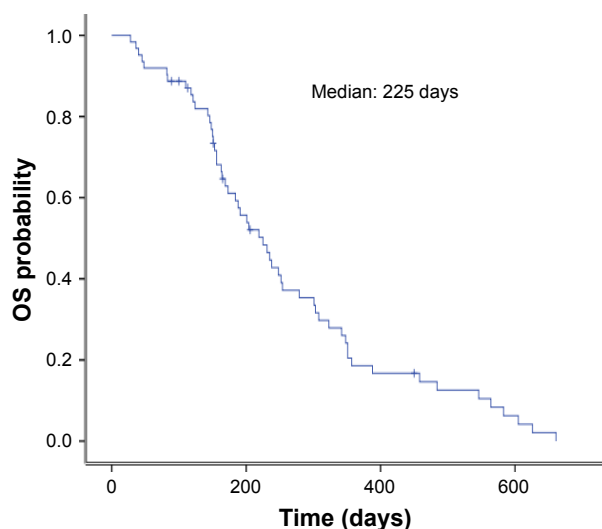


Figure 2 Kaplan-Meier curve of OS after apatinib dosing.
Abbreviation: OS, overall survival.

Table 2 Univariate analysis of the current population (n=62)

Characteristics	PFS	95% CI	P-value	OS	95% CI	P-value
Gender			0.51			0.24
Male	95	72–125		176	165–256	
Female	122	87–142		234	199–277	
Age (years)			0.43			0.34
>60	110	107–133		231	168–266	
≤60	117	87–121		201	176–254	
PS			0.06			0.04
0–1	132	106–157		254	226–312	
2	87	55–125		156	117–204	
Line of therapy			0.43			0.45
Second	126	75–131		234	176–265	
Further	111	87–129		199	167–254	
Smoking history			0.23			0.55
Yes	98	67–119		204	187–255	
No	124	89–132		255	211–269	
Location of tumor			0.44			0.25
Upper and middle third	101	78–125		187	167–254	
Lower third	117	111–135		231	207–288	

Abbreviations: OS, overall survival; PFS, progression-free survival; PS, performance status.

Platinum-based agents are currently a standard first-line treatment for advanced ESCC, and the median PFS has a range of 4–6 months.^{13–15} Half of the patients unresponsive to first-line treatment might receive a second-line therapy. Yet, the median PFS remains at a range of 2–4 months.^{16,17} For patients who have failed second-line chemotherapy, no definitive chemotherapeutic regimen has been recommended. New treatment strategy is urgently needed for achieving a better PS.

Several studies have identified the blockage of VEGFR-2 as a promising therapy for inhibiting angiogenesis.^{18,19} Apatinib, the first oral VEGFR-2 inhibitor, has previously

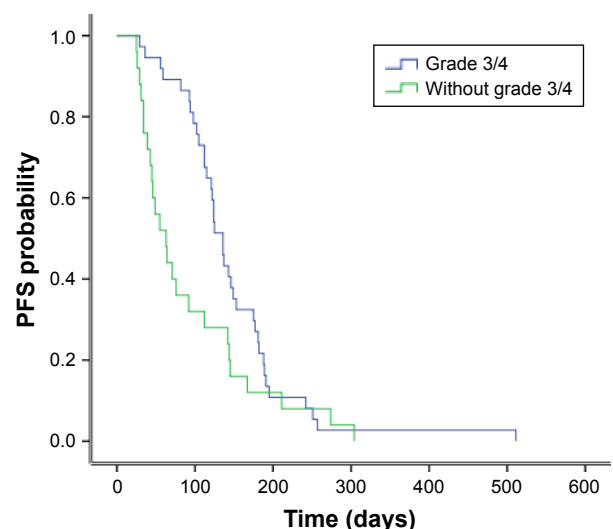


Figure 3 Comparison of PFS between patients with and without grade 3/4 toxicities.
Abbreviation: PFS, progression-free survival.

Table 3 Clinical profile of patients with PFS >6 months

Case	Gender	Age (years)	Smoking	Line of therapy	Grade 3/4 toxicity	PFS (days)	OS (days)
1	Male	56	Yes	Second	Yes	188	252
2	Male	63	Yes	Third	Yes	181	254
3	Male	64	No	Second	Yes	195	357+
4	Female	54	No	Fifth	No	251	661
5	Male	65	Yes	Second	Yes	304	564
6	Female	48	No	Fifth	No	189	216
7	Male	63	Yes	Third	Yes	242	458
8	Male	64	No	Second	Yes	511	583
9	Female	62	No	Second	Yes	251	279
10	Female	54	No	Third	No	274	348
11	Male	57	Yes	Third	Yes	191	303
12	Male	54	Yes	Second	No	182	191
13	Male	50	Yes	Fourth	No	211	351

Abbreviations: OS, overall survival; PFS, progression-free survival.

demonstrated survival benefits for metastatic gastric cancer.¹² Although approved domestically for gastric cancer treatment, apatinib was also effective for patients with advanced breast carcinoma and lung cancer who are unresponsive to standard pretreatment.^{20,21} In the current study, the values of DCR and ORR were 74.2% and 24.2%, respectively. There was a trend of better efficacy compared with second-line chemotherapy for advanced ESCC.⁵ Interestingly, patients with grade 3/4 toxicities had a longer PFS than those without grade 3/4 toxicities. Patients with hypertension and hand-foot syndrome benefited more than those with other adverse events. Together with previous study,¹² our results indicated that some toxicities would be predictive factors for the efficacy of apatinib treatment.

Hand-foot skin reaction, proteinuria and hypertension were the most common adverse events in apatinib treatment, with grade 3/4 adverse events occurring in over 60% of patients with gastric carcinoma.^{11,12} Over 20% of patients experienced dose modifications with a recommended daily dose of apatinib (850 mg) treatment in a Phase III trial.¹² In another trial, the recommended daily dose was 500 mg and grade 3/4 toxicities significantly decreased, and the efficacy

was similar to those of high dose for breast carcinoma.²⁰ In the current study, a recommended dose of 500 mg was used. The results showed that grade 3/4 toxicities occurred in over half of the patients. Although different daily apatinib doses were used for gastric carcinoma (850 mg) and breast carcinoma (500 mg), similar toxicities were observed. It was considered that several patients with gastric carcinoma underwent previous gastrectomy, and the absorption ability of apatinib might be lowered.

Retrospective nature and a small sample size were two major limitations of the current study. In addition, the dose of 500 mg apatinib adopted in this study was not widely recommended. Hence, this dose must be confirmed by further prospective studies. However, without prospective clinical studies in the literature, our study may be deemed as meaningful.

Conclusion

Our results support that apatinib is efficacious for advanced ESCC as salvage treatment. However, further prospective studies are required to fully elucidate its efficacy and toxicity.

Table 4 Major toxicities of apatinib dosing

Toxicity	Total (%)	Grades 3/4 (%)	Dosage reduction (%)	Discontinuation (%)
Hand-foot syndrome	32 (51.6)	10 (16.1)	2 (20.0)	1 (33.3)
Hypertension	13 (21.0)	7 (11.3)	2 (20.0)	1 (33.3)
Proteinuria	15 (24.2)	7 (11.3)	2 (20.0)	1 (33.3)
Hepatic injury	12 (19.4)	5 (8.1)	0 (0.0)	0 (0.0)
Fatigue	9 (14.5)	3 (4.8)	2 (20.0)	0 (0.0)
Esophagitis	4 (6.5)	3 (4.8)	2 (20.0)	0 (0.0)
Nausea/vomiting	9 (14.5)	2 (4.8)	0 (0.0)	0 (0.0)

Disclosure

The authors report no conflicts of interest in this work.

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