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Efficacy and survival analysis of apatinib combined with capecitabine chemotherapy for second-line treatment of advanced esophageal cancer

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This study explore the efficacy, toxic and side effects and survival impact of apatinib combined with capecitabine chemotherapy for the second-line treatment of advanced esophageal cancer. The clinical data of 76 patients with advanced esophageal cancer treated from January 2015 to April 2020 have been retrospectively analyzed. They are divided into experimental and control groups according to different treatment methods. The experimental group (n=29) underwent oral apatinib targeted therapy (250 mg/once/d) combined with oral capecitabine chemotherapy (1000 mg/m^2 according to the body surface area on D1-14). Maintenance therapy with apatinib has been conducted after 4-6 cycles. The control group (n=47) received the second-line chemotherapy. After more than 2 cycles of chemotherapy, complete response is achieved in 0 cases, partial response in 19 cases, stable disease in 6 cases, and progressive disease in 3 cases. Overall response rate (ORR) is found to be 67.86% and the disease control rate is 89.28%. The median progression-free survival (mPFS) and the median overall survival (mOS) are 6.7 months and 8.9 months, respectively. Karnofsky Performance Status score of 2 points, liver metastasis, elevation of tumor marker squamous cell carcinoma and unsatisfactory efficacy are independent prognostic factors. In control group, ORR was 34.04%, and mPFS and mOS are 3.9 months and 7.4 months, respectively. No severe drug-related toxic and side effects have been observed, except for 1 patient who voluntarily discontinued treatment due to grade III hypertension. Apatinib combined with capecitabine chemotherapy shows good overall efficacy with satisfactory safety and tolerance for the second-line treatment of advanced esophageal cancer.

Keywords: Advanced esophageal cancer, Apatinib, Capecitabine, Chemotherapy, Efficacy, Survival

Esophageal cancer is one of the common digestive system malignancies in China. In terms of pathological types, adenocarcinomas are dominated in foreign countries, while squamous cell carcinoma (SCC) account for more than 95% in China[1]. Currently, patients with esophageal cancer have been mostly in the mid-late stage at the initial diagnosis, losing the opportunity for radical surgery[2-5]. In clinical treatment, therefore, patients primarily undergo comprehensive treatments such as chemotherapy and radiotherapy[6-9]. At present, fluorouracil (FU)-, platinum- and paclitaxel-based combination chemotherapy is adopted in the first-line systemic therapy. However, no standard regimen for the second-line treatment of advanced esophageal cancer has been recommended yet[10]. Chemotherapy drugs are more preferred for the second-line treatment, but have less prominent efficacy. There has been some progress in the second-line treatment of advanced esophageal cancer with the R&D of new drugs and the emergence of new treatment strategies. Apatinib, a China-made anti-angiogenic drug, suppresses tumor angiogenesis through selectively competing for the ATP binding site of vascular endothelial growth factor receptor 2 (VEGFR-2) and blocking the downstream signaling pathways, ultimately achieving tumor treatment[11]. Apatinib as molecular targeted drugs has been successfully applied in the treatment of advanced gastric cancer. However, patients with advanced esophageal cancer may have weak tolerance to combination chemotherapy due to poor general conditions at the time of the second-line treatment. Therefore, apatinib combined with oral capecitabine chemotherapy was adopted in the second-line treatment of advanced esophageal cancer in this paper, achieving satisfactory clinical efficacy and tolerance.

Experimental Section

General data

Inclusion criteria were as follows: (i) patients diagnosed with advanced esophageal cancer, and with at least one measurable lesion according to the RECIST, (ii) those with an expected survival period

>3 months, (iii) those with normal liver and kidney functions, hemogram and electrocardiogram, (iv) those who gave their informed consent, and (5) those with failed first line of treatment using paclitaxel combined with cisplatin.

Exclusion criteria were as follows: (i) patients with inability to swallow, chronic diarrhea or intestinal obstruction that significantly affected drug absorption and administration, (ii) those who could not tolerate chemotherapy due to liver, kidney or hematopoietic diseases, (iii) those who had tumors in other organs within 1 year before the start of treatment, (iv) those allergic to the drugs used, or (v) pregnant or lactating women.

The clinical data of 76 patients with advanced esophageal cancer treated from January 2015 to April 2020 were retrospectively analyzed. They were divided into experimental and control groups according to different treatment methods. They were all diagnosed as SCC using endoscopic biopsy of esophageal lesions or aspiration biopsy of postoperative metastatic lesions. In the experimental group (n=29), there were 13 males and 16 females aged 48-72 years old, with a median of 63 years old. Lymph node metastasis occurred in 11 out of the 29 patients. The Karnofsky Performance Status (KPS) score was 0-1 points in 19 cases and 2 points in 10 cases. The tumor marker SCC was elevated in 7 out of the 29 patients. All patients used to use taxanes and platinums rather than FU in the first-line chemotherapy. The control group (n=47) treated with the second-line chemotherapy included 33 males and 14 females aged 51-75 years old, with a median of 67 years old. Lymph node metastasis occurred in 19 out of the 47 patients. The KPS score was 0-1 points in 27 cases and 2 points in 20 cases. The tumor marker SCC was elevated in 11 out of the 47 patients. All patients used to use taxanes and platinums rather than FU in the first-line chemotherapy. The baseline data had no significant differences and were comparable between the two groups (Table 1).

Table 1 — Clinical data of patients

Variable		Experimental group (n=29)	Control group (n=47)	P
Gender	Male	13	33	0.0329
	Female	16	14	
Lymph node metastasis	Yes	17	20	0.2381
	No	12	27	
KPS score	≥80	20	27	0.3427
	<80	9	20	
SCC	Elevation	7	13	0.1942
	No elevation	22	34	

Clinical treatment

In experimental group, all patients orally took apatinib (specification: 0.25 g; Jiangsu Hengrui Pharmaceutical Co., Ltd., China; China SFDA Approval No. H20140103; 250 mg/time) half an hour after meals once a day. Meanwhile, capecitabine (specification: 0.05 g; Nanjing Yoko Pharmaceutical Co., Ltd., China; China SFDA Approval No. H20223015) was orally taken at a dose of 1000 mg/m^2 according to the body surface area half an hour after meals twice a day on D1-14, and the administration was repeated every 3 weeks. Capecitabine was orally administered by each patient for at least 2 cycles, during which blood pressure was regularly monitored, and liver and kidney function as well as blood and urine routine tests were conducted every week. Clinical efficacy was assessed by CT and/or MR every 2 cycles of capecitabine treatment.

In control group, 17 patients underwent irinotecan + cisplatin chemotherapy: 180 mg/m^2 irinotecan injection (specification: 5 mL:100 mg; Jiangsu Hengrui Pharmaceutical Co., Ltd., China; China SFDA Approval No. H20061276; *i.v. gtt.*) on D1, 75 mg/m^2 cisplatin injection (specification: 50 mL:50 mg; Qilu Pharmaceutical Co., Ltd., China; China SFDA Approval No. H20213819; *i.v. gtt.*) on D1-3. Twenty-one patients underwent irinotecan + FU or capecitabine chemotherapy: 180 mg/m^2 irinotecan injection (*i.v. gtt.*) on D1, 500 mg/m^2 FU injection (specification: 10 mL:0.25 g; Shanghai Xudong Haipu Pharmaceutical Co., Ltd., China; China SFDA Approval No. H31020593; *i.v. gtt.*) on D1-5 or 1000 mg/m^2 oral capecitabine twice a day. Vinorelbine + cisplatin chemotherapy was adopted in 7 cases: 25 mg/m^2 vinorelbine injection (specification: 1 mL:10 mg; Hangzhou Sanofi Minsheng Pharmaceutical Co., Ltd., China; China SFDA Approval No. H31020593; *i.v. gtt.*) on D1 and D8, and 75 mg/m^2 cisplatin injection on D1-3. Capecitabine chemotherapy alone was used in 2 cases: 1000 mg/m^2 oral capecitabine twice a day. Clinical efficacy was assessed by CT and/or MR every 2 cycles of chemotherapy.

Criteria for clinical assessment

The clinical efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST)[12]: (i) Complete response (CR): The lesions

disappear after treatment. (ii) Partial response (PR): The sum of the longest diameter of lesions decreases by ≥30% after treatment. (iii) Progressive disease (PD): The sum of the longest diameter of lesions increases by ≥20% after treatment or there are new lesions. (iv) Stable disease (SD): After treatment, the sum of the longest diameter of lesions decreases not so far as PR or increases not so far as PD. The efficacy was assessed by imaging examination every 2 cycles of oral capecitabine chemotherapy.

Survival analysis

All patients were followed up after treatment by WeChat, telephone and regular review. The time to progression (TTP) was defined as the duration from the start of treatment to the progression of tumor lesions. Overall survival (OS) was defined as the duration from the start of treatment to the patient's death of esophageal cancer.

Observation of adverse reactions

The adverse reactions were classified into grade 0-IV according to the World Health Organization (WHO) evaluation criteria for adverse events of chemotherapeutic drugs.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. The overall response rate (ORR) = (CR cases + PR cases)/total cases (n). The disease control rate (DCR) = (CR cases + PR cases + SD cases)/total cases (n). The count data were compared using the Fisher's test or χ^2 test. Kaplan-Meier survival analysis was conducted and the log-rank test was performed. $P<0.05$ was considered statistically significant.

Results

Treatment outcomes

In experimental group, 1 patient discontinued apatinib treatment due to hypertension during the first cycle of treatment, and the remaining 28 patients completed more than 2 cycles of chemotherapy. The median number of chemotherapy cycles was 4 (2-6), and the efficacy could be assessed. CR was achieved in 0 cases, PR in 19 cases, SD in 6 cases and PD in 3 cases. The ORR was 67.86% and the DCR was 89.28%. The median progression-free survival (mPFS) reached 6.7 months. In control group, all patients completed more than 2 cycles of chemotherapy. The median number of chemotherapy cycles was 3.8 (2-6), and the efficacy could be assessed. CR was achieved in 0 cases, PR in 16 cases, SD in 24 cases and PD in 7 cases. The ORR was 34.04% and the DCR was 85.10%. The mPFS and mOS were 3.9 months and 7.4 months, respectively (Table 2).

Toxic and side effects

The adverse reactions in experimental group during treatment were recorded. In terms of hematological toxicity, there were 12 cases (42.86%) of leukopenia and 4 cases (14.29%) of thrombocytopenia. In terms of non-hematological toxicity, hypertension occurred in 10 cases (35.71%), including 1 case who discontinued treatment due to grade III hypertension, and the blood pressure in the remaining 9 cases with grade I-II hypertension could be kept normal by antihypertensive drugs. Other adverse reactions including hand-foot syndrome in 8 cases (28.57%), proteinuria in 5 cases (17.86%), fatigue in 11 cases (39.29%) and nausea and vomiting in 6 cases (21.43%) were all effectively relieved after prompt symptomatic treatment, and they could be tolerated by patients during treatment, with no need of drug withdrawal or dosage reduction, which did not affect the clinical treatment. In control group, the hematological toxic reactions included leukopenia in 19 cases (40.42%) and thrombocytopenia in 21 cases (44.68%). The non-hematological toxic reactions included hypertension in 10 cases (21.28%), hand-foot syndrome in 17 cases (36.17%), proteinuria in 12 cases (25.53%), fatigue in 20 cases (42.55%), and nausea and vomiting in 16 cases (34.04%). The adverse reactions had no statistically significant differences between experimental group and control group ($P>0.05$) (Table 3).

Survival analysis results

The follow-up rate was 100% as of November 1, 2020. The mPFS in experimental group (6.7 months) and control group (3.9 months) had a statistically significant difference ($P<0.01$) (Figure 1). The mOS also had a statistically significant difference between experimental group (8.9 months) and control group

Table 2 — Short-term efficacy [n (%)]

Group	CR	PR	SD	PD	OR(%)
Experimental group (n=29)	0	19	6	3	67.86
Control group (n=47)	0	16	24	7	34.04
χ^2		8.3820			
P		0.0151			

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate.

Table 3 — Main adverse reactions [n (%)]

Group	Leukopenia		Thrombocytopenia		Hypertension		Hand-foot syndrome		Proteinuria		Fatigue		Nausea and vomiting	
	I-II	III-IV	I-II	III- IV	I-II	III- IV	I-II	III- IV	I-II	III- IV	I-II	III- IV	I-II	III- IV
Experimental group	10	2	3	1	9	1	6	3	3	1	5	3	5	1
Control group	14	5	9	12	10	0	13	4	7	7	16	5	12	6
P	0.6757		0.3217		0.9999		0.6613		0.5882		0.6460		0.6287	

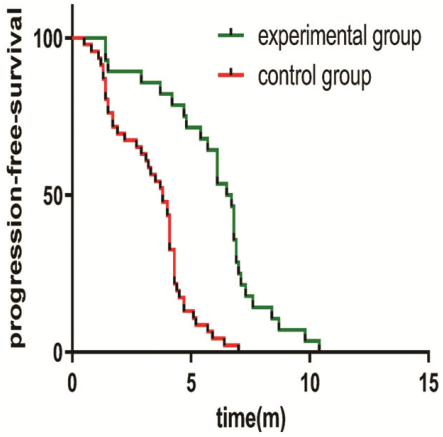

Fig. 1 — PFS of two groups.

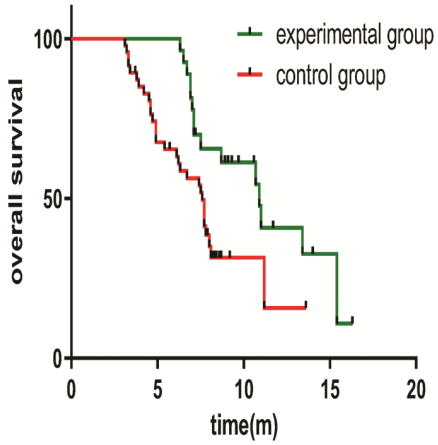

Fig. 2 — OS of two groups.

(4.5 months) (P=0.0147) (Figure 2). At the end of follow-up, there were 5 survivors in experimental group and 3 survivors in control group.

Prognostic factors affecting PFS

It was found by univariate analysis that PFS was not related to age, gender or smoking history (P>0.05), but related to lymph node metastasis, KPS score and SCC level (P<0.05) (Table 4). According to further multivariate Cox regression analysis, KPS score and SCC level were independent prognostic factors for PFS of patients (Table 5).

Table 4 — Univariate analysis results

Variable	n	mPFS (d)	P
Age (Y)			
≥60	10	158	0.3260
<60	18	182	
Gender			
Male	13	189	0.5625
Female	15	172	
Smoking history			
Yes	17	165	0.1754
No	11	185	
Lymph node metastasis			
Yes	16	125	0.0432
No	12	213	
KPS score			
≥80	20	205	0.0499
<80	8	193	
SCC			
Elevation	6	161	0.0096
No elevation	22	180	

Table 5 — Multivariate Cox regression analysis results

Variable	P	Hazard ratio (HR)	95% CI
Lymph node metastasis	0.6431	1.781	0.971-3.352
KPS score	<0.01	2.075	1.203-3.753
SCC	<0.01	2.158	1.166-3.805

Discussion

Due to less specific early clinical symptoms, most patients with esophageal cancer have been in the mid-late stage when diagnosed, and surgical treatment can be performed in less than 40% of patients. Therefore, patients with advanced esophageal cancer are primarily treated with chemotherapy. Moreover, patients with advanced esophageal cancer are often too weak in physical conditions to tolerate high-intensity chemotherapy, so the selection of chemotherapy drugs is faced with increasingly higher requirements. Anti-tumor angiogenesis and tumor-targeted therapies have become research hotspots in the field of esophageal cancer treatment so far, and they have also been gradually used in clinical treatment.

Apatinib, an anti-angiogenic drug independently developed by China, is an anti-VEGFR-2 tyrosine

kinase inhibitor, and it blocks VEGF signal transduction in tumor cells and inhibits angiogenesis through competitive binding to the tyrosine ATP-binding site in tumor cells and suppressing its phosphorylation[13]. Meanwhile, it can also inhibit platelet-derived growth factor receptor-β and c-Kit, thereby resisting the tumor cell growth. After drug administration, apatinib is mainly metabolized through feces and urine at a rate of 80% within 96 h, so it is highly safe[14]. In a single-arm open-label phase II study on apatinib monotherapy for unresectable metastatic esophageal cancer, Li *et al*.[15] enrolled 26 cases for the efficacy analysis, with a median follow-up period of 5.34 months. The results showed that PR was achieved in 2 cases (7.7%) and SD in 14 cases (53.8%), and the ORR and DCR were 7.7% and 61.5%, respectively.

Capecitabine, a new-generation oral drug of FU, is absorbed in the gastrointestinal tract basically in the form of drug substance, and it exerts an anti-tumor effect ultimately in the form of 5-FU after metabolism. It has been found that thymidine phosphorylase, an enzyme required in the last link of capecitabine metabolism, has a far higher concentration in tumor tissues than that in normal tissues, so that it concentrates in tumor tissues to exert a tumor-selective cytotoxic effect, with little impact on normal tissues. Therefore, capecitabine is selectively activated in tumor tissues, greatly increasing its concentration in tumor cells and enhancing its anti-tumor effect, and its systemic toxicity is also greatly relieved, making efficient targeted therapy possible. Obvious cytotoxicity of capecitabine to esophageal cancer EC9706 cell lines *in vitro* was found by Cheraghi *et al*.[16]. FU + platinum combination therapy was often adopted in the first-line treatment of advanced esophageal cancer previously. Then the new-generation taxanes have been widely used in the treatment of esophageal cancer, and taxane + platinum combination therapy is also recommended for the first-line treatment of advanced esophageal cancer. To sum up, the chemotherapy of esophageal cancer has made little progress in the last few decades, whereas the attention has been paid to targeted therapy and immunotherapy at present.

In this study, apatinib + capecitabine chemotherapy was conducted on 29 patients with advanced esophageal cancer. One patient discontinued apatinib treatment due to grade III hypertension during the first cycle of treatment, and the remaining 28 patients completed more than 2 cycles of chemotherapy. The ORR was 67.86% and the DCR was 89.28%. The incidence rates of leukopenia and hypertension were high, but the general conditions of patients were good, and the adverse reactions could be effectively relieved after prompt symptomatic treatment. No statistically significant difference was found in adverse reactions between experimental group and control group ($P>0.05$). Chi *et al*.[17]. reported that the disease control rate of 39 patients with esophageal SCC treated with apatinib combined with capecitabine was 87.2%, and the common adverse events were mostly grade I to II. As reported by Kanekiyo *et al*.[18], ORR and DCR were 21.2% and 60.6%, respectively, among 33 advanced esophageal cancer patients treated with docetaxel + nedaplatin second-line chemotherapy. Taken together, apatinib combined with capecitabine is effective and safe for the treatment of patients with advanced esophageal cancer who have failed first-line therapy, which may be attributed to the following reasons. Firstly, apatinib works through competitive binding to the tyrosine ATP binding site of tumor cells, which inhibits the phosphorylation process to block the vascular endothelial growth factor signal transduction and angiogenesis in tumor cells[19]. Meanwhile, apatinib can also inhibit platelet production factor receptor-β and c-kit to suppress tumor cell growth. Apatinib is mainly metabolized through feces and urine after administration, and about 80% can be metabolized within 96 h, so it has high safety[20]. Secondly, capecitabine is selectively activated in tumors by being converted into 5-FU in the presence of high-concentration thymidine phosphorylase, thereby enhancing the antitumor effect[21]. The selective activation markedly alleviates the systemic toxicity, allowing efficient targeted therapy[22].

According to the follow-up results herein, mPFS and mOS were 6.7 months and 8.9 months in experimental group, 3.9 months and 4.5 months in control group, respectively. Consistently, among the advanced esophageal cancer patients undergoing combination chemotherapy in the second-line treatment, ORR and DCR were about 30% (23.3-39.3%) and 70% (66.73-73.1%), and mOS was nearly 8 months[23-25], further verifying that the efficacy of apatinib + capecitabine chemotherapy was superior to that of the second-line chemotherapy on the treatment of advanced esophageal cancer. The KPS score and SCC level were independent prognostic factors for

PFS of patients. The KPS score <80 points, poor physical conditions and elevation of SCC level suggest the late tumor stage, high tumor burden and weak tolerance to treatment, and, as a result, the efficacy is impacted.

In conclusion, the general conditions of patients with advanced esophageal cancer are poor in the late stage. The patients have a good compliance with the convenient and simple oral medication of apatinib and capecitabine, enabling them to enjoy a normal life at home. The sample size was small in this study, so further clinical studies are required.

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