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Original Article

Effect of different doses of apatinib mesylate combined with chemotherapy on advanced oral cancer

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Abstract: Objective: To investigate the therapeutic effect and safety of different doses of apatinib mesylate combined with chemotherapy in the treatment of advanced oral cancer. Methods: Totally 100 patients with advanced oral cancer admitted to our hospital from January 2019 to July 2020 were retrospectively analyzed and divided into a control group (500 mg apatinib mesylate combined with chemotherapy) and an experimental group (250 mg apatinib mesylate combined with chemotherapy). The two groups were compared in terms of the incidence of adverse reactions, treatment effective rate, disease control rate, objective response rate, Karnofsky performance status (KPS) score (quality of life), score of the mental status scale in non-psychiatric settings (MSSNS), survival rates and vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2 (VEGFR-2) after treatment. In addition, logistic regression was used to analyze the influencing factors for KPS<85 after oral cancer treatment. Results: The treatment effective rate, disease control rate, objective response rate, KPS score (quality of life), survival rates in the experimental group were all significantly improved compared to those in the control group (all P<0.05), and the incidence of adverse reactions, MSSNS score, and the levels of VEGF and VEGFR-2 after treatment in the experimental group were significantly lower than those in the control group (all P<0.05). Furthermore, a history of smoking, a history of drinking, a tooth brushing index <3, the frequency of teeth cleansing ≤1 time per year, a history of oral diseases >3 times, and poor nutritional status were independent risk factors for KPS<85 after oral cancer treatment. Conclusion: Apatinib mesylate (250 mg) combined with chemotherapy can reach optimal efficacy with highest safety but least adverse effects for patients with advanced oral cancer.

Keywords: Apatinib mesylate, chemotherapy, advanced oral cancer, safety, effectiveness, different doses

Introduction

Oral cancer generally refers to the malignant tumors in the oral cavity, including tongue cancer, gum cancer, etc. Patients with oral cancer suffer long-lasting or repeated oral ulcers and feel pain during eating and speaking, which greatly reduces their quality of life [1-3]. Generally, the preferred treatment for such patients is surgery. However, surgery is more suitable for patients with early tumors, as they are more likely to have complete resection that can effectively inhibit cancer recurrence because of their smaller tumor tissues [4-6]. For patients with advanced oral cancer, chemotherapy is usually recommended to inhibit and inactivate tumor cells, which aims to slow down the progression, inhibit tumor cell growth and prolong the survival of patients [7-9]. Apatinib mesylate is a drug intended for the treatment of advanced cancers. At present, it is commonly used with a high dose for treatment. Despite obvious therapeutic effect, its side effects are relatively extensive, so, many patients fail to adapt to the high-dose treatment. This study mainly evaluated the therapeutic effect and safety of 250 mg and 500 mg apatinib mesylate combined with chemotherapy in the treatment of patients with (advanced) oral cancer.

Materials and methods

Materials

A total of 100 patients with advanced oral cancer admitted to our hospital from January 2019 to July 2020 were enrolled and divided into a control group and an experimental group based

on the treatment method, with 50 cases in each group. Patients in the control group were 29-72 years old, and those in the experimental group were 30-71 years old. This study was approved by the hospital ethics committee (2018-12-11).

Inclusion/exclusion criteria

Inclusion criteria: (1) Patients with clinical manifestations of oral cancer in the middle or late stages; (2) Patient at an age of ≥18 years old; (3) Patients with normal liver and kidney functions; (4) Patients without other organic diseases, and history of allergies; (5) Patients voluntarily participated in the study and signed an informed consent form.

Exclusion criteria: (1) Patients with a consciousness disorder or unable to cooperate with the research; (2) Patients with other organic diseases; (3) Patients with early oral cancer.

Methods

Patients in the control group were treated with 500 mg apatinib mesylate (producer: Jiangsu Hengrui Pharmaceutical Co., Ltd.; SFDA approval number: H20140104; specification: 0.25 g) combined with chemotherapy, 2 tablets each time, once a day, until they developed severe intolerance. In contrast, patients in the experimental group received 250 mg apatinib mesylate combined with chemotherapy, 1 tablet each time, once a day, until they developed severe intolerance [10-12].

Both groups of patients received conventional chemotherapy. Specifically, Tigio capsules (producer: Jiangsu Hengrui Pharmaceutical Co., Ltd.; SFDA approval number: H20100135; Specification: 20 mg) were administered according to their body surface area: 40 mg each time and twice a day for those with the body surface less than 1.25 m^2; 40 mg in the morning and 60 mg in the evening (twice a day) for those with the body surface area of 1.25-1.50 m^2; 60 mg each time and twice a day for those with the body surface area larger than 1.5 m^2.

Indicators

The two groups were compared in the following items: the incidence of adverse reactions, treatment effective rate, disease control rate, objective response rate, Karnofsky performance status (KPS) score (quality of life) [11], score of the mental status scale in non-psychiatric settings (MSSNS) [12], survival rates within 1 month, 2 months, and 3 months after treatment and the levels of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2 (VEGFR-2) after treatment [13].

Treatment efficacy was classified into markedly effective, effective and ineffective. Markedly effective: complete relief with focus cleared; Effective: partial relief without enlarged target lesion; Ineffective: no relief with increased lesion.

The lower the expression levels of VEGF and VEGFR-2, the greater the probability of survival of the patient.

The response evaluation criteria for solid tumors (RECIST) include: Complete response (CR): disappearance of all target lesions; Partial response (PR): at least a 30% decrease in the sum of the longest diameter of the measured lesions; Progressive disease (PD): a 20% or greater increase in the sum of the longest diameter of measured lesions or more new lesions; Stable disease (SD): insufficient lesion shrinkage to qualify for PR nor sufficient increase to qualify for PD [13-15]. Objective response rate (ORR) = (CR + PR)/total number*100%; disease control rate (DCR) = (CR + PR + SD)/total number*100%.

KPS has a full score of 100 points, and the higher the score, the better the health condition and the higher the tolerance to the side effects of treatment.

The MSSNS score has a dividing line of 60 points with a score below 60 indicating normal mental state, a score of 60 to 70 indicating mildly abnormal mental state, and a score of more than 70 indicating abnormal mental state.

Statistical analysis

The data in this study were all processed by the statistical analysis software SPSS20.0. The measurement data were expressed as "mean ± standard deviation" (x±S), and their comparison among multiple groups was performed by the single-factor analysis of variance or repeat-

Table 1. Statistical comparison of materials ($\bar{x}\pm s$)

Group		Experimental Group	Control Group	X^2/t	P
Gender (male/female)		25/25	26/24	0.36	0.55
Age (year-old)		47.62±4.25	47.31±4.53	0.35	0.73
Height (cm)		169.82±9.86	169.76±9.26	0.03	0.98
Weight (kg)		75.59±6.02	75.00±5.96	0.49	0.62
Course of Disease (months)		3.39±0.69	3.32±0.73	0.49	0.62
Hypertension (number of cases)		10	11	0.06	0.81
Diabetes (number of cases)		10	7	0.64	0.42
Hyperlipidemia (number of cases)		4	6	0.44	0.51
Tumor Types	Tongue Cancer	22	20	0.16	0.69
	Gum Cancer	25	26	0.04	0.84
	Lip Cancer	3	4	0.15	0.70

Table 2. Comparison of effective rate of treatment between the two groups

Group	Markedly effective	Effective	Ineffective	Effective rate [n (%)]
Experimental group	33	12	5	45(90)
Control group	16	18	16	34(68)
X^2				7.29
P				0.007

Table 3. Comparison of the incidence rate of adverse reactions between the two groups

Group	Proteinuria	Leukopenia	Hypertension	Total Incidence Rate (%)
Experimental Group	2	0	0	4%
Control Group	5	1	3	18%
X^2				5.01
P				0.03

Table 4. Comparison of disease control rate and objective response rate between the two groups

Group	CR	PR	SD	PD	Disease Control Rate (%)	Objective Response Rate (%)
Experimental Group	2	38	9	1	98%	80%
Control Group	0	29	10	11	78%	58%
X^2					9.47	5.66
P					0.002	0.017

ed measures analysis of variance, and pairwise comparison by the LSD-t-test. The count data were expressed by percentage (%), and their comparison among multiple groups was analyzed by χ^2. In addition, *Logistic* regression was used to analyze the influencing factors for KPS<85 after oral cancer treatment. P<0.05 means that the difference is statistically significant.

Results

Comparison of general information

There was no statistical significance in general data such as gender, age, and course of disease between the two groups (P>0.05). See **Table 1**.

Comparison of treatment efficacy between the two groups

Compared with the control group, the experimental group yielded a more favorable outcome in terms of the effective rate of treatment (P< 0.05). See **Table 2**.

Comparison of the incidence of adverse reactions between the two groups

The experimental group showed a lower incidence rate of adverse reactions than the control group (P<0.05). See **Table 3**.

Comparison of disease control rate and objective response rate between the two groups

The disease control rate and objective response rate of the experimental group were both significantly higher than those of the control group (both P<0.05). See **Table 4**.

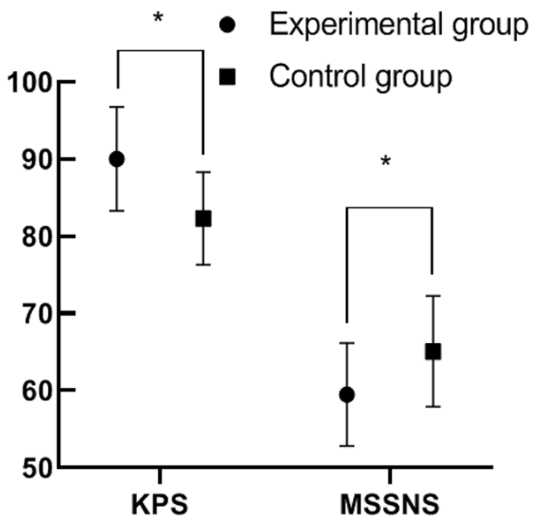

Figure 1. Comparison of KPS scores (quality of life) and MSSNS scores between the two groups. Note: The abscissa indicates the KPS and MSSNS scores from left to right, and the ordinate indicates the points. Comparison of the KPS score of the experimental group (90.03±6.73) with that of the control group (82.30±6.00), t=6.06, *P<0.05, and the comparison result was statistically significant; Comparison of the MSSNS score of the experimental group (59.48±6.66) with that of the control group (65.07±7.19), t=4.03, *P=0.003, and the comparison result was statistically significant.

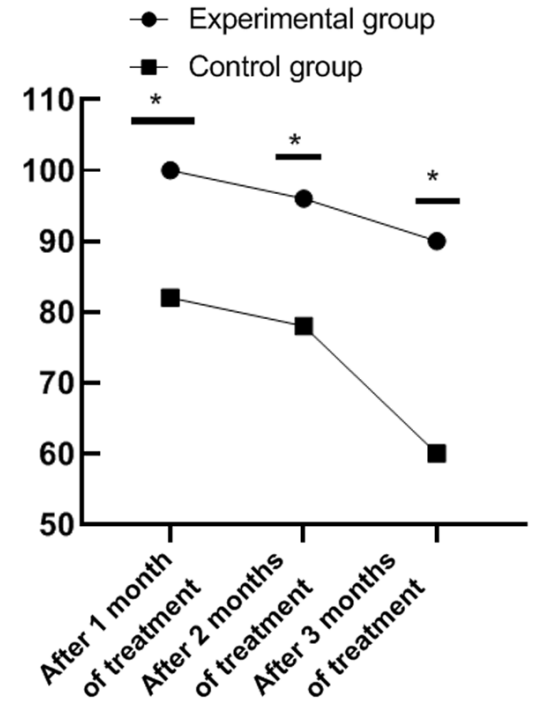

Figure 2. Comparison of survival rates in January, February, and March after treatment between the two groups. Note: The abscissa represents 1 month, 2 months and 3 months after treatment, and the ordinate represents the survival rate of patients. One month after treatment, the survival rate of patients in the experimental group was 100% and that in the control group was 82%, X^2=9.89, *P=0.002, so the comparison result was statistically significant; Two months after treatment, the survival rate of patients in the experimental group was 96% and that in the control group was 78%, X^2=7.16, *P=0.007, so the comparison result was statistically significant; Three months after treatment, the survival rate of patients in the experimental group was 90% and that in the control group was 60%, X^2=12.00, *P=0.001, so the comparison result was statistically significant.

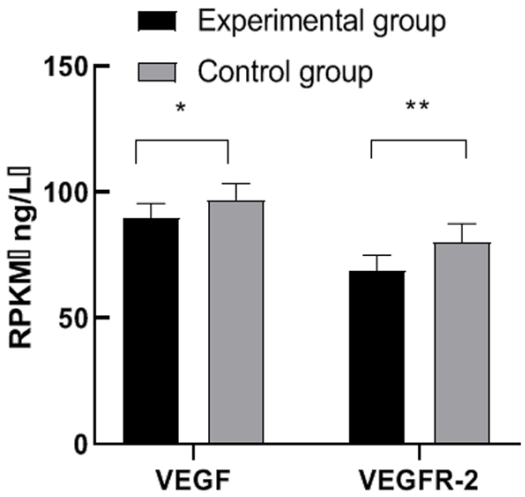

Figure 3. Comparison of VEGF and VEGFR-2 levels after treatment between the two groups. Note: The abscissa represents VEGF and VEGFR-2 from left to right, and the ordinate represents the expression level. Comparison between the VEGF level of the experimental group (89.56±5.88) ng/L and that of the control group (96.88±6.57) ng/L, t=5.87, *P<0.05, and the comparison result was statistically significant; Comparison between the VEGFR-2 level of the experimental group (68.74±6.33) ng/L and that of the control group (80.12±7.42) ng/L, t=8.25, **P<0.01, and the comparison result was statistically significant.

Comparison of KPS scores (quality of life) and MSSNS scores between the two groups

A higher KPS score was obtained in the experimental group than that in the control group, and the experimental group showed a lower MSSNS score, as compared to the control group (P<0.05). See **Figure 1**.

Comparison of survival rates within 1 month, 2 months, and 3 months after treatment between the two groups

Results in **Figure 2** present a superior survival rate in the experimental group than that in the control group 1, 2 and 3 months after treatment (all P<0.05).

Table 5. Univariate analysis of related influencing factors of KPS<85 score after oral treatment

Index	KPS≥85 score	KPS<85 score	X^2	*P*-value
Occupation			1.356	0.964
Physical labour	26	24		
Mental labour	24	26		
Smoking				
Yes	12	37	2.365	0.001
No	38	13		
Drinking			2.964	0.002
Yes	11	36		
No	39	14		
Teeth brushing index			5.364	0.001
<3	13	40		
≥3	37	10		
Frequency of teeth cleaning (year)			9.458	0.002
<1	14	42		
≥1	36	8		
Teeth cleaning			8.452	0.001
yes	47	16		
no	3	34		
Times of oral disease visits			6.354	0.002
<3	36	11		
≥3	14	39		
Nutritional status			4.368	0.004
Normal	38	16		
Poor	12	34		

Comparison of VEGF and VEGFR-2 levels after treatment between the two groups

After treatment, the levels of VEGF and VEGFR-2 in the experimental group were lower than those in the control group (both P<0.05). See **Figure 3**.

Univariate analysis of factors for KPS<85 after oral cancer treatment

After oral cancer treatment, the two groups of patients with different KPS scores had a statistically significant difference in smoking history, drinking history, tooth brushing frequency, cleaning treatment, tooth cleaning at the time of treatment, oral disease history, and nutritional status indicators (all P<0.05, **Table 5**).

Multivariate analysis of factors for KPS<85 after oral cancer treatment

A history of smoking, a history of drinking, a tooth brushing index <3, frequency of cleansing treatments ≤1 time per year, a history of oral diseases> 3 times, and poor nutritional status were independent risk factors for KPS<85 after oral cancer treatment (all P<0.05, **Table 6**).

Discussion

Oral cancer has a relatively high incidence rate, and its manifestations are obvious. Its early symptoms include recurrent oral ulcers and difficulty in opening the mouth. Patients with middle or late oral cancer suffer long-lasting oral ulcers, and there are usually color changes and purulent of the ulcer part [16-18]. Patients with early oral cancer can be treated with tumor resection, which can effectively remove the tumor tissues and inhibit the spread of the tumor cells. However, for those with oral cancer in the middle or late stage, it is difficult to remove the extensive tumor tissues by one-time surgery [19-21]. Therefore, those patients usually undergo chemotherapy to inhibit the growth and development of tumor. Chemotherapy can be combined with other drugs to inhibit the growth of tumor cells, such as apatinib mesylate, a drug specifically used for the treatment of advanced cancer. In clinical application, it has been found that apatinib mesylate can effectively improve the therapeutic effect with a sound clinical efficacy. However, under the most commonly used method of administration of apatinib emesylate, many patients have suffered severe intolerance and some serious complications. Under such circumstances, although the overdose of apatinib mesylate brings the disease under control, it will cause other complications [22-24]. This paper mainly investigated the efficacy and safety of different doses of apatinib mesylate combined with chemotherapy in patients with advanced oral cancer. The goal is to find the safest and most effective dosage of apatinib mesylate.

Table 6. Multivariate analysis of related influencing factors of KPS<85 score after oral treatment

Index	β	SE	Wald	P	OR	95% CI
Smoking	1.074	0.465	5.324	0.026	2.147	0.897-5.364
Drinking	1.136	0.911	1.632	0.001	2.364	1.236-10.355
Teeth brushing <3	1.425	0.934	2.364	0.007	4.156	1.638-13.652
Frequency of teeth cleaning ≤1	1.365	0.998	2.345	0.002	4.637	1.758-15.364
Oral disease visits >3	0.836	0.364	1.524	0.031	2.311	0.564-5.116
Poor nutritional status	1.431	1.456	0.948	0.021	4.634	1.421-12.365

The results showed that the treatment effect, disease control rate, objective response rate, adverse reactions, survival rate of patients, and patient's quality of life were all significantly improved in the experimental group treated with 250 mg apatinib mesylate combined with chemotherapy compared with the control group treated with 500 mg apatinib mesylate combined with chemotherapy. Apatinib mesylate has the advantages of high precision and high efficiency in the treatment of advanced cancer, but due to its irritation, some patients may have serious intolerance. Besides, in this study, apatinib mesylate was administrated until the patient had a severe intolerance to it, which meant that the patient would be treated with apatinib mesylate for a longer time when he/she experienced a longer period before having a severe intolerance reaction, and the treatment for oral cancer would be more effective correspondingly. Therefore, the use of a larger dose of apatinib mesylate will shorten the treatment time for some poorly tolerated patients. A shorter acting time of apatinib mesylate indicates greater compromises of its clinical efficacy. In this study, the 250 mg dose of apatinib mesylate was compared with the 500 mg dose regime, and the results showed that the former demonstrated better overall treatment effect and higher safety. By analyzing the adverse reactions, it is possible to carry out treatment against possible adverse reactions and to investigate the safety of the treatment. Caiping Nie et al. [25] once proposed that the treatment effect of apatinib mesylate combined with chemotherapy for patients with advanced oral cancer was good, and the optimal therapeutic effect and safety were achieved when the dose of apatinib mesylate was 250 mg. The conclusion is consistent with the results of the present study. Moreover, a history of smoking, a history of drinking, a tooth brushing index <3, the frequency of teeth cleansing ≤1 time per year, a history of oral diseases >3 times, and poor nutritional status were independent risk factors for KPS<85 after oral cancer treatment.

In summary, 250 mg apatinib mesylate combined with chemotherapy can reach optimal efficacy with highest safety and least adverse effects on patients with advanced oral cancer.

Disclosure of conflict of interest

None.

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