

Original Research Article

Efficacy of some selected neo-adjuvant chemotherapy regimens in the treatment of advanced oral squamous cell carcinoma, and their effects on immune function

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Abstract

Purpose: To investigate the clinical efficacy of different neo-adjuvant chemotherapy (NACT) regimens in the treatment of advanced oral squamous cell carcinoma (OSCC), and their influence on immune function of the patients.

Methods: Advanced OSCC patients (n = 94) who received NACT served as subjects in this study. They were assigned to 2 different treatment groups. Forty patients received docetaxel and fluorouracil regimen (DF group), while 54 patients received taxotere, cisplatin and fluorouracil regimen (TPF group). Surgery was performed after NACT. Changes in clinical efficacy and immune function were monitored in both groups. The clinical baseline data of patients were assessed prior to the treatments. Independent indicators of prognosis were determined using Cox regression analysis (CRA).

Results: Clinical treatment efficacy was higher in TPF group than in DF group (p < 0.05). Objective remission rate (ORR) in DF group was lower than that in TPF group (p < 0.05). After chemotherapy, both groups had increased levels of CD4+ and CD4+/CD8+, and reduced level of CD8+, when compared with pre-chemotherapy values, with higher levels of CD4+ and CD4+/CD8+ ratio, and lower level of CD8+ in TPF group than in DF group (p < 0.05). Multivariate CRA revealed that the independent factors for prognosis of oral carcinoma (OC) were tumor node metastasis (TNM) stage and lymph node metastasis.

Conclusion: These results indicate that TFP regimen improves clinical efficacy and immune function in patients with advanced OSCC.

Keywords: Neo-adjuvant chemotherapy, Advanced oral carcinoma, Immune function, Docetaxel, Fluorouracil, Taxotere, Cisplatin, Fluorouracil regimen

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INTRODUCTION

Oral cancer (OC) is the most common head and neck carcinoma [1]. The most frequently seen type of OC is OSCC [2]. Statistics show that the

incidence of OC ranks sixth among all tumors, with Southeast Asia being the region with the highest incidence worldwide [3]. Numerous clinical treatments are currently available for OC, and the prognosis of patients can be

substantially improved using combination of adjuvant chemotherapy and surgery [4]. However, surgery is inadvisable for patients at advanced stages of the disease. Thus, for these patients, there is a recourse to radiotherapy and chemotherapy as the main treatment options. Research has revealed that long-term radiotherapy and chemotherapy reduce the sensitivity of tumors to drugs, leading to treatment failure [5]. In addition, the post-chemotherapy recurrence may exceed 50 % [6]. Therefore, it is particularly important to find a new treatment scheme for improving the prognosis of OC patients. Neo-adjuvant chemotherapy (NACT) reduces OSCC tumor load and improves surgical resection and negative margin, and timely treatment of subclinical metastatic lesions reduces tumor metastasis through systemic and systematic cytotoxicity [7]. The cisplatin + 5-fluorouracil (DF regimen), a routine chemotherapy regimen, has become the first-line treatment regimen in clinical practice [8]. A study by Schoenfeld *et al* [9] reported that the new adjuvant i.e. nivolumab or nivolumab plus ipilimumab effectively improved clinical treatment efficacy in untreated OSCC patients. Docetaxel + nedaplatin + tegafur (TPF regimen) is a new regimen for clinical treatment of OC [10]. It has been reported that TPF-induced chemotherapy improved the curative effect in patients with squamous cell cancer of head and neck (SCCHN), when compared with PF-induced therapy [11]. However, TPF-induced chemotherapy has also been reported to be ineffective in improving overall treatment efficacy in patients with SCCHN, resulting in poor prognosis [12]. This research was carried out to compare the effectiveness of PF and TPF in the treatment of advanced OSCC, in an attempt to generate clinical data for development of new therapies for the disease.

METHODS

Clinical data

A total of 94 subjects in advanced stage of OSCC who received NACT in Wuming Hospital Affiliated to Guangxi Medical University were assigned to two groups, based on treatment scheme. Forty patients received DF regimen (DF group), while 54 patients received TPF regimen (TPF group). All patients underwent surgery after NACT.

Inclusion criteria

The included patients were those who conformed with the International Union Against Cancer staging criteria issued in 2002; patients who were

diagnosed with advanced OC based on imaging and pathological tests; those who did not receive anti-tumor therapy prior to this study, and patients who cooperated during the follow-up period.

Exclusion criteria

Patients who were allergic to the chemotherapy regimen used; those who had other immune diseases or malignant tumors, and patients with expected survival time of less than 12 weeks, were excluded from the study. The research was approved by the Medical Ethical Committee of Guangxi Medical University (approval no. 2014-DC263), and was carried out in conformity with the guidelines of Declaration of Helsinki [13].

Treatments

The patients were treated either with DF regimen or TPF regimen. The DF regimen comprised cisplatin (75 - 100 mg/m²) given via intravenous drip for 1 - 2 days, and 5-FU (750 mg/m²) administered via intravenous drip for 2 - 6 days. The TPF regimen consisted of docetaxel (75 mg/m²) which was administered through intravenous drip for 24 h; nedaplatin (80 mg/m²) given via intravenous drip for 1 - 2 days, and tegafur (15 mg/kg) administered via intravenous drip for 2 - 6 days. Following administration of NACT, the patients received surgical treatment involving 2-cm extended resection of the primary lesion. Patients with cN0 underwent selective neck dissection in the I-III region, while those with cN+ underwent radical neck dissection. Tissue defect repair with free flaps was used for large tissue defects to achieve functional

Outcomes evaluated

Before and after NACT, peripheral blood was collected for determination of CD4+, CD8+, and CD4+/CD8+ ratio using an automatic flow cytometer (BD FACS Calibur, USA).

Primary outcomes

Before and after chemotherapy, changes in clinical efficacy and immune function were monitored in both groups.

Secondary outcomes

The clinical baseline data of patients were monitored. Incidence of adverse reactions was monitored in both groups. The patients were followed up, and CRA was used for identification of independent factors for prognosis of OC in the patients.

Therapeutic effectiveness

Patients were assessed based on head computerized tomography (CT), magnetic resonance imaging (MRI), and neck ultrasound. Clinical efficacy of treatment in each group was assessed with RECIST1.1 which was categorized into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) [14]. Thereafter, ORR and disease control rate (DCR) were calculated as shown in Eqs 1 and 2.

$$ORR = \{(CR + PR)/TC\} \dots\dots\dots (1)$$

$$DCR = \{(CR + PR + SD)/TC\} \dots\dots\dots (2)$$

where *TC* is the total number of patients.

Statistical analysis

Counting data are expressed as percentage (%), and were analyzed using *t*-test, while measurement data were processed using chi-squared (χ^2) test. Mann-Whitney test was applied for ranked data. The survival of patients was depicted with K-M survival curve, while Log-rank test was used for analysis. All statistical analyses were done with SPSS version 20.0. Statistical significance of difference was assumed at $p < 0.05$.

Table 1: Comparison of patients' profiles between the two groups

Group	DF (n=40)	TPF (n=54)	P-value	
Age				
	≥60 years old (n=45)	19	24	0.599
	< 60 years old (n=49)	19	30	
Gender				
	Male (n=68)	32	36	0.153
	Female (n=26)	8	18	
Tumor type				
	Gingival carcinoma (n=48)	23	25	0.558
	Tongue cancer (n=32)	12	20	
	Others (n=14)	5	9	
TNM staging				
	Stage III (n=39)	18	21	0.552
	Stage IV (n=55)	22	33	
Lymph node metastasis				
	Metastasis (n=54)	24	30	0.665
	Non-metastasis (n=40)	16	24	

Table 2: Treatment effectiveness in the 2 groups

Group	CR	PR	SD	PD	ORR	DCR
DF (n=40)	1	15	20	4	16	36
TPF (n=54)	4	32	13	5	36	49
Z/ χ^2			-2.332		6.611	0.015
P-value			0.020		0.010	0.903

RESULTS

Patients' baseline data

Comparison of baseline data showed that there were no significant differences in age, gender, tumor type, TNM stage, and lymph node metastasis between the DF group and TPF group ($p > 0.05$, Table 1).

Clinical efficacy

Treatment efficacy was significantly higher in TPF group than in DF group, while DF group had markedly lower ORR than the TPF group. However, DCR was comparable in TPF- and DF-treated patients. These results are shown in Table 2.

Changes in immunological indices before and after chemotherapy

The immunological indices of patients were compared before and after chemotherapy. It was found that there were no significant differences in the levels of CD4+, CD8+, and CD4+/CD8+ ratio between the two groups before chemotherapy ($p > 0.05$).

However, after chemotherapy, CD4+ level and CD4+/CD8+ ratio in both groups were raised, relative to pre-chemotherapy values, while the level of CD8+ was markedly decreased ($p < 0.05$). As shown in Figure 1 A - C, patients in TPF group had significantly higher post-treatment levels of CD4+ and CD4+/CD8+ ratio, and lower CD8+, relative to DF group ($p < 0.05$).

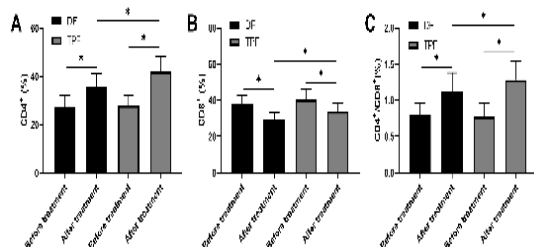


Figure 1: Levels of immunological indexes in patients' peripheral blood before and after chemotherapy, as measured using flow cytometry. * $P < 0.05$

Adverse events

There were no statistically marked variations in incidence of nausea and vomiting, rash, oral mucosa damage, peripheral neurotoxicity, and liver function impairment between DF group and TPF group. These data are presented in Table 3.

Data on Cox regression analysis

After therapy, the patients were followed up until January 2019. Indicators such as chemotherapy

Table 3: Incidence of adverse reactions

Group	Nausea and vomiting	Rash	Oral mucosa damage	Peripheral neurotoxicity	Liver function impairment
DF (n=40)	10	6	6	10	5
TPF (n=54)	13	9	10	14	6
χ^2	0.012	0.047	0.201	0.01	0.254
P-value	0.917	0.827	0.654	0.918	0.614

Table 4: Cox regression analysis

Variable	Univariate			Multivariate		
	P	HR	95 % CI	P	HR	95 % CI
Chemotherapy regimen	0.496	0.860	0.556-1.329			
Gender	0.522	1.168	0.726-1.881			
Age	0.738	0.929	0.603-1.43			
TNM staging	<0.001	3.712	2.326-5.925	<0.001	3.583	2.233-5.750
Tumor type	0.987	0.998	0.739-1.346			
Lymph node metastasis	0.003	0.506	0.322-0.796	0.011	0.550	0.347-0.873
CD4+	0.922	0.997	0.949-1.049			
CD8+	0.893	1.003	0.963-1.044			
CD4+/CD8+	0.745	1.212	0.38-3.862			

(TNM: tumor node metastasis; CD 4+: cluster of differentiation 4 positive; CD8+: cluster of differentiation 8 positive).

regimen, gender, age, TNM stage, tumor type, lymph node metastasis, and CD4+, CD8+, and CD4+/CD8+ levels were selected for Cox univariate regression analysis. Multivariate CRA showed that TNM stage and lymph node metastasis were independent prognostic factors for OC patients. These results are shown in Table 4 and Figure 2.

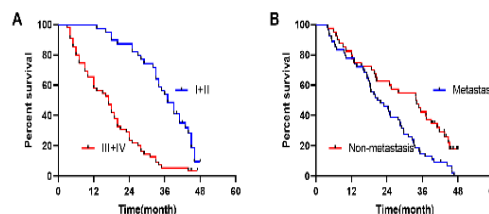


Figure 2: TNM stage and survival of patients with lymph node metastasis. A: survival of patients with low and high TNM stages; B: survival of patients with and without lymphatic metastasis

DISCUSSION

Oral cancer (OC) is a pervasive malignant tumor of the head and neck for which surgery, radiotherapy or chemotherapy can achieve excellent curative effects at the early stage [15]. The postoperative recurrence of lymph node metastasis in patients at the middle and advanced stages may reach 30 – 50 %, with a higher probability of lymph node metastasis during surgery [16].

Currently, patients with advanced or recurrent OC are treated mainly with a combination of radiotherapy and chemotherapy. However, over 50 % of these patients do not survive for up to one year thereafter [17].

Neo-adjuvant chemotherapy (NACT) is a new type of systemic chemotherapy which is performed before surgery or radiotherapy [18]. It has been reported that NACT effectively reduced tumor volume in patients at advanced stages of cancer, thereby improving the resectability and negative margin, and reducing the possibility of subclinical lesion metastasis [19].

In the present study, the improvements in clinical efficacies of DF regimen and TFP regimen in patients after chemotherapy were retrospectively analyzed. The results showed that the overall clinical efficacy in TFP group was better than that in DF group, and ORR in DF group was lower than that in TPF group. This indicates that TFP regimen resulted in significantly enhanced curative effect in patients, which is consistent with previous research results. In addition, a previous study revealed that TPF resulted in treatment effectiveness of 85.2 % in middle and advanced (stage II - IV) head and neck squamous cell carcinoma, which was markedly higher than that of PF regimen (60 %) [20]. The results obtained in the present study are consistent with these findings.

A decrease in immune function after chemotherapy is a common clinical phenomenon. The CD4 cells are the most important immune cells in the human immune system. These cells are expressed by T helper (Th) cells which are receptors for antigen recognition by Th cells [21]. The CD8+ T lymphocytes specifically recognize endogenous antigens presented by MHC-1 molecules which, with the help of CD4+ T lymphocytes, participate in immune response that kills tumor cells [22].

Furthermore, this research showed markedly higher post-treatment CD4+ levels and CD4+/CD8+ ratio, and lower level of CD8+ in TPF group, relative to the corresponding values in DF group. This suggests that TPF regimen had low negative impact on the immune function of patients. A study by Bi *et al* [23] showed that after TPF treatment of patients with locally advanced nasopharyngeal carcinoma, CD4+ level and CD4+/CD8+ ratio were enhanced, while CD8+ level was decreased, which is consistent with results obtained in this study. Results of Cox regression analysis revealed that TNM stage and lymph node metastasis were independent prognostic factors for patients.

Limitations of the study

There are some limitations in this study. In the first place, the sample size used was small, indicating the likelihood of bias in the results obtained. Secondly, some immunological indicators were absent from the data analyzed in this study. In subsequent studies, a larger sample size will be used, and other immunological parameters will be assayed, so as to validate the findings in the present investigation.

CONCLUSION

The results obtained in this study have demonstrated that TFP regimen enhances clinical efficacy and immune function in patients with advanced OSCC.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yilei Liang conceived and designed the study, and drafted the manuscript. Fujun Li and Jiajie Huang collected, analyzed and interpreted the experimental data. Zhenni Zhang revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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