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Neoadjuvant Chemotherapy for Locally Advanced Oral Squamous Cell Carcinoma: A Single Center Study

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Research Article

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ABSTRACT

Objective: Aimed to evaluate the effect and response from the adjuvant chemotherapy for locally advanced oral squamous cell carcinoma.

Methods: Retrospectively collected 46 patients with local late oral squamous cell carcinoma admitted from 2017 to 2021. The patients were treated with TPF induction chemotherapy. All patients completed at least 2 cycle of TPF（PF）regimen (75 mg/m2 of docetaxel on day 1+75 mg/m2 of cisplatin on day 1+750 mg/m2 of 5-fluorouracil on days 1 ~ 5, one cycle every 21 days), The primary end-points were overall response rate, safety of therapy and overall survival were evaluated.

Results: After two cycles of TPF treatment, patients continued receiving surgery followed by radiotherapy or chemotherapy, include 5 patients were received PF. The complete remission rate was 6.25% (2/32), and the objective remission rate was 71.88% (23/32). Most of the adverse factors of chemotherapy response are alleviated. The median follow-up time was 26 months, and the median OS was 25.51 ± 3.81 months.

Conclusion: Neoadjuvant chemotherapy, such as TPF or PF, plays an important role in the comprehensive treatment of advanced OSCC and postoperative assessments of white blood cell can provide high-quality prognostic information.

Keywords: Neoadjuvant chemotherapy; Docetaxel; Cisplatin and 5-fluorouracil (TPF); Cisplatin+5-fluorouracil (PF); Radiotherapy; Oral squamous cell carcinoma

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INTRODUCTION

In 2018, the global incidence rate of Head and Neck Cancer (HNC) was 247.6 per 100,000[1]. Oral Squamous Cell Carcinoma (OSCC) is the most common malignant tumor, which is treated with surgery in the early stage and with comprehensive treatment including surgery, radiotherapy and chemotherapy in the late stage. Currently, surgical procedures include extensive resection of the primary lesion and appropriate neck dissection. Due to the high frequencies of Lymph Node Metastasis (LNM) and Distant Metastasis (DM), which are the common consequences of tumors, the prognosis of OSCC patients remains poor, with a high local recurrence rate and a 5-year survival rate of 50% [2,3]. Given the low cure rate and high mortality of OSCC, it is important to minimize the loss of oral cavity function caused by surgery, so as to improve the quality of life of patients.

Nowadays, some strategies have been proposed to improve patient prognosis by combining chemotherapy, surgery and radiotherapy, while chemotherapy will inevitably cause side effects, particularly myelosuppression that poses a serious threat to the survival rate and quality of life of patients [4]. With the understanding of the biological characteristics of HNC and the progress of new chemotherapeutic agents, Neoadjuvant Chemotherapy (NC) has been put forward. NC is mainly used for the treatment of advanced oral cavity cancer. Induction chemotherapy decreases the distant recurrence rate from 38% to 14% in advanced OSCC [5], while chemoradiotherapy only decreases the local recurrence rate and seems not to have any impact on distant metastasis [6]. At present, the docetaxel, cisplatin and 5-fluorouracil (TPF) regimen has been regarded as the standard chemotherapy regimen for Head and Neck Squamous Cell Carcinoma (HNSCC) [7].

Hence, this study aimed to evaluate the effect and toxicity of docetaxel, cisplatin, and Fluorouracil (5-FU) in the induction chemotherapy for advanced OSCC in our hospital. The tumor Complete Response Rate (CRR), safety of therapy, and Overall Survival (OS) caused by TPF or PF were evaluated.

MATERIALS AND METHODS

Data collection

Altogether 46 patients with locally advanced OSCC admitted from January 1st, 2017 to December 31th, 2021 in the hospital were retrospectively collected, including 41 males and 5 females, with the age of 31-83 years. All the studies were performed following a protocol approved by the Shanghai Jiao-tong University and Guizhou Medical University (V20161010).

The patient inclusion criteria were as follows, (1) patients with OSCC confirmed by histopathology or cytology [8]; (2) patients without previous surgery or chemoradiotherapy; (3) patients with untreated stage III or IVA locally advanced OSCC; (4) the correct function of CT/MRI was that the cardiovascular system, liver, kidney and bone marrow received chemotherapy and surgery; (5) tumors were located in the mouth, including lips, tongue, gums or oral mucosa on the floor of the mouth, or the posterior triangle of molars; (6) evaluation of physical conditions: The Karnofsky scoring system was used for evaluation, and those with ≥ 60 points were included in the study group.

Patients exclusion criteria were shown below, (1) those with a history of chemotherapy or radiotherapy; and (2) those with a distant metastasis.

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Treatment

The induction chemotherapy regimen was as follows the Table 1 [9]. After each cycle, myelosuppression and liver and kidney functions were evaluated after 21 days. Patients were given 2 cycles of chemotherapy. The treatment response was evaluated clinically and radiologically, and all patients were scanned before and after chemotherapy (CT/MRI). The final response evaluation and surgical decision were decided by the surgeon. Surgery was performed at last 2 weeks after the completion of chemotherapy, and the patients received radiotherapy at a dose of 55-60 GY at 4 weeks after surgery.

Table 1. Chemotherapy regimen used.

	TPF(docetaxel+cisplatin+5-fluorouracil)	PF(cisplatin+5-fluorouracil)
Patients	42 Docetaxel:75 mg/m2 Cisplatin:75 mg/m2	4 Cisplatin:75 mg/m2
Dose of chemotherapy	5-fluorouracil:750 mg/m2 continuous infusion for three days	5-fluorouracil:750 mg/m2 continuous infusion for three days
Note: Cycle to be repeated every 21 days		

Efficacy evaluation

The efficacy was evaluated according to the World Health Organization (WHO) solid tumor efficacy evaluation standard (RECIST 1.1) [10]. The efficacy evaluation and corresponding symptoms were shown below. Complete Remission (CR) indicated that the lesion subsided completely. Partial Remission (PR) suggested that the volume decreased by 30% or no new lesions appeared after induction chemotherapy. Progressive Disease (PD) suggested at least 20% increase in baseline lesion length or new lesions. Stable Disease (SD) indicated that the lesion volume decreased by less than 30% or increased by less than 20%, and no new lesions appeared. Toxicity was evaluated according to the CTCAE version 3.0. According to the efficacy, CR/PR was defined as therapeutic sensitivity, whereas SD/PD as therapeutic insensitivity.

Follow-up

All patients were followed up until disease progression or death. OS was measured from the date of inclusion to the date of death of any cause. All statistical analyses were carried out using Graph Pad Prism 7.0.

RESULTS

The study was conducted between January 1st, 2017 and December 31th, 2021, during which 46 patients were included and randomly divided into three groups. The slow randomization of this study was due to the high requirements for patient inclusion, the limited number of advanced resectable oral cancer, the unwillingness of surgeons to start chemotherapy for resectable tumors, and the increasing trend of radiotherapy and chemotherapy for potentially resectable tumors as conclusive treatment.

Finally, 21 patients received TPF/PF+Surgery+Radiotherapy, 15 underwent post-surgery+TPF/PF, and 10 received NC, including 1 dying of leucopenia and 1 being withdrawn from chemotherapy because of angina. The median age of patients was 61 (range, 31-83) years, with the mean of 60+10.7 years. There were 5 females among the

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participants. Of the 44 patients, the CRR was 6.25% (2/32), and the Objective Remission Rate (ORR) was 71.88% (23/32), meanwhile, 4 (12.50%) patients had SD, and 3 (9.37%) had PD (Table 2). The total alleviation rate was 76.70%. The main oral cavity cancer was shown below Table 3. The most common tumor sites included the tongue, floor of the mouth and posterior molar area. Among the tumors, there were 20% well-differentiated, 57.50% moderately-differentiated and 22.50% poorly-differentiated ones. In addition, 27.50% of tumors were at T2, 27.50% at T3 and 45% of tumors invaded two or three anatomic regions. Only 13 (32.50%) patients had no lymph node involvement. All patients were divided into groups below Table 4.

Table 2. Efficacy of induction chemotherapy with TPF.

TPF						PF				
Variable		CR	PR	SD	PD	CR	PR	SD	PD	Remission rate (%)
Diff	well	1	3	1	1	0	0	0	0	66.67
	mod	1	15	2	1	0	1	0	0	85.00
	poor	0	5	1	2	0	1	0	0	66.67
	T2	0	4	2	0	0	0	0	0	66.67
	T3	1	6	1	2	0	1	0	0	72.73
Tumor	T4	1	12	1	2	0	1	0	0	82.35
	N0	1	12	1	0	0	1	0	0	86.67
	N1	0	7	2	2	0	1	0	0	66.67
LN	N2	1	3	1	2	0	0	0	0	57.14
Total		6	67	12	12	0	6	0	0	76.7
Note: CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease.										

Table 3. Site of primary tumor.

Site	No. (%)
Tough	16(34.78)
Floor of Mouth (FOM)	11(23.91)
Gingiva	5(10.87)
Buccal	2(4.35)
Palate	2(4.35)
Retromolar trigone (RMT)	9(19.57)
Parotid gland	1(2.17)

Table 4. Follow-up treatment after chemotherapy with TPF.

Treatment types	Total
Chemotherapy+surgery+radiotherapy	21
Chemotherapy+chemotherapy or radiotherapy	10
Surgery+chemotherapy	15
n	46

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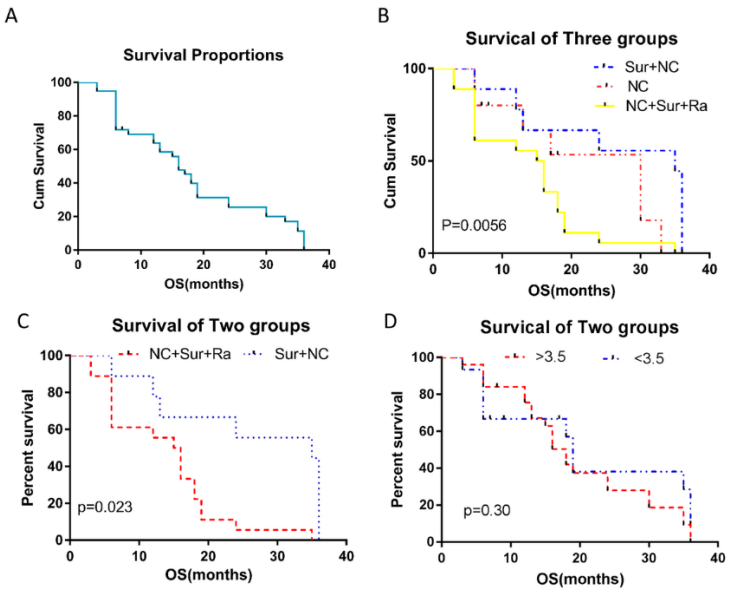
After chemotherapy, 36 cases were confirmed to have no tumor cells after surgery, no matter whether they received pro-chemotherapy or post-chemotherapy. As shown in Table 4, chemotherapy plus chemotherapy or radiotherapy increased the morbidity (2/10). The follow-up time of patients was stopped in October 1st, 2022, resulting in the median follow-up time of 20 (3-53) months, and 13 patients (28.26%) received follow-up for more than 3 years. Three patients (6.52%) died of disease progression at about 1-10 months after treatment. It was observed from Figure 1A that, the OS was 25.51 ± 3.81 months, and the median OS was 26 ± 0.25 months. Our data revealed that the OS was statistically significant among the three groups (P=0.056, ratio=0.4429, CI=0.199-0.9858, Figure 1A). The treatment was significant when comparing the NC+Sur+R group with Sur+NC group (P=0.023, Figure 1B). The median OS of Sur+NC group was 35 months (ratio=2.258, confidence interval (CI)=1.014-5.026). These results were mainly confirmed by multivariate analysis for independent risk factors. NC+Sur+R (Hazard Ratio [HR]=3.812, CI=1.513-9.601) and patients with oral cavity cancer (HR=0.2624, CI=0.1042-0.6609) had a higher rate of NC+Sur (Figure 1C). It is well known that most patients have nausea, vomiting and hematological toxicity after chemotherapy.

In most cases, nausea and vomiting are mild, and only a few serious reactions need treatment. Among them, myelosuppression is the most serious side effect, which results in the reduction of leukocyte and neutrophil numbers, the decrease of hemoglobin level, or thrombocytopenia, and requires granulocyte infusion or injection with platelet colony stimulating factor, while blood transfusion is required for severe complications. Therefore, in this study, a medicine was administered to increase the number of leukocytes before chemotherapy. In this study, only 1 patient had decreased numbers of leukocytes and finally died. Our data found that the leukocyte myelosuppression rate was about 13.04%, in the meantime, the basic White Blood Cell (WBC) count was 3.5*109/l, which was important (Figure 1D). The ratio of two groups was 0.9474, and the corresponding 95%CI was 0.4618 to 1.943 (HR=1.5024, CI=0.6881-3.277).

Figure 1. Kaplan Meir diagram of survival. A. All patients after neoadjuvant chemotherapy. B and C. Overall survival of 3 groups of patients. D. survival curve for white blood cell. **Note:** Sur: Surgery; OS: Overall survival; NC: Neoadjuvant Chemotherapy; Ra: Radiotherapy; P<0.05; (—) NC+ Sur+Ra; (----) NC; (-·-·-) Sur+NC; (·····) Sur+NC; (- - - -) NC+ Sur+Ra; (----) >3.5; (-·-·-) <3.5.



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DISCUSSION

OSCC is the most common malignant tumor in head and neck. NC is one of the most effective methods to treat OSCC which has been advocated recently by doctors and achieves satisfactory results. The TPF, TP and PF regimens are commonly used in the treatment of HNSCC. As shown in a review, the preoperative TPF regimen can increase the 3, 5 and 10-year larynx preservation rates by 12.8%, 15.9%, and 23.8%, separately [11]. Our department adopts the TPF regimen together with the Ninth People's Hospital of Shanghai Jiao Tong University. Several phase III clinical trials have shown that TPF is more beneficial than PF in the treatment of HNC [12]. A prospective study reports that the TPF remission rate is 60.8%, proving that the TPF regimen is more effective on the treatment of HNC [13]. This study proved that the TPF/PF regimen was more effective on the treatment of OSCC. The remission rate was 76.70%, which slightly decreased by 2.70% compared with that reported in literature, and reported identically by sun [14,15]. Overall, the target response rate was 76.70%, much higher than that of 46% reported by Fu [16].

The current results suggest that more studies can be conducted on surgery combined with induction chemotherapy for OSCC, with no increase in the death or recurrence rate. According to literature review, when induction chemotherapy is used, the lymph node metastasis of OSCC is limited to specific cases [17]. Similarly, induction chemotherapy is also effective and recommended for the treatment of laryngeal, hypopharyngeal, and nasopharyngeal carcinoma [13,18]. In theory, preoperative chemotherapy and radiotherapy may be recommended, because the complete tumor vascular system allows more effective drug release into the tumor [19]. Early induction chemotherapy helps to kill small metastases, reduce the incidence of distant metastasis and ensure a favorable prognosis. The blood concentration of drugs has the potential to improve organ retention and maximize the effect of individualized treatment due to the integrity of blood vessels. Nevertheless, many studies have shown that chemotherapy is well tolerated among patients with HNSCC. Maji indicated that regulation of Signal Transducer and Activator of Transcription 3 (STAT3) and glycogen synthase kinase 3 beta-mediated Mcl-1 modulated the TPF resistance in OSCC [20]. This study suggested that in patients with OSCC, TPF reduced tumor recurrence after chemotherapy, changed the treatment plan, and enabled some patients to avoid organ resection. Therefore, NC, as an alternative to the organ function preservation treatment, is effective and feasible. The ideal preoperative adjuvant chemotherapy is not only effective with few side effects, but also time-consuming. The operation can be delayed when poor curative effect is achieved. In our study population, few side effects were reported, and most patients did not seem to have any serious adverse reaction. Six patients (13.04%) had grade 3-4 myelosuppression, which was relieved after timely symptomatic treatment, but did not affect the treatment plan. In addition, 21 patients received TPF/PF+Surgery+Radiotherapy, 15 underwent post-surgery+TPF/PF, and 10 took NC, including 1 dying of leucopenia and 1 being withdrawn from chemotherapy due to angina. There were 28% of patients receiving follow-up for more than 3 years. The disease progression rate was 8.70%, which showed that some patients who received chemotherapy plus radiotherapy had poor effect, while some patients attained good effect and avoided surgery. Further research is warranted to determine how to distinguish these patients.

The expression of biomarkers such as GDF15, Notch1 and Annexin A1 in tumors, invasion, or reduction in the number of circulating tumor cells can predict the benefits of TPF induction therapy [21-23]. At present, no markers have been established in clinical routine. The studies demonstrate that the increased preoperative Fib and PLR levels are associated with poor outcome of OSCC [24]. In our study, 3.5 or 3.0 was analyzed as the critical value of

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OS, which was not significant but important. The problem might be caused by the small sample size of WBC data. Surprisingly, the HR value of NC+Sur+R compared with Sur+NC was high, which could not be explained. It remained unclear about whether the difference between preoperative and postoperative chemotherapy was significant among different groups, in accordance with the results reported by Sadighi [25]. A phase III study including 157 patients does not show any significant difference between radiochemotherapy and induction, followed by chemoradiotherapy, which was supported by our data. Wang reported a median Progression-Free Survival (PFS) of 16 months, which was shorter than that reported in the present study [26,27]. However, the OS was lower in this previous study compared with that in the present study (23.20 months).

The global treatment compliance in our series of reports was similar to that observed in other reports on induction chemotherapy followed by radiotherapy. Although induction chemotherapy with TPF is the gold standard for the preservation of oral cavity function, its role in the treatment of oropharynx and oral cavity tumors and in the inoperable patients remains unclear. However, many studies have reported the development of tumor tolerance. A clinical phase III study reveals that the docetaxel regimen appears to be more effective than TPF [28.29]. Therefore, the prognosis of TPF is worth studying. microRNA-92b is a marker for predicting the response to TPF induction chemotherapy and evaluating the prognosis of patients with advanced OSCC [30]. In addition, in our previous studies, the expression of stromal cell derived factor-1 and Nerve Growth Factor (NGF) was up-regulated in the tumor stage of TNM, while NGF protected salivary glands from radiotherapy damage [31]. Further studies should focus on this topic and explore the mechanism of stromal cells-derived factor-1 pathway in induction chemotherapy and the roles of physiological and biochemical indexes in the prognosis of TPF chemotherapy.

CONCLUSION

Certain limitations should be noted in this work. Firstly, this was a retrospective study with a relatively small sample size. Secondly, this study did not reach any consensus on the optimal dose classification of Intensity Modulated Radiotherapy (IMRT) for OSCC. Therefore, the radiotherapy strategy from the Ninth People's Hospital of Shanghai Jiao Tong University was adopted. Thirdly, considering these limitations, the conclusions of this study should be further verified. Multicenter studies with new strategies examining OSCC are very important. Consequently, the prognosis of TPF is worth studying. In conclusion, the results show that the TPF regimen plays a pivotal role in OSCC, and the WBC ratio is important for patient prognosis prediction. So prospective clinical trials with larger samples are required to further study this chemotherapy regimen.

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Declaration of competing interest

All the authors have declared that there are no competing interests.

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