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Original Article

Clinical study on prescribing trends and quality of life assessment in terminally ill patients with oral squamous cell carcinoma treated with palliative chemotherapy

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Abstract: Introduction: The prevalence of oral squamous cell carcinoma (OSCC) is increasing drastically in developing countries and it has a complex pharmacotherapy with a poor prognosis, resulting in a high mortality rates. Therefore, there is a need to perform drug utilization studies of palliative chemotherapeutic agents to rationalize the drug therapy in OSCC to reverse the condition. Aim: We aimed to investigate the drug-utilization patterns and analyze the quality of life assessment of OSCC patients on palliative chemotherapy. Methodology: A prospective longitudinal study was conducted in the Cancer Hospital after ethical approval. Patient characteristics, treatment profile, recurrence profile, and quality of life were assessed. Data collection was done using a case record form and a quality of life (QoL) questionnaire. Results: Out of 104 OSCC patients receiving palliative care treatment, 97 (93.3%) patients were male, and 7 (6.7%) were female. In the present study, 83 patients had recurrent cancer, while 21 were newly diagnosed with metastatic disease. In this work, all 104 patients had Stage 4 malignancy. In the present study the drug combinations were as follows; methotrexate as monotherapy, while Cisplatin was prescribed in combination with methotrexate, 5-Fluorouracil (5-FU), and Docetaxel with a ratio of 38%, 42%, and 49%, respectively. The subjective assessment of therapy was assessed by a questionnaire that revealed a statically significant ($P \leq 0.05$) improvement in patient symptoms. Conclusions: Tailored drug therapy approaches as palliative chemotherapy should be adopted with clinically intervention for managing terminally ill OSCC patients with less incidence of toxicity.

Keywords: Oral squamous cell carcinoma, Cisplatin, methotrexate, quality of life

Introduction

Cancer-related morbidity and mortality in India have increased significantly in recent years [1]. The incidence rate of cancer in India was 1.15 new cases per 100,000 in the population in 2018 and is expected to double by 2040 due to demographic changes [2]. Oral squamous cell carcinoma (OSCC) is the most common type of oral carcinoma and ranks 12th as the most common cancer globally. However, OSCC is the most common type of cancer in India, accounting for 40% of all new cancers. Most oral cancers in India are diagnosed at a late stages [3]. OSCC is staged using the TNM standards, which consider the disease's features such as tumor size, the nodal status of metastases, and metastasis to a distant organ. OSCC manifests in the early stages as an erytholeukoplastic region with no symptoms, but as it progresses, ulcers and lumps appear with uneven edges that are stiff to the touch. Diagnostic criteria include assessing lumps or swelling in any part of the oral cavity, completing a visual examination of the oral cavity, tongue, floor of the mouth, salivary glands, gums, and teeth throat examination through an endoscope [29]. A multidisciplinary approach, such as early disease surgery or radiation therapy (stage I and II) and combinations of surgery, radiation therapy, and chemotherapy, are used to treat stage III and stage IV disease.

In our study, we analyzed patients with Recurrent and Metastatic Oral Squamous Cell Carcinoma receiving one of the four regimens, i.e., methotrexate alone, Cisplatin with Methotrexate, Cisplatin with 5-Fluorouracil or Cisplatin with 5-Fluorouracil and Docetaxel. There is a lack of research in India on the drug utilization of palliative chemotherapy in OSCC. With this perspective, we aimed to study the pattern of drug use and efficacy of palliative chemotherapy, thus recognizing treatment-related complications and adopting therapeutic approaches that enhance the quality of life.

Methodology

Ethical approval

The study was conducted after approval by the Institutional Ethics Committee of the Hospital. All the patients gave their oral and written consent to participate in the study.

Design and site of study

A prospective observational study was performed at the Medical Oncology Department of our Hospital between July 2017 and February 2018.

Criteria for inclusion

1. Patients over 18 years of age of either sex were included. 2. Histologically proven oral squamous cell carcinoma cases were considered. 3. Stage 4 disease at the time of initial diagnosis or recurrence (in case of recurrence, patients must have been adequately treated as per NCCN guidelines). 4. Patients willing to provide informed written consent voluntarily were included.

Criteria for exclusion

Patients that developed disease progression throughout the research were excluded. As a result, there were 21 inoperable cases which were removed from the prescribing routine and quality of life assessment out of a total of 104 cases.

Study parameters

The parameters analyzed included demographic data, associated risk factors, occurance site, and oral squamous cell carcinoma stage. The validated Quality of Life (QOL) questionnaire was used twice, first at the time of the baseline evaluation and secondly after three cycles of palliative chemotherapy. QOL questionnaire included Physical fitness and Functional assessment scale and related parameters including 35 questions. Scoring in QOL questionnaires were done from a 0-8 scale. Symptomatic improvement and clinical toxicity were also measured. Effectiveness of treatment was evaluated using a paired t-test ($P< 0.05$). Toxicity grading was done as per common Toxicity Criteria v3.0 and compared with earlier published clinical studies.

Statistics

Demographic and clinical variables were evaluated using descriptive statistics as frequencies and percentages.

ECOG staging: Doctors use these scales and criteria to decide if a patient's condition is improving, assess how the disease impacts the patient's day-to-day capacity, and identify appropriate care and prognosis. Health control experts use them [23]. QOL related effectiveness of treatment evaluation was conducted using a paired t-test ($P<0.05$).

Results

Demographic and disease-related information

A total of 104 OSCC patients were enrolled in the study, from them 21 patients were newly diagnosed with inoperable metastasis. They were excluded from the study, while 27 patients presented with stage II and 56 patients presented with stage III upon their first clinical diagnosis of OSCC and were considered for the study (**Table 1**). Out of 104 patients, 97 (93.3%) patients were male, and 7 (6.7%) were female, including the inoperable cases, which indicate a higher prevalence of malignant oral carcinoma in males. The median age of the patients was found to be 57.50±12.54 years. A higher prevalence rate of OSCC was observed in the age group of 60-70 years. Out of 104 patients, 48 (46.15%) male patients were addicted to tobacco and alcohol, and the use of betel quid was prominent in males. It was observed that a total of 16 male patients and three female patients had a family history of cancer, and

Table 1. Clinical Parameters of OSCC patients

Sr No	Clinical Parameters	No of Patients (N=83)
1	Stage II	27
2	Stage III	56
	Tumor Size	
1	T1	13
2	T2	9
3	T3	23
4	T4	33
	Nodal Metastasis	
1	N0	14
2	N1	15
3	N2	49
	Histopathological Grading	
1	Well Differentiated	31
2	Moderately Differentiated	48
3	Poorly Differentiated	7
	ECOG PS	
1	0	38
2	1	36
3	2	12

Table 2. Clinical parameters of relapse in OSCC patients

Sr. no	Area	No of patients
1	Local site	
	Tongue	61
2	Metastatic site	-
	Lungs	34
	Liver	26
	Bones	32
	Sub-mandible region	17
	Sub-auricular region	29
	Throat	38
	Alveolus	22

associated members were the first-line relatives. In the present study (N = 83) (inoperable cases were excluded), the tongue was the most prominent site of OSCC affecting 61 (73.49%) patients, followed by Gingivobuccal site 19 (22.9%), and alveolus 6 (7.22%). The clinically advanced step was fortified with tumor sizes of T3 and T4 in 23 and 33 patients, respectively. The lymph node involvement was observed as N1 in 15 patients and N2 in 49 patients (**Table 1**). The secondary site of metastasis was the throat, lungs, liver, bones, and alveolus in the study population (**Table 2**).

Prescribed palliative chemotherapy information

The combination of drug therapy included either two or three neoplastic drugs. Cisplatin was used in conjunction with methotrexate, 5-FU, and Docetaxel, with a wide range of DCR, observed to be 38%, 42%, and 49%, respectively. Paclitaxel plus carboplatin was integrated in 13 patients who reported a DCR of 43%. The three-drug combination included Docetaxel, Cisplatin, and 5-FU, which was prominently utilized in 28 patients with a DCR of 39% (**Table 3**).

Supportive care

To reduce the chemotherapy-associated adverse effects, supportive care provided was antiemetic, gastrointestinal (GI) drugs [proton pump inhibitors (PPIs)], granulocyte-colony-stimulating factors (GCSEs), and other agents (**Table 3**).

WHO core prescribing indicators

WHO core prescribing indicators were used to analyze the drug therapy integrated into OSCC patients. The treatment was found to be similar to past research. All the anticancer drugs prescribed were as per the Essential Drug List. The IV route administered all anticancer medicines. As drug therapy is personalized drug therapy, it involves multiple team members, and hence there is less chance of any error. The anticancer drugs were prescribed as per their generic name with a precise dose and diagnosis mentioned in the prescription (**Table 4**).

Effectiveness assessment by the quality of life questionnaire (QoL)

The European Organization of Research and Treatment of Cancer has developed a survey to analyze the subjective outcomes of cancer patients. The questionnaire is a useful tool to analyze the individual results of OSCC patients. A significant improvement (P = 0.05) was seen in all domains of the QoL tool. These improvements are the result of the tailored dose therapy, and it was potentially adequate to control the symptoms of metastatic cancer at follow-up of three cycles of chemotherapy (**Table 5**). In the present study, the toxicity of grade 1, grade 2, and grade 3 was observed. The toxicity

Table 3. Palliative chemotherapy and supportive therapy in OSCC patients

Sr no	Drug Therapy	No of Patients	Disease Control Rate (%)
	Palliative chemotherapy in OSCC patients		
1	Cisplatin + 5 FU	6	42
2	Cisplatin + Methotrexate	13	38
3	Docetaxel + Cisplatin	13	49
4	Paclitaxel + Carboplatin	13	43
5	Docetaxel + Cisplatin + 5-FU	28	39
	Supportive therapy in OSCC patients		
6	Domperidone + Pantoprazole (10 MG + 40 MG) BDS	83	-
7	LIQUID PARAFFIN (3 TSF) BDS	13	-
8	MULTI-VITAMIN (2 TABS/DAY) BDS	31	-
9	Folic acid (2 TABS/DAY) BDS	25	-
11	TRAMADOL + PCM (1 TAB) SOS	26	-
12	FLIGRASTIM (300 µg) OD/28 DAYS	01	-
13	MORPHINE (10 mg) SOS	10	-

Table 4. WHO prescribing indicators for OSCC patients

Sr. No	WHO PRESCRIBING INDICATORS	N (%)
1	Total number of prescription	83
2	Total number of drugs prescribed	815
3	Average number of drugs per prescription	7.4 (6.78%)
4	Average cytotoxic drugs per prescription	1.4 (3.01%)
5	Percentage of IV cytotoxic drugs prescribed	815 (100%)
6	Percentage of IV adjuvant drugs prescribed	74 (71.08%)
7	Percentage of cytotoxic drugs prescribed from EDL	100%
8	Percentage of cytotoxic drugs prescribed from WHO model list	100%
9	Percentage of adjuvant drugs prescribed from EDL	73.50%
10	Percentage of adjuvant drugs prescribed from WHO model list	78.97%
11	Percentage of drugs prescribed by generic name	87%

observed was hematological toxicity, cluster symptoms of chemotherapy, renal toxicity, and conjunctivitis. The toxicity grading was done as per Common Toxicity Criteria (**Table 6**). In the present study, as tailored drug therapy was integrated, the level of toxicity was observed to be minimal. The toxicity level of grade 1, grade 2, and grade 3 was observed. The toxicity observed was hematological toxicity, cluster symptoms of chemotherapy, renal toxicity, and conjunctivitis. The toxicity grading was done as per Common Toxicity Criteria v3.0. These data were compared with the published data of clinical trials. TAX323, EXTREME, and SPECTRUM. In these three studies, platinum-based chemotherapy combined with another anti-neoplastic drug (variant) was used to determine its clinical efficacy in a similar patient population. A prominent level of toxicity was observed in these clinical trials, but also effective interventions were given to minimize these toxicities (**Table 7**).

Discussion

Our research focuses on the clinical profile of OSCC patients, treatment patterns of OSCC patients, and the effectiveness of palliative chemotherapy on patient quality of life. In one study, the Specific Quality of Life Questionnaire version 2.1 was used with 14 different questions to assess migraine-related QOL, which may help to support this study's findings [26].

The male to female ratio in the rural population was 5:1, while a 2:1 ratio in the urban population was documented in one study [7], supporting our study results. According to a previous

Table 5. Effectiveness assessment of palliative chemotherapy using QoL

Sr No	Parameters of QOL-35	No of patients	Critical t value	Statistical t value	*p value*
1	PHYSICAL FITNESS ASSESSMENT				
1.1	Capable to do routine work	45	1.89	4.54	0.034
1.2	Capable to do strenuous work	67	1.88	2.32	0.021
1.3	Bed ridden	23	1.92	4.13	0.0076
1.4	Work at job/home	78	1.45	6.78	0.027
1.5	Capable of long walk	52	1.78	4.54	0.033
2	FUNCTIONAL ASSESMENT SCALE				
2.1	Pain in swallowing	23	1.43	4.66	0.0045
2.2	Slurring of speech	32	1.35	4.77	0.00567
2.3	Unable to open mouth	45	1.26	4.87	0.0121
2.4	Limited to work	64	1.18	4.98	0.0432
2.5	Bleeding	35	1.09	5.08	0.00231
3	Pain	46	1.01	5.19	0.000034
4	Dyspnea	43	1.99	4.56	0.00345
5	Cancer related fatigue	54	2.03	3.76	0.00432
6	Insomnia	23	2.45	6.4	0.01111
7	Anorexia	67	1.34	7.8	0.00987
8	Vomiting	12	2.54	4.56	0.0432
9	Nausea	10	1.78	2.54	0.00054
10	Constipation	8	1.02	3.56	0.00998
11	Diarrhea	12	0.98	5.45	0.0078
12	Emotional functioning	59	2.12	3.2	0.0002
13	Cognitive functioning	4	1.46	4.54	0.049
13.1	Agitation	67	3.59	5.32	0.0022
13.2	Cut off from social contact	34	3.28	6.1	0.01111
13.3	Worried about future	62	1.15	6.88	0.00987
14	Social contact	34	1.34	6.45	0.0432
15	Social eating	53	2.21	5.65	0.00054
16	Lack of interest	22	1.89	5.34	0.00998
17	Teeth ache	43	1.89	4.54	0.0078
18	Xerostomia	8	1.88	2.32	0.0022
19	Sticky saliva	12	1.92	4.13	0.049
20	Coughing	36	1.45	6.78	0.003
21	Feeding tube	48	1.78	4.54	0.0012
22	Weight loss	21	1.45	3.42	0.0032

study, Asia, particularly India, accounts for 57.5 percent of all oral squamous cell carcinoma cases worldwide [8]. A previous study found an exponential increase in the incidence of recurrence for patients of both genders between the ages of 40 and 70, which matched the findings of our study. The previous study's findings were comparable to the current study [9]. In one study on drug utilization, patients were reported to be between the ages of 51-60 years (37.5 percent), 61-70 years (20 percent), which supports the current study [27], while another clinical study revealed that admitted patients were between the ages of 61-70 years [28], which supports the current study. The elderly were found to have a higher rate of recurrence of malignant oral cavity tumors, which can be a feature of the amplified aging and senescence process, with a gradual decline in the body's immunity.

A total of 19 patients in the current study had a family history of cancer, and it was discovered that associated members were the first-line

Table 6. Clinical Toxicity of palliative chemotherapy in OSCC patients

TOXICITY	No of patients (%)		
	GRADE-1	GRADE-2	GRADE-3
Anemia	14 (13.4%)	0	1(0.9%)
Thrombocytopenia	7 (6.7%)	0	0
Neutropenia	4 (3.8%)	5	2 (1.9%)
Acute kidney injury	0	0	0
Stomatitis	3(2.8%)	1(0.9%)	3(2.8%)
Conjunctivitis	3(2.8%)	2(1.9%)	0
Lethargy	1(0.9%)	0	1(0.9%)
Nausea	1(0.9%)	0	0
Vomiting	0	0	0
Diarrhea	1(0.9%)	0	0
Anorexia	3(2.8%)	2 (1.9%)	3(2.8%)

Table 7. Comparison of toxicity profile with other clinical trials

Sr No	TOXICITY	No of Patients			
		PRESENT STUDY	TAX323 [19]	EXTREME [20]	SPECTRUM [21]
		N= 83	N=173	N=219	N=325
1	Neutropenia	15	133	49	103
2	Anemia	6	16	29	39
3	Thrombocytopenia	7	9	24	21
4	Acute Kidney Injury	0	0	0	10
5	Neurotoxicity	0	1	-	0
6	Lethargy	2	5	11	0
7	Nausea	1	1	0	0
8	Vomiting	0	1	12	0
9	Diarrhea	1	5	11	15
10	Stomatitis	2	1	-	0
11	Anorexia	0	8	0	29

relatives. A previous study found no significant inverse relationship between family history and OSCC mortality, but it did suggest that having a family history of cancer may be associated with a higher risk of developing an aggressive form of malignant tumors. Another study [24] investigated the risk of OSCC in patients with a family history of cancer and concluded that early age of onset could be a feature of hereditary cancers.

In the current study, 48 (46.15 percent) of 104 male patients were addicted to tobacco and alcohol, and betel quid use was prevalently in males. A previous study [10] found that people who consume tobacco in any form, alone or in combination with alcohol, were at a higher risk of developing oral cavity cancer. Previous research [11] found that 67.45 percent of patients with malignancy of the oral cavity were associated with tobacco and alcohol use, which supports our findings. The use of betel liquid was also found to have similar effects on cancer. Other risk factors included poor oral hygiene, poor nutrition, a sedentary lifestyle, and occupational hazards.

An earlier study [12] found that the mandible alveolus (70%) was the most common site of the primary tumor, followed by the buccal mucosa (30%), tongue (18%), the base of mouth (8%), palate (4%), and lip (4%). It was also concluded that the primary tumor location is determined by which area of the mouth receives the greatest exposure to carcinogens; however, the results were quite different from our study because these epidemiological data are subject to change depending on the area and population of the study.

When compared to radio and chemoradiotherapy alone, receiving multimodality treatment (postoperative radiotherapy and adjuvant chemotherapy) improved overall and time to recurrence. The study also suggested that late diagnosis was the primary cause of poor DFS even after multimodality treatment [13], which is supported by our findings.

Palliative chemotherapy is a comprehensive therapeutic approach for the treatment of OSCC. Cisplatin was used in conjunction with methotrexate, 5-FU, and Docetaxel, with a wide range of DCR, observed to be 38%, 42%, and 49%, respectively. Taxanes have been reported to have a 30-42 percent response rate with better survival benefits. The addition of platinum compounds to taxanes results in a response rate of 26 to 28 percent with 8.1 months of median survival [14], which lends some support to our study results.

Along with cancer chemotherapy, supportive care is required to alleviate the toxicities asso-

ciated with chemotherapy and the symptoms of OSCC. Tramadol and Paracetamol combinations were used in this study to control pain, whether it was generalized or neuropathic. Morphine was used to alleviate severe pain. Filgrastim is a granulocyte colony-stimulating factor used to treat chemotherapy-induced leukopenia, a common side effect of all chemotherapeutic agents. A previous study [22] found that patients with unresectable cancer and loco-regional failure could be managed with only supportive care. The addition of chemotherapeutic drugs, on the other hand, results in better symptom control.

The previous study found that the use of anticancer drugs was rational, with 70% of drugs prescribed from the National essential drug list [15], so the majority of the results supported our findings.

The QoL questionnaire proved to be a more effective tool for quick and easy subjective assessment of OSCC patients. With a significance level of 0.05, improvement was seen in all domains of the QoL tool. In one clinical study, the health-related quality of life (HRQoL) of oral patients receiving palliative chemotherapy was assessed, and it was discovered that HRQoL was low and that early palliative care may improve QoL [16]. In a previous study, it was discovered that treatment modalities had a negative impact on QoL in patients with head and neck cancer. The most severe or complete loss of taste and smell was observed, as well as weight loss, dry mouth, viscid saliva retention, pain, loss of appetite, nausea, and vomiting, and fatigue. Analyzing the selected factors revealed that tumors in the larynx and/or hypopharynx had the most severe impact on QoL [17]. Recent studies found no significant differences in quality of life as measured by the EORTC QLQ-H&N35, with the exception of speech disorders ($P = 0.04$), dry mouth ($P = 0.03$), and feeling ill ($P = 0.04$), and patients had relatively high scores on physical functioning, position functioning, and quality of life in three classes, whereas emotional and cognitive functioning were lower, which supports our study results [25].

The type and intensity of toxicity differ from person to person. These frequently render some drugs incompatible in different patients. To deal with this, chemotherapy was administered in cyclic form along with several anti-allergic drugs, which has an effect on the cost of therapy [18]. Previous studies TAX323 trial [19], EXTREME trial [20], and SPECTRUM trial [21] were used to compare toxicity profiles.

Study strength

This study demonstrated certain clinically significant concerns, such as the advanced clinical situations in patients with OSCC among enrolled patients, higher usage of palliative chemotherapy utilization of supportive agents. This study helped to promote the use of tailored anticancer drug therapy in combination with supportive drug therapy for comprehensive management of terminally ill patients with oral carcinoma.

Study limitation

The study had limitations, such as the low sample size of the study. We did not compare chemotherapeutic agents with the guidelines approved by various regulatory authorities. Further investigations related to drug utilization study in the different study sites and commonly occurring malignancies will be required to get a more expansive view on qualitative chemotherapy and supportive care.

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Disclosure of conflict of interest

None.

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